Prostate Cancer

EDITED BY: Gerald Andriole and Manfred Wirth



An International Consultation on Prostate Cancer

Berlin, Germany, October 16-20, 2011

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Abbreviations Used in the Text

%p2PSA	Prostate-specific antigen (PSA) isoform p2PSA
%pPSA	Ratio of the pPSA to fPSA
¹⁵³ Sm	samarium
¹⁸⁸ Re	rhenium
18-FDG	18-F-deoxyglucose
18F-FDHT	18-F-fluorodihydrotestosterone
²²³ Ra	radium
25(OH)D	25-hydroxy vitamin D
³² P	phosphorus
3D	three dimensional
3D-CRT	three-dimensional conformal radiotherapy
5ARI	5α-reductase enzyme inhibitor
5-HT	5-hydroxytryptamine (serotonin)
⁸⁹ Sr	strontium
8-OHdG	8-hydroxydeoxyguanosine
ACS	American Cancer Society
ACT	alpha-1-antichymotrypsin

ACTH	adrenocorticotropic hormone
ADAM (proteins)	A disintegrin and metalloprotease
ADC	Apparent Diffusion Coefficient
ADT	androgen deprivation therapy
AHCPR	Agency for Health Care Policy and Research
AID	activation of induced cytidine deaminase
ALCP	alkaline phosphatase
ALS	acid-labile subunit
AMACR	α-methylacyl-CoA racemase
AP	abdominal perineal
AR	androgen receptor
ARFI	termed acoustic radiation forse impulse
ARR	absolute risk reduction
ART	adjuvant radiotherapy
ASAP	atypical small acinar proliferation
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
ATCB (study)	α -Tocopherol, β -Carotene Cancer Prevention
AUA	American Urological Association
AUC	area under the curve

BASING	band selective inversion with gradient dephasing
BCR	Biochemical recurrence
BLSA	Baltimore Longitudinal Study of Aging
BMD	bone mineral density
BP	bisphosphonate
BPH	benign prostatic hypertrophy
bPSA	benign PSA
BRFS	biochemical recurrence-free survival
BT	brachytherapy
CAPRA	Cancer of the Prostate Risk Assessment
CARET (trial)	Carotene and Retinol Efficacy Trial
cDNA	complementary DNA
CDR	cancer detection rate
CGA	Chromogrannin A
CI	confidence interval
CIN 3	high-grade precancerous cervical lesions
COLD	Cryo On-Line Data
СОХ	cyclooxygenase
cPSA	
	complexed PSA

CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CSS	cancer-specific survival
СТ	computed tomography
CTIBL	cancer treatment-induced bone loss
СТх	C-telopeptide
CVD	cardiovascular disease
СҮР	cytochrome P450
D2 PCa	metastatic prostate cancer
DCE MRI	dynamic contrast-enhanced magnetic resonance imaging
DD3	differential display code 3
DES	diethylstilbestrol
DFS	disease-free survival
DHEA-S	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DNMTs	DNA methyltransferases
DRE	digital rectal examination
DSS	disease-specific survival
DVT	deep venous thrombosis
DWI	diffusion-weighted imaging

EAU	European Association of Urology
EBRT	external beam radiotherapy
ECE	extracapsular extension
ECOG	Eastern Cooperative Oncology Group
ED	erectile dysfunction
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMT	epithelial-mesenchymal transition
EORTC	European Organization for Research and Treatment of Cancer
EPC	early prostate cancer
EPC ePCA	early prostate cancer early prostate cancer antigen
EPC ePCA ePLND	early prostate cancer early prostate cancer antigen extended pelvic lymph node dissection
EPC ePCA ePLND ERC	early prostate cancer early prostate cancer antigen extended pelvic lymph node dissection endorectal coil
EPC ePCA ePLND ERC ERSPC	early prostate cancer early prostate cancer antigen extended pelvic lymph node dissection endorectal coil European Randomized Study of Screening for Prostate Cancer
EPC ePCA ePLND ERC ERSPC ESTs	early prostate cancer early prostate cancer antigen extended pelvic lymph node dissection endorectal coil European Randomized Study of Screening for Prostate Cancer expressed sequence tags
EPC ePCA ePLND ERC ERSPC ESTs ETS	early prostate cancer antigen early prostate cancer antigen extended pelvic lymph node dissection endorectal coil European Randomized Study of Screening for Prostate Cancer expressed sequence tags E26 transformation-specific
EPC ePCA ePLND ERC ERSPC ESTs ETS ETV1	early prostate cancer antigen early prostate cancer antigen extended pelvic lymph node dissection endorectal coil European Randomized Study of Screening for Prostate Cancer expressed sequence tags E26 transformation-specific Ets variant gene 1
EPC ePCA ePLND ERC ERSPC ESTs ETS ETV1 f/t PSA	early prostate cancer antigen early prostate cancer antigen extended pelvic lymph node dissection endorectal coil European Randomized Study of Screening for Prostate Cancer expressed sequence tags E26 transformation-specific Ets variant gene 1 ratio of free to total PSA

FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
fPSA	free PSA
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
Gleason (8 – 10)	high-grade prostate cancers
GM-CSF	granulocyte-macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
GSTP1	glutathione S-transferase P1
GU	genitourinary
GWAS	genome-wide association studies
Gy	Gray (units of irradiation)
H&E	hematoxylin and eosin
HDACs	histone deacetylases
HER-2	human EGF receptor-2
HER2/neu	human Epidermal growth factor receptor 2 (also known as ErbB-2)
HGF	hepatocyte growth factor
HGPIN	high-grade prostate intraepithelial neoplasia
HIFU	high intensity focused ultrasound
HIS	immunohistochemical studies

hK2	human glandular kallikrein 2
HR	hazard ratio
HR-MAS	high-resolution magic angle spinning
HRQoL	health-related quality of life
HSP	heat shock protein
IAD	intermittent androgen deprivation
ICUD	International Consultation on Urological Diseases
IGF-1	insulin-like growth factor 1
IGF-1R	insulin-like growth factor 1 receptor
IGFB-3	insulin-like growth factor binding protein 3
IGRT	image-guided radiotherapy
IL-6	Interleukin-6
IL-6sR	interleukin-6 soluble receptor
IMRT	intensity modulation radiotherapy
iNOS	inducible nitric oxide synthase
iPSA	intact PSA
IPSS	International Prostate Symptom Score
IRAEs	immune-related adverse events
IV	intravenous
kPa	kilopascals

LET	linear energy transfer
LHRH	luteinizing hormone-releasing hormone
LNPCa (cells)	A type of human prostate cancer cell line
LR	likelihood ratio
LRP	laparoscopic prostatectomy
LUTS	lower urinary tract symptoms
MAGI2	membrane associated guanylate kinase, WW and PDZ domain containing 2
MCM5	mini-chromosome maintenance-5
mCRPC	metastatic castration-resistant prostate cancer
MFS	metastasis-free survival
MI	mechanical index
MION	monocrystalline iron oxide nanoparticles
MISP	minimum initial service package
mm	micrometre
mpMRI	multiparametric MRI
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRS	magnetic resonance spectroscopy
MRSI	magnetic resonance spectroscopic imaging
MSKCC	Memorial Sloan-Kettering Cancer Center

mTOR	mammalian target of rapamycin
NADT	neoadjuvant androgen deprivation therapy
NASPCC	National Alliance of State Prostate Cancer Coalitions
NCCN	National Comprehensive Cancer Network
NE	neuroendocrine cells
NED	neuroendocrine differentiation
NFKB	nuclear factor kappa-β
NNT	number needed to treat
NPV	negative predictive value
NS	not significant
NSAIDs	Nonsteroidal antiinflammatory drugs
NSE	neuron-specific enolase
NTx	N-telopeptide
ONJ	osteonecrosis of the jaw
OPA	occupational physical activity
OPG	osteoprotegerin
OR	odds ratio
ORP	open prostatectomy
OS	overall survival
РААСТ	Patient Advocates for Advanced Cancer Treatments, Inc.

PAP	prostatic acid phosphatase
PARP	Poly ADP-ribose polymerase
PARP1	Poly [ADP-ribose] polymerase 1 (also known as NAD+ ADP- ribosyltransferase 1)
PCa	prostate cancer
PCA3	prostate cancer antigen 3 (also known as DD3)
PCC	Prostate Cancer Canada
PCCN	Prostate Cancer Canada Network
PCCTC	Prostate Cancer Clinical Trials Consortium
PCEC	Prostate Conditions Education Council
PCF	Prostate Cancer Foundation
PCLO (trial)	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PCPT	Prostate Cancer Prevention Trial
PCRI	Prostate Cancer Research Institute
PCSM	Prostate-cancer specific mortality
PCTGG	Prostate Cancer Trialists' Collaborative Group
PDGFR	platelet-derived growth factor
PET	positron emission tomography
PFS	progression-free survival
PHEN	Prostate Health Education Network
PHS	prostate histoscanning

PI	pixel intensity
РІЗК	phosphoinositide 3-kinase
PI3K-AKT- mTOR	phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin
PIA	proliferative inflammatory atrophy
PIE	Partners In Excellence
PIN	prostatic intraepithelial neuplasia
PIN	prostatic intraepithelial neoplasia
PIVOT	Prostate cancer Intervention Versus Observation Trial
PLND	pelvic lymph node dissection
ppm	parts per million
pPSA	pro-PSA
PPV	positive predictive value
PRESS	point-resolved spectroscopy
Pro-GRP	pro-gastrin releasing peptide
PSA	prostate-specific antigen
PSAD	PSA density
PSADT	PSA doubling time
PSAD-TZ	PSA density transition zone
PSAV	PSA velocity
PSMA	prostate-specific membrane antigen

pT3 PCa	pathologic stage T3 prostate cancer
PTEN	phosphatase and tensin homologue
QMSP	quantitative methylation-specific PCR
QoL	quality of life
RARP	robotic-assisted radical prostatectomy
RBCs	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumours
REDUCE	Reduction by Dutasteride of Prostate Cancer Events study
RF	radiofrequency
RP	radical prostatectomy
RPA	recreational physical activity
RR	relative risk
RRP	radical retropubic prostatectomy
RT	radiotherapy
RT-PCR	reverse transcriptase polymerase chain reaction
SBRT	stereotactic body radiotherapy
SEARCH	Shared Equal Access Regional Cancer Hospital
SEER	Surveillance Epidemiology and End Results
SELECT	Selenium and Vitamin E Cancer Prevention Trial
Sen	sensitivity

SNPs	single nucleotide polymorphisms
SNR	signal-to-noise ratio
SONAR	Sound Navigation and Ranging
Spec	specificity
SPECT	single photon emission computerized tomography
SPME	solid-phase microextraction
SRE	skeletal-related event
SRT	salvage radiotherapy
STAT3	signal transducers and activators of transcription 3
SVI	seminal vesical invasion
SWOG	Southwest Oncology Group
ТВК1	TANK binding kinase 1
TERT	telomerase reverse transcriptase
TGF- 1	transforming growth factor-beta 1
ТНІ	tissue harmonic imaging
ТКІ	tyrosine kinase inhibitors
ТМА	transcription-mediated amplification
TNF-alpha	TNF-alpha
ТОР2В	topoisomerase 2B
ТРА	total physical activity

tPSA	total PSA
TROPIC	XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer
TRUS	transrectal ultrasonography
UCSF-CAPRA	University of California, San Francisco, Cancer of the Prostate Risk Assessment
UGT	uridine diphospho-glucuronosyltransferase
UICC	Union for International Cancer Control
US	United States
Us TOO	Us TOO International Prostate Cancer Education & Support Network
USPIO	Ultrasmall superparamagnetic iron oxide
USPSTF	US Preventive Services Task Force
VACURG	Veterans Administration Cooperative Urological Research Group
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor
VSS	very selective saturation
WHO	World Health Organization
WPRT	whole pelvic radiotherapy
WWPCC	World Wide Prostate Cancer Coalition
XMRV	xenotropic murine leukemia virus-related virus
ZA	zoledronic acid

Preface

No disease is more vexing than prostate cancer. This disease has bewildered researchers, clinicians, epidemiologists and most importantly, patients and their families for over a century. Although we have learned much about the diagnosis, risk factors and optimal treatments for men with this disease over the last two decades, we need to learn more so that we can do an even better job caring for our patients. It is in that spirit that we have assembled this monograph. By bringing together a multidisciplinary team of experts from around the world, we hope to provide a solid framework for current and future students of this disease. Fortunately, our task was made easier as we could build upon the prior ICUD on Prostate Cancer edited in 2006 by Drs. McConnell, Denis, Akaza, Khoury and Schalken. Their work provided us, and our team of writing colleagues, a very solid foundation upon which to start.

In this edition, we have structured the chapters to proceed in a logical progression starting with epidemiology and the molecular biology of prostate cancer. Then we review the salient issues related to cancer prevention and early detection of prostate cancer with PSA, new biomarkers and new imaging modalities. The next section relates to treatment, starting with a historical review of prostate cancer therapies, followed by a review of current options for low- and intermediate- risk localized disease, of high-risk localized, and clinically advanced disease of metastatic disease and of castration-resistant disease. Finally, we conclude the book with a very important chapter on patients' perspectives. No physician can consider himself an expert on prostate cancer care unless he understands his patients' perspectives, fears and anxieties, and is aware of resources within the community that are available to help men navigate through their treatments.

We hope that this text will stimulate more research into this protean disease and will provide students of prostate cancer with a rock-solid reference. It has been both a pleasure and a privilege to work with our outstanding colleagues, and to participate in this year's ICUD on Prostate Cancer.

Gerald L. Andriole Manfred Wirth



Evidence-Based Medicine Overview of the Main Steps for Developing and Grading Guideline Recommendations

P. Abrams, S. Khoury, A. Grant

Introduction

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years, consultations have been organized on BPH, prostate cancer, urinary stone disease, nosocomial infections, erectile dysfunction and urinary incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence-Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001, www.cebm.net).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the consultations organized by ICUD. It is highly desirable that the recommendations made by the consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly "mapped" onto the Oxford system.

1. First Step

Define the specific questions or statements that the recommendations are supposed to address.

2. Second Step

Analyze and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer-reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer-reviewed journals in the relevant field but not yet published.
- Abstracts published in peer-reviewed journals should be identified. If of sufficient interest, the author(s) should be asked for full details of methodology and results. The relevant committee members can then "peer review" the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non-peer-reviewed supplements will not be included. An exhaustive list should be obtained through:
 - The major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index).
 - II. The table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How are papers analyzed?

Papers published in peer-reviewed journals have differing quality and level of evidence. Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimize the possibility of bias and to maximize attribution.

It is influenced by:

The type of study, whose hierarchy is outlined below:

- Systematic reviews and meta-analysis of randomized controlled trials
- Randomized controlled trials
- Non-randomized cohort studies

How well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increases the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard checklists** is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the checklist is to give a quality rating for individual studies.

How well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted checklist. The CONSORT statement and the checklist are available at www.consort-statement.org.

- Case-control studies
- Case series
- Expert opinion

2.3 How are papers rated?

Papers are rated following a level of evidence scale.

ICUD has modified the Oxford Centre for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (i.e., therapy, diagnosis, differential diagnosis/ symptom prevalence study) the Oxford Centre for Evidence-Based Medicine Website: www.cebm.net.

3. Third Step: Synthesis of the Evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. Fourth Step: Considered Judgment (Integration of Individual Clinical Expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgment as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgment based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence-based medicine requires the integration of individual clinical expertise with the best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannized by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient. On the other hand, without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgment, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency, as well as applicability, generalizability and clinical impact.

5. Fifth Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence, and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now four levels of evidence instead of five.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation for Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost-effectiveness. It is accepted that, at present, little data exists on cost-effectiveness for most interventions.

6.1 Levels of evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

Level of Evidence	Criteria
I	 Incorporates Oxford 1a, 1b Usually involves: meta-analysis of trials (randomized controlled trials [RCTs]) or, a good-quality RCT or, "all or none" studies in which treatment is not an option (e.g. in vesicovaginal fistula)
II	 Incorporates Oxford 2a, 2b and 2c Includes: <i>Iow-quality RCT</i> (e.g. < 80% follow-up), <i>meta-analysis</i> (with homogeneity) of <i>good-quality prospective cohort studies</i> May include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group
111	 Incorporates Oxford 3a, 3b and 4 Includes: good-quality retrospective case-control studies, where a group of patients who have a condition are matched appropriately (e.g. for age, sex, etc.) with control individuals who do not have the condition good-quality case series, where a complete group of patients, all with the same condition, disease or therapeutic intervention, are described without a comparison control group
IV	 Incorporates Oxford 4 Includes <i>expert opinion</i>, where the opinion is based not on evidence but on "first principles" (e.g. physiological or anatomical) or bench research. The <i>Delphi process</i> can be used to give expert opinion greater authority: involves a series of questions posed to a panel answers are collected into a series of "options" these "options" are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made

6.2 Grades of recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence, the grades of evidence may apply either positively (procedure is recommended) or negatively (procedure is not recommended). Where there is disparity of evidence, for example if there were three well-conducted RCTs indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgment as to the grade of recommendation given and the rationale explained.

Grade A recommendation usually depends on consistent level I evidence and often means that the recommendation is effectively mandatory and placed within a clinical-care pathway. However, there will be occasions where excellent evidence (level I) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level II evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level I evidence.

Grade B recommendation usually depends on consistent level 2/3 studies, or "majority evidence" from RCTs.

- Grade C recommendation usually depends on level 4 studies or "majority evidence" from level 2/3 studies or Delphi processed expert opinion.
- **Grade D** "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group, it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommends that, as a minimum, any test should be subjected to three questions:

- 1. Does the test have good technical performance? For example, do three aliquots of the same urine sample give the same result when subjected to dipstick testing?
- 2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
- **3.** Does the test have good therapeutic performance, that is, does the use of the test alter clinical management? Does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

Conclusion

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost-effectiveness, and also factors such as patient preference.

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Levels of Evidence	Description
I	Meta-analysis of RCTs or high-quality RCT
II	Low-quality RCT or good-quality prospective cohort study
Ш	Good-quality retrospective case-control study or cohort study
IV	Expert opinion

Abbreviation: RCT= randomized controlled trial

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Grades of Recommendation	Description
А	Usually consistent with level I evidence
В	Consistent level II or III evidence or "majority evidence" from RCTs
C	Level IV evidence or "majority evidence" from level II or III studies
D	No recommendation possible because of inadequate or conflicting evidence

Abbreviation: RCT= randomized controlled trial

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1.1 Introduction

Prostate cancer is a common cause of morbidity and mortality in developed countries worldwide, particularly in Europe and North America. Prostate cancer differs from many other solid tumours in that the prevalence of latent disease – the number of men with undetected prostate cancer – far exceeds the number of men diagnosed with, or dying from, the disease.

Autopsy studies show that cancerous cells can be found in the prostates of 30-40% of men at age 60 (1), rising to 60-70% by age 80 (2), yet the eventual risk of death from prostate cancer is only about 3% for a 50-year-old man in the United States (1).

The high prevalence of latent prostate cancer complicates the study of its epidemiology, as incidence rates are affected by early detection and screening intensity (3,4). Screening intensity relates directly to the use of digital rectal examinations and the prostate-specific antigen (PSA) blood tests. In addition, indirect detection through performance of prostatectomies for presumed benign prostatic hyperplasia (BPH) can uncover incidental prostate cancers.

Even prostate cancer mortality data seems to be influenced by the intensity of screening efforts. For example, in the United States, both prostate cancer incidence (as expected) and mortality (unexpected) increased with the introduction of widespread PSA testing in the late 1980s and early 1990s (5). The influence of screening intensity on prostate cancer incidence and mortality data needs to be kept constantly in mind in interpreting epidemiologic data.

1.2 **Descriptive Epidemiology**

Prostate cancer continues to be a worldwide public health problem, with an estimated 899,102 cancers (13.6% of all new cancers in men) diagnosed in 2008, and 258,133 deaths (6.1% of all cancer deaths in men) (6). Among all cancers, both the percentages of new prostate cancer diagnoses, and prostate cancer deaths, have increased since 2002. The highest incidence rates for prostate cancer continue to be found in North America, Western Europe, Northern Europe, and Australia (Figure 1). More developed regions have an average age-adjusted incidence rate of 61.7 per 100,000 compared to 12 per 100,000 in less developed regions (**Figure 1**). These differences in incidence rates likely reflect screening practices in more and less developed regions. However, many low incidence regions have high prostate cancer mortality (**Figures 2 and 3**). For example, countries in Middle Africa have an incidence rate of 16.4 per 100,000, but a mortality rate of 13.4 per 100,000. Eastern Asia continues to have the lowest incidence and mortality rates for prostate cancer in the world. Japan has an age-standardized incidence of prostate cancer of 22.7 per 100,000 and a prostate cancer mortality rate of 5 per 100,000. All other eastern Asian nations are lower than these rates. As seen in the previous data from 2002, populations with African ancestry continue to have the highest rates of prostate cancer mortality.



FIGURE 1

Prostate Cancer Incidence and Mortality Rates.

Source: Ferlay, J., Shin, H. R., Bray, F. et al. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer. 2010

FIGURE 2

Estimated Age-Standardized Incidence Rate per 100,000 (prostate cancer, all ages)

Source: Ferlay, J., Shin, H. R., Bray, F. et al. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer. 2010

Estimated age-standardised rate per 100,000 Prostate, all ages



Prostate, all ages

FIGURE 3

Estimated Age-Standardized Mortality Rate per 100,000 (prostate cancer, all ages)

Source: Ferlay, J., Shin, H. R., Bray, F. et al. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer. 2010 Estimated age-standardised rate per 100,000 Prostate, all ages



As ethnic groups move between nations, patterns of cancer in the population may change. Using a combination of data resources, Rastogi and colleagues examined the rates of cancer for South Asians in India, Singapore, the United Kingdom, and the United States. The age-adjusted rates of prostate cancer in South Asian men were 4.6/100,000 in India, 9.9/100,000 in Singapore, 33.7/100,000 in the UK, and 54.9/100,000 in the US (7). Such differences may be the result of screening practices or a true change in disease incidence within an ethnic group due to changes in exposure to environmental factors.

1.3 Special Section: Update of Prostate Cancer in Western Asia and the Middle East

The incidence of prostate cancer in Western Asia and the Middle East has been perceived to be much lower than that of western countries. Nevertheless, there has been a notable increase in the prevalence of PSA screening as well as variability of prostate cancer detection in different regions. The reported incidence varies between 3.5/100,000 in Saudi Arabia to 21.5/100,000 in Lebanon (8,9). While these are considered lower figures compared to those from the western hemisphere, they are quite high compared to the prevalence in Asian countries. The variability of PSA screening and prostate cancer detection in the Middle East has been recently examined and it seems to be mostly related to differences in practices between countries, as well as a function of the relative pattern of referral to tertiary care institutions. Furthermore, there is relative paucity of tumour registries and organized data collection in this regard. In 2010, a prostate cancer for adaptation and implementation in Middle Eastern and North African regions (10). The reasons for this were mostly related to the wide range in the prevalence among countries in the Middle East. There was a clearly

high incidence of advanced disease at the time of diagnosis noted by the committee. Furthermore, there is indirect evidence pointing towards a delay in the diagnosis of prostate cancer in the region and a higher percentage of locally advanced disease at diagnosis. Al Geizawi *et al.* examined the data from six institutions in five counties in the Middle East and found significant differences in PSA awareness, screening practices, and prostate cancer detection (11). In this study, there seemed to be a much higher prostate cancer diagnosis in Lebanon, Syria, Jordan and Iraq compared to costal and Gulf States like Kuwait, UAE, and Saudi Arabia. Furthermore, in the formal states of Lebanon, Syria, Jordan and Iraq, prostate cancer diagnosis is usually made at a higher stage, perhaps related to the absence of screening. These data are further confirmed by observations from tertiary referral centers. For example, the prevalence of T1C disease among a cohort of 396 radical prostatectomy patients at the American University of Beirut, one of the biggest prostate cancer centers in the region, was only 49% as compared to more than 90% in European and American institutions (Khauli *et al.*, unpublished observations).

There is a clear change in the dietary habits of the population in the Mediterranean region indicating a change of the "healthy Mediterranean diet" to a more westernized diet (11,12). Furthermore, this has been noted to be true in urbanized regions in the Middle East wherein the diagnosis of prostate cancer is higher. The demographics also may be affected by referral to tertiary care centers that go across country borders which is increasing the likelihood of diagnosis of prostate cancer and its prevalence in a country like Lebanon versus the countries in the Saudi Arabian peninsula. Because 65% of the population is currently younger than 30 years, even if the incidence of prostate cancer is lower than that of the West, the scope of the problem will only become more significant over the next 20 years as the population ages and presumably has access to improved medical care.

1.4 Risk Factors

The six years since the 2005 publication of the International Consultation on New Developments in Prostate Cancer and Prostate Diseases report have witnessed many exciting developments in the field of prostate cancer. Major screening trials have published their results and helped increase knowledge of the natural history of the disease. However, the issues of overdiagnosis and overtreatment continue to be factors in prostate cancer. Chemotherapeutics have advanced, with new treatments for prevention, localized, and metastatic disease.

The field of epidemiology has not been quiescent during this period. Research continues into risk factors for prostate cancer, with continued attention paid to potentially modifiable risk factors, as well as in primary and secondary prevention. In this section on prostate cancer risk factors, we provide an update on prostate cancer epidemiology.

1.4.1 **Smoking**

As a major health problem throughout the world, smoking continues to generate interest as a potential risk factor for prostate cancer incidence, progression, or recurrence.

Smoking has not been consistently associated with prostate cancer incidence. In a systematic review and meta-analysis of the literature, Hickey et al. showed no clear association between smoking and prostate cancer incidence 13). An ecologic analysis using regional lung cancer rates as a surrogate marker for smoking rates also showed no association between lung cancer incidence and prostate cancer incidence within regions of the United States participating in the Surveillance, Epidemiology and End Results Program (14). A review of smoking and prostate cancer mortality and progression risks by Zu and Giovannucci established a strong link between smoking and prostate cancer death. Most cohort studies showed a 30% increase in the risk of prostate cancer mortality among current smokers compared to non-smokers or never-smokers. Risks of advanced disease at diagnosis, fatal prostate cancer, and worse prognosis are all increased among current smokers (15). These conclusions were supported by a recent meta-analysis of 24 prospective cohort studies that examined the relationship between smoking and prostate cancer. Current smokers had no increase in risk of incident prostate cancer (RR 1.04; 95% CI 0.87 to 1.24), but increasing pack-years of smoking was associated with prostate cancer incidence. Risk of fatal prostate cancer was significantly increased among current smokers (RR 1.14; 95% CI 1.06 to 1.19), with the heaviest smokers showing a 24% to 30% increased risk of fatal prostate cancer compared to nonsmokers (16).

Further support for the influence of smoking on prostate cancer-specific mortality comes from a recent report from the Health Professionals Follow-Up Study. Smoking at the time of prostate cancer diagnosis was associated with increased overall and cardiovascular disease (CVD) mortality (17). Among current smokers compared to non-smokers, the authors found both an increase in prostate cancer-specific mortality (HR 1.61; 95% CI 1.11-2.32), and risk of recurrence in current smokers. Patients who had quit smoking for at least 10 years appeared to have prostate cancer-specific mortality risks similar to those who have never smoked. Similar results were found in the NIH-AARP Diet and Health Study. Watters and colleagues found that smoking decreased the overall risk of prostate cancer incidence, but increased the risk of dying from prostate cancer. Current smokers were at increased risk of death from prostate cancer (HR 1.69), while former smokers had a cumulative incidence of recurrence of 34.3% compared to 14.8% among former smokers, and 12.1% among never smokers (19). Similarly, in a population-based case-control study from four health maintenance organizations, men who died from prostate cancer were more likely to be smokers than non-smokers (OR 1.5; 95% CI 1.1 to 2.0) (20).

Contrary to these results, smoking at the time of diagnosis with prostate cancer was associated with death from other causes, but not prostate cancer specific death in a study using the CaPSURE database (21). Smoking was associated with more advanced disease among men undergoing radical prostatectomy in a large multi-institutional database, but was not associated with an increased risk of biochemical recurrence after surgery (22). In a long-term follow up of the Whitehall study from London with 578 prostate cancer deaths in 17,934 men, no association between smoking and prostate cancer mortality was found (23).

Although the results of some studies are inconsistent, current data suggest smoking may be a risk factor for aggressive prostate cancer and disease recurrence after treatment of prostate cancer.

A proposed mechanism for smoking as a risk factor for prostate cancer is cadmium exposure. Within the prostate, cadmium is thought to form a complex with selenium and protein, effectively detoxifying the cadmium. When the cadmium levels are too high, or selenium levels too low, this sequestration does not occur, and the risk of cancer may increase (24). Another proposed mechanism is CpG hypermethylation, which was found to be increased in smokers compared to non-smokers (25).

1.4.2 Alcohol

Alcohol intake continues to show inconsistent associations with prostate cancer risk. In agreement with prior studies, overall alcohol consumption showed no association with prostate cancer in a case-control study from King County, WA. Lifetime intake of red wine was associated with a reduced risk of prostate cancer (OR 0.94; 95% CI 0.90 to 0.98 for each additional glass of red wine consumed each week) (26). However, these results were not confirmed in the Health Professionals Follow-up Study based on assessments of recent red wine consumption (27). Similarly, in the VITamins and Lifestyle study, white wine consumption was associated with an increased risk of prostate cancer (HR 1.27; 95% CI 1.08 to 1.49), but red wine, beer, and liquor did not have associations with prostate cancer risk (28). Again, only more recent wine intake was assessed. Red wine consumption was also not associated with prostate cancer risk in the California Men's Health Study (29). In the NIH-AARP cohort study, an association between alcohol intake and non-advanced prostate cancer risk was found (HR 1.25 for consumption of \geq 6 drinks per day; CI 1.13 to 1.37). No associations were found between alcohol consumption and advanced prostate cancer (30). No associations between alcohol intake and prostate cancer risk were found in the ATCB study (31) or in a population-based case-control study from Sweden (32).

Heavy alcohol consumption was associated with increased risk of prostate cancer in the Prostate Cancer Prevention Trial (PCPT). In the combined treatment and control arms of the trial, drinking more than four drinks per day on more than five days per week increased the risk of high-grade prostate cancer (RR 2.17; 95% CI 1.42 to 3.30). Interestingly, heavy drinking appeared to nullify the preventive effect of finasteride on reduction of low-risk prostate cancer (33). More research is needed to confirm these results, and to confirm the reliability of the assessment of heavy alcohol consumption.

Based on these results, there is no clear association between alcohol consumption and prostate cancer incidence. Issues of duration, timing, and quantity of exposure still need to be elucidated, particularly given the interesting results seen in the PCPT.

1.4.3 **Physical activity**

Data continue to accumulate on the beneficial impact physical activity imparts on prostate cancer risk and survival. So far, data appear to be stronger for impacts on prostate cancer progression and survival than for prostate cancer incidence. In the Health Professionals Follow-up Study, no association was found between physical activity (recorded at baseline and updated every two years) and total prostate cancer. For men older than 65 years of age, vigorous physical activity (29 metabolic hours per week or more) was associated with decreased risks of aggressive prostate cancer (RR 0.33; 95% CI 0.17 to 0.62) and fatal prostate cancer (RR 0.26; 95% CI 0.11-0.66) (34). In additional examination of this data, Kenfield *et al.* found that physically active men had lower rates of all-cause and prostate cancer-specific mortality (35). Similar results were found in a study using the CaPSURE database. Patients who walked briskly for three hours per week or more had a lower risk of prostate cancer progression than patients who walked at an easy pace for less time (HR 0.43 95% CI 0.21-0.91) (36).

Further evidence has been published supporting the notion that physical activity may reduce the incidence of advanced prostate cancer. In a study of 29,110 Norwegian men, compared to men with no recreational physical activity, men with the highest category of activity had a relative risk of 0.64 (95% CI 0.43-0.95) for incidence of advanced prostate cancer, and 0.67 (95% CI 0.48-0.94) for prostate cancer death (37). Patel *et al.* examined the American Cancer Society Prevention Study II Nutrition Cohort. Recreational physical activity was determined from a questionnaire at cohort enrollment in 1992/3 as well as a previous questionnaire in 1982. No relationship between physical activity and overall prostate cancer was found, but the risk of aggressive prostate cancer (defined as clinical stage III or IV, Gleason score 8 or higher, regional or distant disease from state cancer registries, or prostate cancer-specific death) was reduced among men with the highest levels of physical activity (RR 0.69; 95% CI 0.52-0.92) (38). Data from the European Prospective Investigation into Cancer and Nutrition supported an inverse association between advanced prostate cancer risk and occupational physical activity, but not recreational physical activity (39). In a population-based study of Swedish men, an inverse association was found between lifetime physical activity and prostate cancer risk (16% decrease; 95% CI 2-27%) (40).

Attempts to quantify the impact of timing of physical activity on prostate cancer risk and interactions of physical activity with other health factors have been done in a few studies. One set of results was reported from the NIH-AARP Diet and Health Study, where patients with diabetes had a decreased risk of prostate cancer. This effect was strongest among men with the highest levels of physical activity (RR 0.41; 95% CI 0.23 to 0.74) (41). In the full study, neither exercise at baseline, nor exercise during adolescence, was associated with total prostate cancer, advanced prostate cancer, or fatal prostate cancer risk (42). Among black men however, physical activity during ages 19 to 29 years was associated with a decreased risk of prostate cancer (RR 0.65; 95% CI 0.43 – 0.99) 43).

Although some inconsistency is seen in these results, the overall evidence points to physical activity being associated with a reduced risk of aggressive prostate cancer. No evidence for an impact on total prostate cancer has been found.

1.4.4 **Obesity**

As the obesity epidemic continues to grow in developed nations, and becomes an increasing problem in middle-income nations, interest in the impact of obesity on cancer risk is increasing. Multiple studies have examined the association between obesity and prostate cancer risk over the past few years. The relative risks of advanced prostate cancer were 1.06 (1.01 to 1.1) for each 5-cm increase in waist, and 1.21 (1.04-1.39) for each 0.1-unit increase in waist-hip ratio in the European Prospective investigation into Cancer and Nutrition cohort (44). In a prospective study of 335,169 men from Sweden with height and weight collected at baseline and followed for an average of 22 years, men in the top quantile of BMI (>27) were significantly more likely to develop fatal prostate cancer than men in the lowest BMI quantile (<21.9) (RR 1.28; 95% CI 1.11 to 1.49) (45). From the NIH – AARP Diet and Health Study, Wright et al. determined that as weight increased, the risk of dying from prostate cancer increased. Interestingly, this association with fatal prostate cancer was seen in relation to adult weight gain from age 18 (46). In a study of 752 men with prostate cancer diagnosed from 1993 to 1996 with BMI assessed one year prior to prostate cancer diagnosis, men who were obese (BMI \geq 30 kg/m²) had an increased prostate cancer mortality (HR 2.64; 95% CI 1.18-5.92) compared to the normal BMI group (BMI < 25 kg/m²). Risk of developing metastatic disease was also increased in the obese men (HR 3.61; 95% CI 1.73 - 7.51) (47).

From these and other studies, obesity appears to be associated with decreased detection of total prostate cancer. A detection bias due to hemodilution of PSA levels in obese men has been proposed as a cause of the decreased incidence of prostate cancer with increasing BMI (48). However, most studies that have investigated measures of obesity, and advanced or fatal prostate cancer risk have observed positive associations. The underlying causes of these associations remain to be elucidated.

Hyperinsulinemia has been proposed as a mediating factor between obesity and prostate cancer mortality. A marker of insulin secretion is plasma C-peptide levels. From the Physicians Health Study, Ma and colleagues assessed the impact of pre-diagnostic body-mass index and plasma C-peptide concentration on prostate cancer-specific mortality (49). They found that overweight (BMI 25.0 to 29.9 kg/m²) and obese (BMI > 30 kg/m²) men had a higher risk of dying from prostate cancer than normal weight men (HR 1.47; 95% CI 1.16 to 1.88 for overweight, and HR 2.66; 95% CI 1.62 to 4.39 for obese men). This trend was stronger for men diagnosed in the PSA era (defined as 1991-2007) than the pre-PSA era. In a subset of men with C-peptide concentrations available for analysis, men with the highest C-peptide concentrations had the highest risk of prostate cancer mortality (HR 2.38; 95% CI 1.31 to 4.30). In a test for the interaction between BMI and C-peptide concentrations, controlling for clinical factors, men with a BMI over 25 kg/m² and a high C-peptide concentration had a 4-times higher risk of mortality than patients with a BMI less than 25 kg/m² and a low C-peptide concentration had a 4-times higher risk of mortality than patients with a BMI less than 25 kg/m² and a low C-peptide concentration had a 4-times higher risk of mortality than patients with a BMI less than 25 kg/m² and a low C-peptide concentration had a 4-times higher risk of mortality than patients with a BMI less than 25 kg/m² and a low C-peptide concentration had a 4-times higher risk of mortality is a risk factor for prostate cancer mortality.

Closely related to obesity is the metabolic syndrome. A recent report highlighted the association of metabolic syndrome with prostate cancer mortality after controlling for death from other causes. The conditional probability of death from prostate cancer among men in the Uppsala Longitudinal Study of Adult Men was 7.3%-units higher in men with metabolic syndrome than in men without the syndrome (OR 1.64; 95% CI 1.03 to 2.23) (50). In a long-term study of 16,209 men recruited to

a cohort study in Oslo in 1972 to 1973, combinations of either two or three risk factors involved in the metabolic syndrome (e.g. high body-mass index, elevated non-fasting glucose, high triglycerides, and hypertension) were associated with increased prostate cancer risk (RR 1.23; p=0.04 for two, and RR 1.56; p=0.00 for three factors) (51).

Overall, the results for obesity suggest positive associations with prostate cancer mortality. Syndromes, such as hyperinsulinemia and the metabolic syndrome, closely linked to obesity also confer higher risks of prostate-cancer mortality. These data confirm the importance of maintaining a normal body weight for overall health.

1.4.5 **Diet and nutritional supplements**

The concept of nutritional supplementation for prostate cancer chemoprevention was assessed in two recent randomized trials. In the Physician's Health Study II, the role of vitamin E and C supplementation in prostate cancer was assessed. Men, aged 50 and older, were randomized to 400 IU of vitamin E every other day and 500 mg of vitamin C daily. After a mean follow-up time of eight years, 1008 prostate cancers were found among the 14,641 participants. Vitamin E and C supplementation had no effect on prostate cancer risk, and no modifications of the effect by different prostate cancer risk factors were found (52). The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomized 35,533 men (aged 50+ for Blacks, 55+ for others) to four treatment groups (selenium, vitamin E, selenium + vitamin E, and placebo). At a median follow up of 5.46 years, selenium, vitamin E, or the combination did not prevent prostate cancer (53). Further analysis of this trial with a follow up time beyond seven years showed that supplementation with Vitamin E significantly increased prostate cancer risk (HR 1.17; 99% CI 1.004 – 1.36; p=0.008) (54).

Further analysis of large cohort studies support these null findings. In a case-control study nested in the PLCO trial, serum selenium was not associated with prostate cancer risk (55). Plasma selenium concentration was not associated with prostate cancer risk in a case-control study nested in the European Prospective Investigation into Cancer and Nutrition (56). Multivitamin use was not associated with prostate cancer risk in the Cancer Prevention Study II, except in participants who also used vitamin A, C, or E supplements, where an increase in prostate cancer risk was found (RR 1.15; 95% CI 1.05 to 1.26) (57). Supplemental vitamin E intake was not associated with decreased prostate cancer risk in the NIH-AARP Diet and Health Study (58), or in the VITamins and Lifestyle study (59). In contrast, in the ATCB study, a study conducted among smokers, higher baseline serum levels of alpha-tocopherol (vitamin E) were inversely related to both incidence of overall prostate cancer (RR 0.80; 95% CI 0.66 to 0.96), and the risk of advanced disease (RR 0.56; 95% CI 0.36-0.85).The inverse association was greatest amongst men who received supplementation during the trial (60). Of note, the ATCB cohort is composed of heavy smokers and asbestos-exposed individuals, and as such may not be generalizable to other populations.

Further support that smokers may benefit from Vitamin E supplementation emerged from the PLCO trial. Among male smokers in the screening arm of the PLCO trial, the age-adjusted rate of advanced prostate cancer was 492 per 100,000 person-years in non-users of vitamin E compared to 153 per 100,000 person-years among men who took supplemental vitamin E (400 IU/day) (61). Additional support for this effect of vitamin E in smokers was found in a sub-analysis of the Age-Related Eye

Disease Study that randomized patients with age-related macular degeneration to one of four arms (placebo, antioxidants, zinc, and antioxidants plus zinc). Patients who received antioxidants had a significant decrease in prostate-cancer diagnoses compared to the placebo group (RR 0.6; 95% CI 0.49 to 0.86). This finding was found to be significant only among current smokers. (62)

Multivitamin use has not been associated with prostate cancer risk. Folate supplementation appeared to be a risk factor for development of prostate cancer in the aspirin/folate Polyp Prevention Study (HR 2.63; 95% CI 1.23 to 5.65) (63). In addition, no association between multivitamin use and risk of localized prostate cancer was seen in the NIH-AARP Diet and Health Study. An increased risk of advanced and fatal prostate cancer was seen among men who used multivitamins more than seven times per week compared to non-users (RR = 1.32; 95% CI 1.04 to 1.67 advanced, and RR = 1.98; 95% CI 1.07 to 3.66, fatal) (64). Among smokers participating in the Carotene and Retinol Efficacy Trial (CARET) trial, dietary supplement use was associated with a nonsignificant increased risk of aggressive prostate cancer, defined as a Gleason score of greater than or equal to 7 and/or stage III/ IV, (RR 1.36; 95% CI 0.87 to 2.13). However, men who took the study vitamins plus another dietary supplement had a significantly elevated RR of aggressive prostate cancer of 1.52 (95% CI 1.03 to 2.24) (65). A cohort study based on a subset of patients from the Prostate Cancer Prevention Trial (PCPT) demonstrated no effect of long-chain n-3 fatty acids, vitamin D, vitamin E, or selenium on prostate cancer risk (66). Overall, these results suggest that multivitamins and supplements have no protective effect on prostate cancer.

A broad line of inquiry in cancer risk involves exposures during development that may predispose individuals for later development of cancer. One such exposure is childhood diet, which is often assessed indirectly by anthropometric measures. Although limited by a small number of incident prostate cancer cases, in a study of the Boyd Orr cohort with follow up of more than 59 years, Whiteley and colleagues found no association between childhood measures of anthropometry and prostate cancer risk (67).

Interestingly, coffee consumption may be associated with a reduced risk of prostate cancer. From the Health Professionals Follow-Up Study, men who consumed six or more cups of coffee per day had lower adjusted relative risk of prostate cancer than non-drinkers (RR 0.82; 95% CI 0.68-0.98) (68). The effect was stronger for fatal prostate cancer where coffee drinkers (defined as consuming > 6 cups per day) had a RR of 0.40 (95% CI 0.22 – 0.75). The RR reduction for coffee drinkers was observed in relation to both regular and decaffeinated coffee consumption.

While prostate cancer risk overall was not influenced by consumption of fruits and vegetables, the risk of aggressive prostate cancer was decreased among men with high intake of cruciferous vegetables (RR 0.60; 95% CI 0.36 to 0.98, high versus low intake) (69). A biologic mechanism for this finding was suggested in a randomized trial of genetic changes within the prostate after a 12-month broccoli-rich diet. Consumption of broccoli resulted in an interaction with the GSTM1 genotype that led to changes in the signalling pathways within the prostate (70).

The role of lycopene in relation to prostate cancer risk is unclear. No association between lycopene/ tomato consumptions and overall or aggressive prostate cancer risk was found in the PLCO study (71). Similarly, no effect was found in the PCPT trial (66). In a review of the health claims for lycopene and tomato-based products, the United States Food and Drug Administration (FDA) found no credible evidence for an association between lycopene consumption and prostate cancer risk reduction (72). In the Multiethnic Cohort study, data on food and nutrient intake was collected at the initiation of the study between 1993 and 1996. No associations between prostate cancer risk and dietary factors, including lycopene, were found in this study (73). In addition, no associations between plasma concentrations of carotenoids, retinol, or tocopherols and overall prostate cancer risk were found in the European Prospective Investigation into Cancer and Nutrition Study. Carotenoids, including lycopene, were associated with a decreased risk of advanced prostate cancer (0.35; 95% CI 0.17 to 0.78) (74).

Meat consumption continues to be examined as a risk factor for prostate cancer. Support for the hypothesis that well-done meat is a risk factor for prostate cancer was provided by an early analysis of data from the PLCO study. Participants in the screening arm of the study who consumed more than 10 g/day of very well-done meat had a 1.4-fold (95% CI 1.05 to 1.92) increased risk of prostate cancer compared to participants who did not consume well-done meat (75). African-American men in the United States appeared to be at an increased risk for prostate cancer based on their meat consumption, especially from processed-meat consumption in the Cancer Prevention Study II Cohort (76). Furthermore, no effect of meat consumption on prostate cancer risk was seen among Caucasians in that study. Consumption of processed meat was associated with a non-significant increase in prostate cancer risk in the CLUE II study (HR 2.24; 95% CI 0.90 – 5.59) (77). In contrast, data from the multiethnic cohort study did not support a role for fat or meat intake in prostate cancer risk (78). Similar negative results were found in the Carotene and Retinol Efficacy Trial (79). Overall, there are inconsistent results with regards to the effect of meat consumption on prostate cancer risk.

Vitamin D deficiency is common in the United States, and has been inconsistently associated with prostate cancer risk. A study by Li *et al.* examined interaction between vitamin D levels and vitamin D receptor (VDR) gene polymorphisms. Men with a less functional VDR and low 25(OH)D levels had a significant increase in the risk of aggressive prostate cancer (OR 2.5; 95% CI 1.1 – 5.8) (80). In contrast, vitamin D levels were not associated with risk of prostate cancer in a nested case-control study of men participating in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (81).

Results from the Carotene and Retinol Efficacy Trial suggest that higher dairy intake is associated with a decreased risk of aggressive prostate cancer (HR 0.59; 95% CI 0.40 to 0.85) (79). The reduced risk associated with calcium intake was not found in the NIH-AARP or PLCO studies (82,83). Calcium intake was associated with an increased risk of prostate cancer in the European Prospective Investigation into Cancer study (84). Dietary calcium intake was positively associated with low-grade prostate cancer risk and inversely associated with high-grade (Gleason score 8-10) prostate-cancer risk in the PCPT study (66).

Although migration studies suggest elements of the Western diet could predispose to prostate cancer risk, no evidence for an increase in prostate cancer among men who consume a Western diet compared to a prudent diet was found in the Health Professionals Follow-up Study (85). Combined with the above reviewed results, this study suggests that simple dietary modifications are unlikely to have major impacts on prostate cancer incidence or mortality.

1.4.6 **Medications**

Non-steroidal anti-inflammatory drugs (NSAIDS), including aspirin (ASA), are widely used medications for chronic or recurrent inflammatory conditions, as well as for the treatment and secondary prevention of cardiovascular disease. A meta-analyses of data prior to 2003 revealed a protective association for the use of ASA with prostate cancer (summary OR = 0.9; 95% CI 0.8-0.99), particularly in advanced disease (summary OR = 0.7; 95% CI 0.5 – 0.9) (86). No significant association with non-ASA NSAID use and prostate cancer risk was found, although the OR was less than 1 (OR 0.87; 95% CI 0.6-1.2). In an update of this meta-analysis, Mahmud *et al.* found consistent reductions in risk among ASA users for total prostate cancer (pooled OR 0.83; 95% CI 0.77 to 0.89) and advanced prostate cancer (pooled OR 0.81; 95% CI 0.72 to 0.92) (87). As in the prior meta-analysis, associations between the use of non-aspirin NSAIDS, or all NSAIDS, were less consistent.

Other studies provide additional evidence supporting the role of ASA in decreasing prostate cancer risk. In a population-based case-control study from King County Washington, a 21% reduction in the relative risk of prostate cancer was found among current users of aspirin compared to non-users (95% CI 0.65 to 0.96). Use of other NSAIDS or acetaminophen was not associated with prostate cancer risk (88). In the Health Professionals Follow-Up Study, men who used two or more adult-strength aspirin tablets per week had a 10% lower risk of prostate cancer than non-users. Although no associations were found between aspirin use and regionally advanced cancer, the risk of high-grade and lethal cancers was reduced among men using six or more adult strength ASA tablets per week (HR 0.72; 95% CI 0.54 – 0.96) (89). Providing further support for a role of ASA in lowering risk of mortality from solid tumours, Rothwell *et al.* found a decreased risk of death from solid tumours in patients randomized to the ASA arms of three studies of cardiovascular prevention with ASA. Although overall mortality from solid tumours decreased, no firm conclusions could be reached regarding prostate cancer due to only 37 patients developing prostate cancer (90).

In contrast to these results, male members of the VITamins and Lifestyle cohort were assessed for associations between NSAID or ASA use and prostate cancer risk. No association between NSAID use (low-dose ASA, regular-strength ASA, ibuprofen, or any non-ASA NSAID) and prostate cancer risk were found, except for a suggestion of a reduced risk for high-grade prostate cancer (Gleason score 4+3=7 or 8-10) (HR 0.73; 95% CI 0.53-1.02) in users of regular-strength ASA (91). In the aspirin/folate Polyp Prevention Study, men randomized to the aspirin group had no significant difference in prostate cancer incidence compared to the placebo group (63).

Based on the cumulative literature, prostate cancer risk appears to be decreased through the use of ASA. This protective association has not been seen consistently for other NSAIDS.

Statin medications have also been evaluated in relation to prostate cancer risk. In a cohort of 55,875 men from the Veterans Affairs New England Health Care System who were taking statins or anti-hypertensive medications, statin users were significantly less likely to be diagnosed with prostate cancer (HR 0.69; 95% CI 0.52 to 0.90). This reduction in risk was observed for high grade, defined as Gleason score \geq 7 (4+3) (HR 0.86; 95% CI 0.24 to 0.65), but not low grade, defined as Gleason score \leq 7 (3+4) (HR 0.86; 95% CI 0.62 to 1.20), prostate cancer. While high total cholesterol levels showed a weak association with prostate cancer risk, the association was much weaker than the

association seen with the use of statins (HR 1.02; 95% CI 1.00 to 1.05) (92). These findings build on previous results by Platz *et al.* showing that statin use was associated with decreased prostate cancer risk in the Health Professionals Follow-up Study. For current statin use versus no statin use, the relative risk of advanced disease was 0.51 (95% CI 0.30 to 0.86), and the risk of metastatic or fatal prostate cancer was 0.39 (95% CI 0.19 to 0.77), although these results are based on small numbers (93). Results from the California Men's Health Study also found an association between decreased prostate cancer and statin use. Patients who have used statin for over five years had a 28% decreased rate of prostate cancer (adjusted rate ratio 0.72; 95% CI 0.53 – 0.99). No difference in association with advanced disease was found, and the association appeared to be restricted to men who were also regular NSAID users (94). More large studies on the impact of statin medications on prostate cancer incidence and mortality are needed.

1.4.7 **The insulin-like growth factor system**

Insulin-like growth factors (IGF-1 and IGF –2) are nutritionally regulated peptides. Their structure is similar to proinsulin, that play a key role in somatic growth and development in early-life, and in tissue repair, cell proliferation, metabolic regulation, and apoptosis throughout life in a wide variety of cells and tissues (95), including the prostate (96). In the circulation, most (>99%) IGF-1 and IGF–2 form complexes with one of six different binding proteins (IGFBP-1 to -6), the vast majority (>90%) being with IGFBP-3 and an additional acid-labile protein subunit. Studies reviewed in the prior edition of this consultation on prostatic disease suggested an increased risk of prostate cancer with higher circulating levels of IGF. In an analysis of 12 prospective studies examining the role of insulin-like growth factors on prostate cancer risk, Roddam *et al.* found that high circulating levels of IGF-1 were associated with a moderately increased risk of prostate cancer (OR 1.38 highest versus lowest quantile of IGF-1 concentration; 95% CI 1.19 to 1.60) (97). No association was found between IGF-2 or IGFBP-II concentrations and prostate cancer risk. Higher circulating levels of IGF-3 were related to incidence of low-grade (Gleason sum < 7) prostate cancer, but not high-grade prostate cancer in a nested case-control study within the Health Professional Follow-Up study (98).

As a disorder of insulin response, diabetes may have an association with prostate cancer risk. A history of diabetes was associated with a decreased risk of total prostate cancer in the PLCO trial (RR 0.80; 95% CI 0.68 to 0.95). Subgroup analyses showed no relationship between diabetes and aggressive prostate cancer; except in a subgroup of men with diabetes and a low BMI (98). Prostate cancer incidence did not differ among men exposed to diets with high insulin response in the Health Professionals Follow-Up Study (100). Also, men with diabetes had a lower risk of prostate cancer diagnosis, which was stronger in the pre-PSA era (before 1994), and the risk declined with increasing duration of diabetes (101).

1.4.8 Infection

Sexually transmitted infections (STIs) and other urogenital infections have emerged as possible risk factors for prostate cancer. Until more recently, most studies on this topic were smaller case-control studies with retrospective and self-reported assessment of histories of gonorrhea, syphilis, or any STIs. The results of these studies were summarized in two meta-analyses, both of which estimated statistically significant positive associations for gonorrhea and any self-reported STIs, and a suggestive positive association for syphilis in studies conducted through 2004 (102, 103). Larger casecontrol studies performed since these meta-analyses have also generally supported a positive association between STIs and prostate cancer. Positive associations were observed between a history of gonorrhea and prostate cancer in a recent population-based case-control study of African American men (OR=1.78, 95% CI 1.13 to 2.79) (104), and between a history of any STIs and prostate cancer in another recent population-based case-control study of Canadian men (OR=1.88, 95% CI 1.13 to 3.11) (105). However, no associations were observed for gonorrhea, syphilis, or any self-reported STIs in more recent cohort studies, including the Health Professionals Follow-up Study (106), the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (107), and the California Men's Health Study (108). These null findings in cohort as opposed to case-control studies may suggest that positive casecontrol findings were influenced by biases, such as recall bias, although the role of chance or possibly differences in the STI histories (e.g., number of lifetime STI episodes) in these different populations cannot be ruled out.

Another STI that has been extensively investigated in relation to prostate cancer is human papillomavirus (HPV) infection, particularly infection with high-risk types 16 and 18. This possible relation has been investigated using both serology and DNA detection in prostate tissue. The results from ten of these studies conducted from 1995 to 2003 were summarized in a recent meta-analysis, which found a significant positive association between HPV infection and prostate cancer (OR=1.52; 95% CI: 1.12-2.06) (103). However, results from several large seroepidemiologic studies conducted since this metaanalysis, including those from the Nordic biobank network (109), Health Professionals Follow-up Study (110), Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (107), Department of Defense Serum Repository (111), and Prostate Cancer Prevention Trial (112) have not supported a positive association. Positive associations between HPV or high-risk HPV DNA detection and prostate cancer in other smaller, tissue-based case-control studies have, however, maintained interest in this area (113-115).

Chlamydia trachomatis infection, a common bacterial STI, has also been investigated in relation to prostate cancer in several nested case-control studies. Many of these studies have observed null or even inverse results. In a nested case-control study using banked serum specimens from Finland, Norway, and Sweden, an inverse relation was observed between C. trachomatis antibodies and prostate cancer risk (OR 0.69; 95% CI 0.51-0.94) (116). Null results were subsequently observed in the Health Professionals Follow-up Study (110), the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, except among African-American participants when IgA antibodies were assessed (107), and in the Department of Defense Serum Repository, except among men who provided serum more than 60 months before their prostate cancer diagnosis (111), leaving open the possibility for associations between specific types of chlamydial infections (e.g., chronic infections or infections acquired at a certain age) in relation to prostate carcinogenesis.

Finally, recent new methods of infection detection have opened the door to investigations of several additional infectious agents in relation to prostate cancer. The development of a new serologic assay for Trichomonas vaginalis infection has allowed the study of lifetime exposure to T. vaginalis infection and prostate cancer risk. While no association was observed between T. vaginalis serology and prostate cancer risk in the Prostate Cancer Prevention Trial (117), positive associations were observed in the Health Professionals Follow-up Study, particularly for high-grade cancer (118), and in the Physicians' Health Study, particularly for extraprostatic, metastatic, and lethal disease (119). These preliminary findings suggest that T. vaginalis infection may be associated with risk of more aggressive disease. Development of a viral DNA detection microarray resulted in the discovery of xenotropic murine leukemia virus-related virus (XMRV), a virus that was initially found to be more common in prostate tissue from men homozygous for the R462Q variant of RNASEL, a variant associated with familial prostate cancer (120). Although XMRV was subsequently found to be associated with prostate cancer when compared to benign prostatic hyperplasia controls, and with higher prostate cancer grade in a study of prostate tissue (121), recent work suggests that XMRV detection may have been the result of contamination of prostate specimens or laboratory reagents by mouse DNA (122). Finally, another avenue of prostate cancer etiologic research that is recently gaining attention is mycoplasmas. Persistent exposure to Mycoplasma genitalium and hyorhinis was shown to lead to malignant transformation of human prostate epithelial cells (123), and positive associations for Ureaplasma urealyticum, but not M. hominis seropositivity (124), M. hominis sero- and DNA positivity (125), and M. hyorhinis seropositivity (126), with prostate cancer were observed in several small, recent case-control studies. These preliminary findings suggest that mycoplasmas may be further candidate risk factors for prostate cancer.

Infection might increase prostate cancer risk through associated inflammation and inflammatory reactions in the prostate. However, no evidence for an association between prostate cancer and inflammatory markers including interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF-alpha) were found in the Health Aging and Body Composition study of 2,438 adults, ages 70-79 years (127). Similarly, CRP was not associated with prostate cancer risk in a case-control study nested within the CLUE II study (128), or in a long-term follow-up from a prospective cohort in Rotterdam (129). Also CRP and IL-6 levels were not associated with prostate cancer risk in the Cardiovascular Health Study (130). Research into associations between tissue inflammation and prostate cancer risk are forthcoming, and may make these prior serologic studies less relevant.

1.4.9 **Genetics**

Research into the genetic basis of prostate cancer continues. Several genome-wide association studies and follow-up studies have found and confirmed more than 40 risk-associated SNPs (131-142), and some have been associated with more aggressive prostate cancer (143, 144). In addition, work on sequencing the genome of prostate cancer has progressed. Berger *et al.* sequenced seven primary human prostate tumours and paired normal controls. They found many genomic rearrangements arising from aberrant transcriptional or chromatin events (145). One of the most studied rearrangements is the ETS gene fusion TMPRSS2-ERG (146). This gene fusion was present in 46% of prostate biopsies showing cancer, and 0% of prostate biopsies showing benign disease, in a multicenter North American assessment (147). The presence of this gene fusion has been found to correlate with metastatic disease foci in multifocal prostate cancer (148), and to improve stratification of prostate cancer risk when used as a urinary test (149).

Unlocking the genetic basis of prostate cancer provides potential targets for screening and therapy. Further knowledge on the genetic basis of prostate cancer may help inform research into modifiable risk factors for prostate cancer through improved study of gene environment interactions.

1.5 **Overall Summary**

While progress on identifying risk factors for prostate cancer continues, some of the hope for a simple reductionist approach to cancer prevention has decreased by the null trials of dietary interventions and several chemoprevention agents. As work continues on elucidating modifiable risk factors, additional investigations into exposures at different points in the life cycle are necessary. Although the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trials both showed reductions in the incidence of prostate cancer, such success with use of dietary supplement intervention or other lifestyle modifications would be unexpected. Likely, such behavioural and dietary modifications would need to take place, and be sustained, long before the age at which prostate cancer becomes clinically detectable to have any impact on prostate cancer incidence.

1.6 Natural History

The vast discrepancy between the autopsy prevalence and the clinical incidence of prostate cancer may be attributable to the generally long latency period of the preclinical duration of the disease (Figure 4).



Several studies of prostate cancer latency have been conducted, with fairly consistent results. Broadly speaking, these studies can be broken down into three types: (1) Studies based on retrospective analysis of PSA levels in serial serum samples, stored prior to prostate cancer diagnosis; (2) Statistical or model-based analyses of prospective screening cohorts or populations; and (3) Epidemiologic analyses, comparing latent prevalence based on autopsy studies, with disease incidence. Results of these studies point to a disease latency period of 10 years or more. These studies have also been used to inform about the lead time, which is the time by which screening advances diagnosis (see Figure 4).

1.7 Retrospective Analysis of PSA Levels

In a retrospective analysis of PSA levels, serum samples collected prior to a diagnosis of prostate cancer are analyzed to provide information on PSA to a prostate cancer diagnosis. Serial samples are required so a linear or change point trajectory can be fitted to observed PSA measurements. A change point trajectory identifies a point at which PSA growth accelerates; this point is generally interpreted as a point of transition between benign and malignant states. The duration from the change point to the time of diagnosis is assumed to approximate the preclinical disease duration. In the first such analysis, from the Baltimore Longitudinal Study of Aging (BLSA) (150), the preclinical disease duration was 7 years for localized cases and 9 years for advanced cases. A subsequent analysis estimated the preclinical duration of prostate cancer to be 13 years (151).

A meta-analysis of three retrospective PSA studies (150, 152, 153) that provided a larger case group for analysis than the BLSA, showed that PSA growth and progression from occult to metastatic disease were significantly faster among cases eventually diagnosed with clinically advanced disease compared to localized cancers (154). Moreover, cases with moderate to high Gleason scores (7-10) tended to progress faster than did cases with lower Gleason scores. These findings suggest that tumours destined to become metastatic may be biologically different than localized tumours prior to diagnosis, and perhaps, even from the point of disease onset.

Retrospective stored-serum studies have also been used to estimate the lead time, which depends on the definition of a positive screening test and the number of retrospective samples per individual. The lead time is the duration from the point at which a screening test can detect cancer to the point at which it would have been detected clinically (Figure 4). Gann *et al.* (155), in an analysis of a single sample from subjects on the Physicians' Health Study, estimated a mean lead time of 5.5 years corresponding to a PSA cutoff of 4 ng/ml. Savage *et al.* (156) estimated considerably higher lead times corresponding to a cutoff of 3.0 ng/ml. Swedish cancer registry information was linked to two independent cohorts of men who had blood drawn and stored in 1981-1982 and 1982-1985. The men in the first cohort were all 60 years of age, and the men in the second cohort ranged in age from 51-56 years. The median lead time to prostate cancer diagnosis (based on a PSA level of 3.0 as a threshold for prostate biopsy) was 12.8 years in the younger men and 11.8 years in the older men (156). There were wide variations around these median values, as shown in Figure 5.



This concept has been extended in a recent review of PSA testing at younger ages and prostate cancer risk (157). Multiple studies have shown that a single PSA level can be associated with future prostate cancer risk (155, 158-160). Higher baseline levels of PSA, even when lower than conventional thresholds for prostate biopsy, are related to both future risk of a PSA rising to the level at which biopsy would be recommended, and of prostate cancer being detected. Such baseline levels might be used to inform future screening protocols.

1.8 Statistical or Model-Based Approaches

In statistical or model-based approaches, models for observed cancer incidence in a population with known screening patterns are developed. These models include, as unknown parameters, the distribution of the preclinical duration or the lead time, or other unknown aspects of the disease's natural history from which these can be derived. Two such studies showed a preclinical duration of disease of 12.7 years (161) and 11 to 12 years (162). More recently, in a model developed by Tsodikov *et al.* and fitted to US incidence trends, a case diagnosed in 1973 was estimated to have a latency period of 11.8 years compared with 9.6 years for a case diagnosed in 1987 (163).

Several models have been developed to estimate lead times associated with PSA screening. Telesca *et al.* (164) developed a model that compared the incidence of prostate cancer in the US during the 1990s with the incidence that would have been expected in the absence of PSA. In their study, they estimated the average lead time among US men aged 50 and above to be 4.6 years for whites and 6.8 years for blacks (164). Draisma and colleagues provided a unified estimate of the lead time associated with PSA screening, using three independently developed models of prostate cancer progression and detection (165). All three models were calibrated to US prostate cancer incidence trends. The lead time estimated were produced as a result of the estimated natural histories, and ranged from 5.4 to 6.9 years across the models.

An aspect of natural history that is related to tumour latency, but that has been rather less well studied, is the stage- and grade-specific duration of disease. Of particular interest is the length of the early (localized) stage, or the interval from preclinical onset to metastasis. However, this is challenging to estimate because of its latency. Draisma *et al.* considered nine different disease stages defined by all combinations of three grade (low, moderate and high) and three stage (localized, regional and distant) categories; resulting estimates of the length of the localized stage ranged from 6.95 years (low grade) to 5.25 years (high grade) (161). A recent study by Gulati and colleagues used three independently developed models of prostate cancer natural history that included, as latent events, transitions from disease onset to metastasis, and to clinical diagnosis (166). The models were calibrated to data from the SEER registry on US prostate cancer incidence. The calibration exercise produced estimates of disease onset rates and latent stage durations that best matched observed incidence trends. Results indicated that the average duration from onset to clinical diagnosis ranged from 7 to 14 years and the average duration from onset to metastatic disease (for those with metastatic disease at clinical diagnosis) ranged from 4 to 13 years.

An as-yet unresolved question about the disease's natural history concerns whether prostate tumours dedifferentiate over time. Several model-based analyses have addressed this question. For example Draisma et al. allowed both grade and stage to progress over time in their model and found that allowing dedifferentiation improved the fit of their model to observed data on grade- and stagespecific incidence patterns from the European Randomized Study of Screening for Prostate Cancer (ERSPC); providing evidence for the dedifferentiation hypothesis. A similar analysis by Pashayan et al. using data from the Prostate Testing for Cancer and Treatment (ProTecT) study reached a similar conclusion. (167) Choo et al. (168), studied progression of histologic grade from radical prostatectomy to local recurrence in 43 patients with clinically isolated local recurrence following surgery. Their study found a trend towards a higher Gleason score at the time of local recurrence; at the time of local recurrence (median 3.6 years after surgery), Gleason score was upgraded in 13, downgraded in 7, and remained the same in 23 patients. However, this study does not address whether Gleason score may progress within the primary tumour. Tumour upgrading has also been observed in men on active surveillance. For example, Tosoian et al. reported on the Johns Hopkins active surveillance cohort in which, among 769 men on active surveillance, 255 men underwent intervention at a median of 2.2 years, and among these, 106 showed a Gleason score upgrading at their final pre-treatment biopsy (169). However, because of the known possibility of grade misclassification on prostate biopsy, it is difficult to determine how many of the men who apparently upgraded truly underwent a grade change.

The above-referenced studies of tumour latency do not clearly indicate whether prostate cancer is primarily a disease with a long and relatively slow development phase or several diseases with less aggressive and more aggressive forms. However, the fact that the histological prevalence of prostate cancer far outweighs the number of clinically apparent tumours makes it critical to distinguish life-threatening tumours that require treatment from tumours that will not progress if left alone. This issue becomes particularly important in the context of the use of the PSA test, which can lead to the detection of large numbers of prostate cancer cases, the vast majority of whom would never have known that they had the disease. It has been estimated that, in the absence of PSA, approximately 75% of men with prostate cancer would not have been diagnosed within their lifetimes (162), creating enormous potential for overdiagnosis and overtreatment. Reports of the extent of overdiagnosis vary

and depend strongly on the screening schedule and population. In a combination of three different models of prostate cancer progression and detection, Draisma and colleagues provided a unified estimate of the lead time associated with PSA screening. All three models were developed independently, and were subsequently calibrated to US SEER data. While the fraction of screen-detected cases that were overdiagnosed varied across the models; results indicated that 23% to 42% of cancers detected by PSA screening represent overdiagnosed prostate cancer. (165)

1.9 Epidemiologic Analysis

To identify predictors of disease progression, a number of cohort studies of untreated, conservatively managed men with localized prostate cancer have been conducted. Both long-term and short-term studies have been completed. While results differ depending on study populations, era of diagnosis, and definition of progression, some broad inferences can be made. First, for cases diagnosed prior to the PSA era, disease histology (Gleason Score) is a key predictor, and perhaps the most important predictor of disease progression. In their long-term analysis of 767 men diagnosed between 1971 and 1984 in Connecticut, Albertsen et al. found that over the 20 years following diagnosis, prostate cancer death rates ranged from 6 per 100,000 person-years for men with Gleason scores between 2 and 4, to 121 per 100,000 person years for men with Gleason scores between 8 and 10 (170). A second long-term study, that of Johansson et al. (171), analyzed data from a Scandinavian population cohort diagnosed between 1977 and 1984, and also showed a strong correlation between Gleason score and the risk of prostate cancer death. However, the two studies differed in their assessment of the risk of late (beyond 15 years from diagnosis) disease-specific mortality. Johansson et al. reported a 3-fold increase in prostate cancer death rates after 15 years (171); this was not the case in the Albertsen study et al., which found the risk of late prostate cancer death to be similar to the risk observed within the first fifteen years. Reasons for the discrepancy are not clear (170).

Examining men undergoing conservative management in the PSA era, Lu-Yao *et al.* found that patients diagnosed with prostate cancer in the United States from 1992 to 2002 had better outcomes than patients diagnosed in the 1970s and 1980s (172). The authors examined men with T1 and T2 disease living in areas of the United States covered by the SEER registry. They examined prostate cancer-specific mortality (PCSM) and performed a competing-cause risk analysis for other causes of mortality. They found the 10-year risk of PCSM was 8.3%, 9.1%, and 25.6% for well, moderately, and poorly differentiated tumours, respectively. The 10-year risks of competing causes of mortality were 59.8%, 57.2%, and 56.5% for the well, moderately, and poorly differentiated groups respectively. Uses of chemotherapy or interventions for spinal cord compression were rare (1.6% and 0.9% respectively).

A review by Martin *et al.* (173), summarized progression in five cohorts of patients with clinically localized prostate cancer diagnosed in the PSA era and who were actively monitored for disease recurrence and progression (174-178). In all but one study, the men were followed up for less than five years, which may be too short a period to assess outcomes in prostate cancer patients. The studies were limited to participants with stage T1-T2 disease. The monitoring protocols varied, although all included serial measurement of PSA and DRE assessment. Three also included repeated transrec-

tal ultrasound-guided biopsies (175-178), and others included a variety of clinical measures. As a consequence of these different protocols and definitions, reported progression rates differed with little clear relationship to median duration of follow up, mean age, or median initial PSA level.

Several factors were found to be associated with cancer progression, although findings were not always consistent across all studies. In studies of men diagnosed before the PSA era, for example, grade and stage of cancer are consistently predictive of progression. However, in these five studies of men with localized prostate cancer, only three showed associations between clinical progression and baseline Gleason score (174), cancer stage (178), and prostate volume (176). Further, two of these studies and another, larger study, found no associations between progression and age (175, 176), Gleason score (175, 178), or tumour stage (175). These null findings are not simply explained by the studies being underpowered to detect an effect, since the largest study found no associations (175), but are more likely to reflect the variable protocols and definitions of progression and, possibly, the relatively short period of follow up. Associations of baseline serum PSA with clinical progression were observed in some (176, 178), but not all studies.

The proportion of cancer cases progressing was 25% over a median of 44 months (178), 17% within 29 months (175), and 29% within 23 months following diagnosis (176). Two of the studies followed men using a combination of both clinical (DRE / radiological / clinical evidence of metastases) and biochemical (PSA) criteria, but did not include routine histological surveillance (174, 177). The proportion of men progressing during follow-up varied: in the series of men with T1a disease, 8% of cancers progressed in 88 months (174); in the series of men with T1c disease 33% were defined as having progressed in 23 months (177).

The short-term probability of metastasis was low. In four studies, there was no evidence of metastatic progression after a median of between 23-44.1 months of follow-up (175-178); in men with T1a cancer followed for a median of 7.3 years, 1 man (2%) progressed to bony metastases after 12 years (174).

Additional follow-up data from patients on active surveillance for clinically localized prostate cancer has been published. A recent review on the subject by Cooperberg, *et al.* (179), provides evidence from seven institutional case series on active surveillance. The institutions each had different criteria for including men on the active surveillance protocols, although most included only men with Gleason 3+3 disease (178, 180-183). Two institutions included some men with Gleason 3+4 disease in their active surveillance protocols (184, 185). Follow up was limited in these cohorts, with only the Toronto group having a median follow-up time of over 5 years (82 months) (185). As seen in the prior results, progression varied extensively from 9% to 35%, likely reflecting the different periods of follow up, baseline differences among the cohorts and the differences in definitions of progression, including the use of PSA kinetics to drive treatment in some groups (185), and the reliance on annual biopsies in others (186).

The lengthy interval from diagnosis to metastasis in studies including the Martin review (173) confirms the findings of Pound *et al.* (187), who studied the natural history of progression in a large surgical series. Although all cases in the Pound series underwent radical prostatectomy as primary therapy, they did not receive adjuvant or neoadjuvant hormone therapy, and they were not treated at the time of biochemical recurrence. The time from biochemical recurrence to clinical metastasis

was eight years on average in this cohort, and once the men developed metastases, the average time to prostate cancer death was five years. Furthermore, both the time to biochemical recurrence and the PSA doubling time were predictive of the time to metastasis.

Research in the area of prostate cancer progression is controversial and developing rapidly, focusing on molecular aspects that include germ line and somatic genetic changes. Many molecular studies are being conducted in treated cohorts of patients, which may limit their utility for predicting progression in the absence of treatment. Greater understanding of the molecular and genetic basis of prostate cancer is expected to improve the ability to predict progression, but while there are promising developments (145, 149, 188, 189), no novel markers for predicting progression have yet made it to the clinic.

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New Developments in the Molecular Pathology of Prostate Cancer

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2.1 Abstract

Widespread prostate-specific antigen (PSA) testing leads to the diagnosis of clinically insignificant tumours (overdiagnosis) and potential overtreatment, causing severe morbidity and leading to unnecessary healthcare costs. Prognostic biomarkers to identify men with clinically significant prostate cancer are urgently needed. This chapter will focus on serum PSA and promising novel prognostic biomarkers for prostate cancer arranged by tissue markers, blood markers and urine markers. In addition, the STARD (STAndards for Reporting of Diagnostic accuracy) statement and the REMARK guidelines (Reporting Recommendations for Tumor Marker Prognostic Studies), two initiatives that are important in improving the quality of tumour marker studies, are discussed.

2.2 Introduction

The diagnostic process of prostate cancer is challenging. Diagnosis is based upon prostate biopsies, the gold standard, though there are clear limitations. Prostate biopsies are susceptible to undersampling; 35% of cancers are missed upon first biopsy and the Gleason score is underestimated in 46% of cases (1,2). In addition, biopsies are invasive procedures that cause pain and discomfort. Prostate biopsies are performed if digital rectal examination (DRE) is suspicious for prostate cancer or if serum prostate-specific antigen (PSA) is elevated. These two parameters also have limitations, however. Digital rectal examination has a low reproducibility and a low sensitivity for the diagnosis of prostate cancer (3,4), and PSA has low specificity (25-40%) in the "grey area" of PSA levels (4.0-10.0 ng/ml), resulting in a high negative biopsy rate (5). Furthermore, widespread PSA testing leads to the diagnosis of clinically insignificant tumours (overdiagnosis) and potential overtreatment, causing severe morbidity and leading to unnecessary healthcare costs. Prognostic biomarkers to identify men with clinically significant prostate cancer would be of great benefit.

A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (6). This includes physiological measurements and clinical imaging, but also specific cells, molecules, genes, gene products, enzymes or hormones.

Biomarkers in cancer can have several valuable applications:

- Improve diagnosis
- Improve staging
- Indicate disease prognosis (e.g. indolent vs. clinical significant prostate cancer)
- Monitor response to treatment
- Identify patients for different treatment options
- Serve as a surrogate endpoint in trials
- Serve as a therapeutic target

The optimal characteristics of a biomarker for prostate cancer include:

- Are only produced by tumour tissue
- Require non-invasive tests, and are easy to manage
- Remain as inexpensive as possible
- Detect prostate cancer at an early stage
- Differentiate between indolent and clinically significant tumours
- Have high sensitivity and specificity

Biomarkers are important tools in the era of modern medicine, i.e. individualized medicine. Whereas clinical diagnosis and management of the individual patient is traditionally based upon clinical cohort-based studies with considerable heterogeneity, individualized medicine strives for a "customized" healthcare – that is, patient-specific strategies instead of the standard "one-size-fits-all" approach. Revolutionary advancements in molecular profiling technologies have been made in recent decades. Nucleic acid amplification technologies have allowed for whole genome gene and expression profiling, and have resulted in the discovery of non-coding ribonucleic acids (RNAs), including microRNAs. These developments now enable us to predict with greater accuracy the biological behaviour and therapeutic response for well stratified/homogeneous groups of patients.

Given the heterogeneous character of prostate cancer, it is likely that a panel of biomarkers, including novel biomarkers, will be used in the future to optimize predictive value. Prostate cancer biomarkers can be detected in different diagnostic substrates, each resulting in different clinical decisions (Table 1). This chapter will focus on serum PSA and promising novel prognostic biomarkers identified by molecular profiling studies. We will start by discussing tissue markers, followed by blood markers and, finally, urine markers.

Substrate	Invasiveness	Clinical decision-making
Urine	-	Biopsy
Blood	-	Biopsy
Biopsy specimen	+	Treatment
Prostatectomy specimen (Gleason score and pTNM; tumour node metastasis staging system)	++	Adjuvant treatment

TABLE 1 Different diagnostic substrates for prostate cancer biomarkers.

2.3 Prostate-Specific Antigen

2.3.1 Total PSA

In 1986, PSA was approved by the Food and Drug Administration (FDA) as a marker to monitor treatment in patients with prostate cancer, and in 1994, it was approved as a diagnostic marker. It is currently the only widely used marker for prostate cancer.

Also known as kallikrein 3 or hK3, PSA is a serine protease belonging to the family of glandular kallikrein-related peptidases. The genes for the glandular kallikreins are clustered at chromosome 19q13.3-4 and PSA transcription is regulated by androgens (7). The function of PSA is to liquefy seminal fluid through its action on the gel-forming proteins, semenogelin and fibronectin (8).

Prostate-specific antigen is not a cancer-specific marker; it is produced by both benign and malign prostate epithelial cells. Normally, PSA blood levels are low. A healthy prostate is surrounded by both a continuous layer of basal cells and a basement membrane, which prevent the high concentrations of PSA in the prostate to leak into blood. High PSA blood levels can be caused by an elevated synthesis or an increased release of PSA into blood. An elevated PSA synthesis can be a result of benign prostatic hyperplasia (BPH) and prostate manipulation (9,10). However, PSA expression, and thus PSA synthesis, is slightly decreased in the development and progression of prostate cancer (11). Therefore, the increased PSA blood levels in prostate cancer are assumed to be a result of an increased release of PSA into blood through the disrupted architecture of the prostate, as is seen in prostatitis.

Despite extensive research, difficulty persists in defining the optimal cutoff value for PSA. Traditionally, it is set at 4.0 ng/ml. Using this PSA cutoff provides a sensitive test, with a positive predictive value of 37% and a negative predictive value of 91% (12). In other words, 75% of men with PSA levels of 4.0-10.0 ng/ml who undergo biopsy do not actually have cancer (13). In addition, several studies have shown a substantial probability of prostate cancer within the PSA interval of 0.0-4.0 ng/ml (14-16). The Prostate Cancer Prevention Trial (PCPT), for example, reported that 27% of men with normal DRE and a serum total PSA between 3.1 and 4.0 ng/ml have prostate cancer (16). On the other hand, it has never been demonstrated that lowering the PSA cutoff affects the long-term survival in men with prostate cancer. Furthermore, a lower cutoff will most likely lead to a higher number of unnecessary biopsies and an increased detection of clinically insignificant prostate cancer.

Other factors influence on PSA blood levels, including ethnic background and the use of medication. Men of African descent have higher PSA levels than do Caucasian men, even after adjusting for prostate volume (17,18). Furthermore, men using 5α -reductase inhibitors (such as dutasteride and finasteride) for the treatment of BPH will have lower PSA levels by an average of 50% after 6 months of treatment (19,20). Several studies report that PSA measured before the age of 50 might be indicative of the risk of developing prostate cancer, years or even decades later (21,22). It is also suggested that total PSA levels at age 44-50 may also predict the likelihood of developing advanced prostate cancer, defined as clinical T3 or higher, or metastatic disease at the time of diagnosis (23). This, however, needs further validation before possible implementation into clinical practice.

2.3.2 Risk calculators

Risk calculators, including several predictive factors, have been developed to stratify patients for prostate biopsy. Two well-known calculators that are available online are the PCPT and the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculators (24,25). The former includes serum PSA, DRE results, age, family history of prostate cancer, ethnicity and prior biopsy. The latter includes serum PSA, DRE results, transrectal ultrasonography (TRUS) findings, prior biopsy and prostate volume. The use of risk calculators allows for a more individual assessment of prostate cancer risk and provides a better predictive accuracy compared to PSA alone (26).

2.3.3 **PSA derivatives**

Protein-specific antigen derivatives have been evaluated in an attempt to increase the diagnostic accuracy of total PSA. These include age-specific total PSA cutoffs, total PSA density, total PSA velocity and total PSA doubling time.

Age-specific PSA cutoff values were suggested to enhance the predictive value of PSA. The suggested cutoff values are: 40-49 years old: 2.5 ng/ml, 50-59: 3.5 ng/ml, 60-69: 4.5 ng/ml and 70-79: 6.5 ng/ml. However, the use of an age-specific total PSA cutoff is not validated and is criticized for missing clinically significant cancers in older men (27).

PSA density is defined as the total serum PSA level divided by the volume of the prostate (in grams). A PSA density of 0.15 ng/nl/g or higher is considered abnormal and suspicious for cancer. However, the value of this test remains controversial (28). While PSA density has been correlated with biopsy outcome, tumour aggressiveness and unfavourable pathological features in several studies (29-31), other studies could not validate these results (32,33). In addition, PSA density requires TRUS, which is time-consuming, expensive and causes patient discomfort. Protein-specific antigen density is not widely used in clinical practice.

Protein-specific antigen dynamics have been extensively studied for their assumed predictive value in discriminating between benign and malign conditions of the prostate. The PSA dynamics include PSA velocity, defined as the change in PSA over time, and PSA doubling time, the number of months for a certain level of PSA to increase by a factor of two. Protein-specific antigen dynamics are indisputably correlated with the diagnosis of prostate cancer on biopsy. However, there is insufficient evidence that PSA velocity or PSA doubling time has additional diagnostic value beyond the use of total PSA. Thus, there is no justification for the use of PSA dynamics in clinical decision-making before treatment in early-stage prostate cancer (34). Protein-specific antigen dynamics are, however, valuable in monitoring treatment. Although currently widely used, PSA response to chemotherapy in castrate-resistant prostate cancer (CRPC) patients does not adequately predict long-term benefit. However, recurrence after radical prostatectomy can be monitored with high sensitivity using PSA doubling time.

2.3.4 **PSA molecular forms**

PSA circulates in blood either in a stable complexed form or in an unbound "free" form. Complexed PSA is bound to the proteins: α 1-antichymotrypsin, α 2-macroglobulin and α 1-protease inhibitor. A lower percent-free PSA (free PSA/total PSA x 100) is correlated with a higher probability of finding prostate cancer on biopsy (35,36). The FDA has approved the use of percent-free PSA as a diagnostic marker in men with PSA levels of 4.0-10.0 ng/ml. A cutoff value of 25% is generally used. It should be noted that free PSA is less stable than complexed PSA, causing greater analytic variability. Suboptimal blood sample handling can considerably influence free PSA levels (37).

Free PSA exists in different molecular isoforms, including pro-PSA, BPH-associated PSA (BPSA) and intact free PSA (38,39). Several studies report significantly higher levels of pro-PSA and decreased levels of BPSA and intact free PSA in patients with prostate cancer (40-42). This implies that pro-PSA might be a purer biomarker for prostate cancer than free PSA. Pro-PSA has also been suggested to selectively identify patients with more aggressive prostate cancer, though this additional diagnostic and prognostic value has yet to be validated.

2.4 Novel Prognostic Biomarkers

2.4.1 **Tissue markers**

Once tissue from a patient is available, important decisions have already been made: either a biopsy has been taken or the gland was surgically removed. Thus, the main clinical need at this point is to accurately predict the biological behaviour of the malignant process. If the pathologist is unsure about a diagnosis of invasive prostate cancer, immunohistochemistry using antibodies against the basal cell-specific high molecular weight keratins (34 E12) and alpha-methylacyl-CoA racemase has proven to be helpful (43). It is striking that this is the only molecular pathological application that has been widely accepted and used in prostate cancer. Numerous studies have reported on the potential of biomarkers detected by immunohistochemistry, yet none are routinely used for a better assessment of prognosis. Whereas biomarkers that predict disease progression in patients that were treated with curative intent are routinely used for other malignancies (e.g. breast and colon cancer), so far there has not been a great interest in adjuvant treatment for patients with high-risk localized prostate cancer. Now that better treatment modalities have become available, adjuvant strategies are likely to be considered again and biomarkers indicative of biological behaviour, determined in tissue, will be needed. In this section we will focus on highly potential biomarkers for which standardized methods have been or can be developed.

2.4.1.1 Gene-fusions: TMPRSS2-ERG

The classic example of a gene fusion that is implicated in cancer development is the BCR:ABL fusion in patients with chronic myelogenous leukemia. This fusion results from a reciprocal translocation T(9;22), first recognized as the Philadelphia chromosome. This discovery was revolutionary, as it led to the development of imatinib (44), an inhibitor of the BCR:ABL gene fusion product, transforming the previously fatal leukemia into a manageable chronic disease for many patients.

In prostate cancer, a recurrent fusion of the 5' untranslated region of TMPRSS2 (androgen-regulated transmembrane protease, serine 2) to ETS family genes (oncogenic transcription factors) was discovered in 2005 (45). Oncogene ERG (v-ets erythroblastosis virus E26 oncogene homolog [avian]) is the most common ETS family member involved in gene fusion. TMPRSS2-ERG has been detected in approximately 50% of Caucasian prostate cancer patients. This gene fusion is less frequently seen in men from other ethnic backgrounds; a recent study reported fusion-positive prostate cancers in 31% of African American men and in only 16% of Japanese men (46). Rearrangements with other ETS transciption factors have been identified in approximately 5-10% of PSA-screened prostate cancers: ETV1 (ETS variant 1 gene), ETV4 and ETV5 (47-49). Other fusion partners involved in ETS fusions have been identified in addition to TMPRSS2. Their possible clinical relevance is not yet clear.

As a result of gene fusion with TMPRSS2, the expression of ERG becomes androgen regulated and thus overexpressed. ERG expression can be detected by immunohistochemistry in prostate cancer patients with a high specificity (>95%). It is not seen in benign prostate epithelium (50,51). This suggests that ERG immunostaining can be a diagnostic biomarker, albeit only in approximately half of the prostate cancer patients. The clinical relevance of ETS gene fusions is currently under investigation. Results on a potential prognostic value are conflicting. A worse prognosis of fusion-positive cancers has been reported by several studies (52-54); other studies either could not validate these results (55,56) or found a favourable prognostic association (57,58). A recent large study showed that ERG status had no influence on the risk of PSA recurrence after radical prostatectomy (51). In addition, the authors reported a strong association between ERG positivity and high androgen receptor expression levels. This suggests that ERG status might have predictive value for response to anti-androgen therapy. However, this requires further investigation before implementation into clinical practice can be realized.

2.4.1.2 Ki-67/MIB1-labeling index

Expression of the Ki-67 protein is strictly associated with cell proliferation. Ki-67 (named for the city of origin (Kiel, Germany) and the number of the original clone in the 96-well plate (59)) has therefore been extensively studied for its potential use as a proliferation marker in different types of cancer, including prostate cancer. It can be localized by immunohistochemistry using the mono-clonal antibody MIB-1 (60). The proportion of tumour cells staining positive for Ki-67 is known as the Ki-67 labeling index and has proven to be an independent and significant prognostic biomarker for prostate cancer-specific survival (61,62). Furthermore, the Ki-67 labeling index has repeatedly been shown to be a predictive marker for disease recurrence and for disease progression after radical prostatectomy and radiotherapy (63-65). Although its usefulness has been well established, the Ki-67 labeling index is not currently used in daily practice.

2.4.1.3 **PTEN**

The phosphatase and TENsin homologue (PTEN) is a tumour-suppressor gene, located on chromosome 10q23 (66), and plays a key role in carcinogenesis. PTEN antagonizes the PI-3K/Akt pathway and thereby modulates cell growth/survival and cell migration/adhesion (67). In prostate cancer, PTEN loss has been associated with the proliferation and survival of cancer cells, resistance to castration (68), chemotherapy and radiotherapy (69-71), bone metastasis (72) and recurrence after radical prostatectomy (73). Thus, PTEN is assumed to be a potent prognostic marker and a clear target for novel gene therapies. However, this requires further research.

2.4.1.4 E-cadherin

Cadherins are a family of epithelial cell-cell adhesion molecules that play a key role in preserving epithelial integrity (74). Their function is dependent on calcium, hence their name ("calcium-dependent adhesion"). E-cadherin is the most extensively studied member of the cadherin family. As cancer progresses to an invasive state, intercellular adhesions between tumour cells are disrupted. Thus, aggressive tumour cells are hypothesized to have a loss of E-cadherin. Indeed, decreased E-cadherin expression has repeatedly been shown to correlate with a loss of tumour differentiation and a poor prognosis (75-77) for several tumour types, including prostate cancer. However, large prospective studies will have to define its potential clinical relevance in prostate cancer as either a prognostic biomarker or as a molecular target for therapy.

2.4.1.5 **EZH2**

The Enhancer of zeste homolog 2 gene (EZH2), encoding a Polycomb-group protein, is responsible for maintaining the silent state of genes. This gene mediates the trimethylation of histone H3 lysine 27, leading to repression of transcription and thereby silencing gene expression (78,79). EZH2 is upregulated in various aggressive tumours, including prostate cancer (80-82). Furthermore, it mediates the transcriptional silencing of the tumour suppressor gene E-cadherin (83), thus demonstrating an inverse correlation between dysregulation of EZH2 and repression of E-cadherin during cancer progression. EZH2 upregulation may play a key role in oncogenesis and the progression of cancer. This makes it a promising biomarker of disease progression and a viable target for therapeutic interventions in aggressive cancers.

2.4.1.6 The neuroendocrine phenotype

The expression of a neuroendocrine (NE) phenotype in prostate cancer was first reported almost 25 years ago (84). There is good evidence that the relative fraction of cells with a NE phenotype increases in advanced prostate cancer, yet its use to predict biological behaviour in localized prostate cancer remains controversial. In "pure" NE phenotype cases, i.e. in small cell prostate cancer (a rare entity composing less than 1% of all prostate cancer), the biology of the disease is markedly different from adenocarcinoma of the prostate, and therefore, treatment of this type of prostate cancer is different.

In summary, there is a viable set of candidate prognostic biomarkers available that can be measured by immunohistochemistry. Stratification of patients based on these markers is well within reach, provided that the methods and scoring systems are standardized.

2.4.2 Blood markers

2.4.2.1 MicroRNAs

The discovery of microRNAs (miRNAs) in 2004 was a revolutionary step in understanding the mechanisms regulating gene expression and function (85,86). It has since been reported that miRNAs play an important role in cancer by initiating carcinogenesis and driving cancer progression (87).

MicroRNAs are small endogenous non-coding RNAs, up to 22 nucleotides long, that regulate gene expression post-transcriptionally. They bind to complementary sequences within messenger RNAs (mRNA) and alter their translation by either inhibiting translation or inducing the cleavage of specific target mRNAs (88). In most cases, miRNAs "fine-tune" protein expression (though there is only a modest reduction in the target mRNA concentration) (89). Occasionally, miRNAs cause upregulation or complete destruction of the target mRNA (89-91).

MiRNAs are known to regulate common cellular targeted pathways (intracellular signaling, DNA repair and cellular adhesion/migration) (92-94), androgen signaling (95-97) and apoptosis avoidance (98,99). The exact role of miRNAs in the development and progression of prostate cancer is still being investigated; however, miRNAs are promising potential biomarkers and novel therapeutic targets for prostate cancer.

2.4.2.2 Circulating tumour cells

The importance of circulating tumour cells (CTCs) was already acknowledged in 1869 by Thomas Ashworth, an Australian physician who observed CTCs microscopically (100). Only recent advances in technology have offered a reliable method for the detection of CTCs in blood. Their presence in blood proved to be associated with overall survival in patients with metastatic breast (101, 102), colorectal (103,104) and prostate cancer (105,106).

In CRPC, the CTC number before and after treatment is an independent predictor of survival. This is a strong predictor both as a continuous variable and when using discrete cutoff values (\geq 5 CTC per 7.5 ml of blood vs. <5 CTC) (105-107). Post-treatment CTC numbers have shown to be a stronger prognostic factor for survival than a 50% decline in PSA. The FDA has approved CTCs as a prognostic biomarker to monitor disease status in patients with metastatic breast, colorectal and prostate cancer. To further explore the potential link to survival, CTCs have been incorporated as an exploratory endpoint in several phase II and phase III trials (108).

2.4.2.3 hK2 and uPA

Human kallikrein 2 (hK2) and urokinase plasminogen activation (uPA) are potential future prostate cancer biomarkers, though they are not yet validated. Human kallikrein 2 is from the same gene family as PSA, but differs in its enzymatic activity (109). Several studies have shown that the use of a combination of hK2 with free and total PSA might improve the predictive value for prostate cancer (110,111) and hK2 may also have prognostic value (112,113). The serum protease uPA (urokinase-type plasminogen) might be involved in tumour development and progression through the degradation of the extracellular matrix (114). The potential role of uPA as a biomarker of metastatic prostate cancer needs to be validated in large multicentre studies.

2.4.3 Urine markers

2.4.3.1 **PCA3**

In 1999, Bussemakers *et al.* identified and characterized the differential display clone 3 (later called prostate cancer antigen 3; PCA3) gene. It is one of the most specific prostate cancer genes to date. (115). Prostate cancer antigen 3 is a non-coding RNA located on chromosome 9q21-22. Its function is as yet unknown. It is highly overexpressed in prostate tumours (on average between 70 and 80-fold more) compared to adjacent benign prostate tissues. An upregulation of PCA3 is seen in 95% of primary prostate tumours. Its expression is not found in non-prostate tissue (i.e. in benign and malign tissue from breast, cervix, endometrium, ovary and testis or in cell lines originating from bladder, kidney and ovarian cancer) (115).

In initial PCA3 studies, a real-time reverse transcription polymerase chain reaction (RT-PCR) analysis was used for the quantification of PCA3 mRNA in prostate tissue. Later, Hessels *et al.* developed a dual time resolved fluorescence-based RT-PCR assay to detect PCA3 mRNA in urinary sediments after DRE (116). A urine test provides a non-invasive method to obtain prostate cancer cells, which makes it suitable for clinical purposes. A DRE is performed to mobilize prostatic cells towards the prostatic urethra, which are then flushed out with the first voided urine. (A prostate massage is obsolete and causes needless patient discomfort, as a regular DRE sheds enough cells into urine for analysis.) In 2006, the Progensa PCA3 test was introduced, a transcription-mediated amplification assay (117). This assay is also performed on the first voided urine samples after DRE, but it is a simpler, faster and sufficiently sensitive method compared to the initial RT-PCR based assay and, therefore, is more viable for widespread clinical implementation. The PCA3 test score is the ratio of PCA3:PSA mRNAs multiplied by 1000. The Progensa PCA3 test is commercially available and has been approved by Conformité Européenne (CE) since November 2006 to aid in the decision to take an initial or repeat biopsies. The FDA approval process is currently underway.

The clinical utility of PCA3 and its additional predictive value beyond PSA has been extensively studied. PCA3 has been validated as a reliable predictor of prostate cancer at initial or repeat biopsy (116,118-121). Currently, a cutoff value of 35 is used, resulting in a sensitivity of 47-69% and a specificity of 72-79% (117,119-121). However, the optimal cutoff value is subject to debate. Several studies indicate that a cutoff value of 20 or 25 might be preferable, missing less prostate cancers but still preventing a considerable amount of prostate biopsies (118). Future studies will have to clarify this issue. Furthermore, PCA3 has shown to be an independent predictor of prostate cancer, in addition to established prostate cancer risk factors (age, PSA, DRE, prostate volume and biopsy history) (122,123). The use of PCA3-based nomograms has recently been validated (124), providing a novel tool for clinical decision-making.

It has been hypothesized that PCA3 might be associated with a more aggressive cancer. This was based on the theory that aggressive prostate cancer cells are more invasive and would therefore more easily shed into the prostatic ductal system after DRE (125). However, to date, the prognostic value of PCA3 is considered to be limited. Some studies have found a correlation of PCA3 with the Gleason score (118,120,126), but this is contradicted by a range of other studies that show no additional predictive value for the Gleason score (125,127-129). As concluded by Auprich *et al.*, the clinical value of PCA3 to predict aggressive prostate cancer at radical prostatectomy seems to be marginal at best

(127). However, it has been shown that PCA3 is a valuable predictor of tumour volume and insignificance of prostate cancer (120,127,129). Data on the predictive value for extracapsular extension are conflicting (120,127,130). Furthermore, PCA3 currently has no role in risk assessment during active surveillance protocols, though this requires further investigation in larger studies (129,131).

2.4.3.2 Gene fusions: TMPRSS2-ERG

TMPRSS2-ERG is a fusion of TMPRSS2 (the androgen-regulated trans-membrane protease, serine 2) to ETS family genes (oncogenic transcription factors). (For a complete description of the gene fusion TMPRSS2-ERG, see section 2.4.1.)

A publication in 2006 showed the feasibility of non-invasively detecting TMPRSS2-ERG fusion transcripts in urinary sediments obtained after DRE using an RT-PCR-based research assay (132). Since then, extensive research has been performed on the clinical applicability of this urine test. A sensitivity of 37% and specificity of 93% to predict prostate cancer was reported, resulting in a positive predictive value of 94% (133). Although not yet validated, this test is assumed to improve the specificity of established prostate cancer risk calculators.

2.4.3.3 Urine marker panel

Given the tumour heterogeneity in prostate cancer, the use of a panel of biomarkers may provide the best diagnostic accuracy. Hessels *et al.* evaluated the combination of PCA3 with TMPRSS2-ERG fusion transcripts detected in the urine, showing an improved sensitivity of 73% compared to 62% for PCA3 alone, without compromising the specificity for detecting prostate cancer (133). A recent study confirmed an enhanced predictive value of PCA3 combined with TMPRSS2-ERG (134). These preliminary results on the combined use of PCA3 and TMPRSS2-ERG seem promising but require further validation. Future studies will have to assess the use of other novel biomarker panels.

2.5 Future Perspectives

In the search for novel prognostic biomarkers for prostate cancer, many tumour markers have been proposed. The number of articles published on this subject has increased substantially in the last decade. However, PSA, PCA3 and CTCs are still the only markers used in clinical practice. Many published results on novel prostate cancer biomarkers were not reproducible in subsequent studies and thus may never attain the FDA approved status (Table 2).

TABLE 2 The different stages of biomarker research.

Stages of biomarker research	Corresponding markers in prostate cancer
1. Exploratory, no-intended-use cohort	microRNA, uPA, EPCA-1, EPCA-2, etc.
2.Research use-only assay, evaluated retrospectively	hK2, PTEN, Ki-67, EZH2, E-Cadherin
3.Research use-only assay, evaluated prospectively	TMPRSS2-ERG
4.CE-/FDA-approved	PSA, PCA3, circulating tumour cells

While a double-blind randomized placebo controlled trial is the gold standard for therapeutic studies, biomarker studies are not regulated by clear guidelines. These studies often have poor study design; lack methodological quality and standardized assays; and information on key elements of design and analysis are often not reported. To improve the quality of diagnostic studies, the STARD (STAndards for Reporting of Diagnostic accuracy) statement was developed by a group of scientists and editors in 2003 (135). It consists of a checklist of 25 items and a flow diagram that authors can use to ensure that all relevant information is present. In addition, the REMARK guidelines (Reporting Recommendations for Tumor Marker Prognostic Studies) were published in 2005 (136). These are guidelines for transparent and complete reporting of studies, so that poor studies can be better identified. These initiatives are important steps forward in improving the quality of tumour marker studies, though further improvement of future studies is still warranted.

Other future improvements include the use of a secured database with an audit trail, so that results cannot be manipulated after analysis. Validation of a potential novel biomarker should only be approved after multiple prospective studies using an "intended use" cohort. Furthermore, it should be kept in mind that it is not sufficient to show that a potential novel biomarker is statistically significant in multivariate analysis; the biomarker should improve the predictive accuracy of the multivariate model. In conclusion, future biomarker studies should meet the STARD criteria and should be reported in compliance with the REMARK guidelines.

Though many new biomarkers are ready for validation, studies need to be carefully designed to test their clinical relevance. Once the decision to take a biopsy is made, the man becomes a patient, whether or not he has prostate cancer. This decision presents a difficult challenge, since the man with indolent cancer should not be bothered with a biopsy, yet men with low PSA ranges with aggressive disease must be identified. Thus, there are two main themes in the clinical sphere: 1) develop methods to better predict biopsy outcome, and 2) better predict the prognosis and therapy need/response (Figure 1).

FIGURE 1

The two main themes in the clinical arena of prostate cancer are to predict biopsy outcome and to predict the prognosis and therapy need/ response.

"...A man becomes a patient when the decision to perform a biopsy has been taken..."



2.6 References

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Prostate Cancer Prevention

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3.1 Introduction

This report evaluates evidence regarding strategies for prevention of prostate cancer (PCa). We discuss the rationale behind prevention strategies in general and specifically related to PCa. We describe pharmacologic and non-pharmacological approaches, such as alterations in diet or physical activity patterns. We focus on findings from large Phase III randomized clinical trials that report PCa incidence as their primary outcome. We conclude with recommendations for clinical practice and research.

Prevention entails interventions (pharmacologic, dietary, lifestyle, etc.) given to large numbers of asymptomatic individuals with the goal of reducing future risk of disease incidence, morbidity, and mortality. The main dilemmas around cancer prevention relate to the fact that the intervention is applied to many asymptomatic individuals with the hope that some will benefit. However, even successful prevention strategies provide benefits to few and often require many years to accrue. Thus, a large number of individuals are placed at risk of unnecessary and potentially harmful and costly interventions. Studies to evaluate clinical benefits and harms must be large and long-term and assess benefits and harms that often include conditions for which the prevention strategy is not intended.

The number-needed to-treat (NNT) is a useful statistic for gaining perspective on a preventive intervention. NNT, which here refers to the number of people who need to be treated in order to prevent one case of PCa, is calculated as follows: NNT = 1/ARR; where: ARR (absolute risk reduction) = PCa incidence not treated – PCa incidence treated. Thus, if the incidence of PCa without treatment is 400 cases per 100,000 men per year (the approximate age-adjusted rate for white men in the U.S., age 54-65 years), and an agent has 25% efficacy for reduction in cancer incidence, a total of 1,000 men will have to receive the agent for one year in order to prevent one case. This is a much higher than typical threshold used to assess clinical importance for most treatments unless that intervention is extremely safe and low cost, considering that the primary outcome included to derive the above NNT is based on cancer incidence, not symptomatic disease or death. And, because the 10-year PCa survival of men with PSA-detected PCa, which comprise the vast majority of currently diagnosed PCas exceeds 90 % even without treatment, the NNT to prevent PCa mortality at 10 or even 20 years is obviously much greater.

Furthermore, clinical benefits observed in epidemiologic studies or findings from smaller biomarker trials may not translate into clinical benefits in large randomized trials. Thus, identifying potentially effective prevention strategies that will have a net benefit when considering all relevant clinical outcomes is difficult, time consuming, and costly. The difficulty in demonstrating net benefit from cancer prevention strategies is evidenced by the fact that no widely implemented prevention strategies exist for any cancer (other than interventions that promote healthy lifestyle and have broad-based positive health effects such as smoking cessation, achieving ideal body weight, exercise, etc.).

Cancer chemoprevention, one type of prevention strategy, has been defined as "the use of pharmacological agents to impede, arrest, or reverse carcinogenesis at its earliest stages". (1) Since prevention normally will be applied in large populations that are symptom-and cancer-free, preventive interventions are held to more stringent standards regarding safety and cost, than therapeutic interventions. Additionally, it is important to evaluate the impact of preventive strategies on common serious conditions outside their intended disease (especially heart disease and other cancers). Some preventive agents may have the most promise because of impacts on conditions other than PCa (e.g. aspirin, diet, or exercise to prevent heart disease).

Despite these concerns, PCa is potentially a good candidate for prevention since it is a relatively common cancer and a leading cause of cancer-related deaths. Widespread geographic and ethnic variation in incidence and mortality suggest potentially modifiable risks that might be amenable to prevention strategies. Moreover, the costs of screening and treatment — both in terms of financial costs and morbidity — are extremely high. And, because the vast majority of men with newly diagnosed PCa undergo treatment, and treatments have harms, reduction in incidence may be a clinically meaningful outcome because it is likely to translate into reduction in treatment-related morbidity and mortality. Therefore, reducing PCa incidence could translate into reduced disease specific morbidity and mortality. However, because PCa is slow growing and occurs in older men, the overall impact of this disease on life expectancy is less than with some other cancers.

3.2 Defining Target Populations for Prostate Cancer Prevention

Several strategies for identifying and targeting populations for PCa prevention exist. Prevention could be applied broadly (e.g. all adult men). However, because microscopic foci of PCa are apparent in many men beginning early in adult life — the percent roughly equals their age in years — the exact timing of PCa prevention is not well known and is likely dependent in part on tolerability and costs of interventions and their impact on other health conditions. Furthermore, the high frequency of microscopic PCa even in very young adults suggests that any "prevention" strategies may actually serve to reduce progression to clinically apparent disease rather than prevent de novo PCa. Because microscopic PCa is so common in adults and our likelihood of detecting cancer depends greatly on how hard we look, the concept of preventing detection of clinically relevant disease should be kept in mind as we discuss later the role of PSA testing and diagnostic thresholds used to detect PCa and their role in clinical trial designs and outcomes.

An alternative strategy is to target individuals at increased risk based on either modifiable (e.g. body composition, dietary, exercise habits) or nonmodifiable factors (age, race/ethnicity, family history). This risk-targeted approach offers the benefits of targeting those most likely to benefit while minimizing the costs and harms of prevention strategies. A targeted approach also improves feasibility in terms of study sample size and follow-up duration because the number of incident events will be higher among individuals at increased risk. Unfortunately, to date, no strong risk factors — besides age, family history, and African-American ancestry — have been consistently demonstrated in epidemiological studies. Furthermore, unlike lung cancer, where smoking is the major, readily identifiable and modifiable risk factor, the main risk factors are not modifiable and thus do not lend themselves to preventive strategies other than to assess risk status. Additionally, unlike colon or cervical cancer, PCa screening does not lead to low morbidity procedures that can prevent development of future

cancers by identifying and removing premalignant lesions, such as the removal of adenomatous polyps identified during colonoscopy for colon cancer screening or ablative or excisional therapy for high-grade precancerous cervical lesions (cervical intraepithelial neoplasia [CIN3]) found during PAP smear screening for cervical cancer.

However, epidemiologic studies suggest that certain modifiable risk factors may be present and becomes potential targets for modification. Migrant studies indicate environmental influences on PCa risk, and that these influences affect transition from latent microscopic disease to clinically significant cancer. (4) Additionally, a proportion of PCa incidence is attributable to genetic traits. This phenotype can be caused by not one, but at least several high-penetrance genetic mutations, and a potentially much larger set of low-penetrance genetic polymorphisms. (5) However, during the era of wide-spread PSA testing, increased diagnostic activity among men with a family history of PCa appears to contribute to their increased risk of PCa and to lead to detection bias in epidemiological and genetic studies of familial PCa. Thus, epidemiologic and genetic studies of hereditary predisposition to PCa are affected by this detection bias and likely inflate the estimates of familial PCa risk. (6) Genetic testing is not currently feasible in a clinical setting.

Clinicians and investigators do have one major tool in risk identification, namely the Prostate Specific Antigen (PSA) test. Similar to breast cancer risk prediction that uses readily available personal and family history to assess risk status, various PCa tools have been developed that incorporate PSA, age, race, family history of PCa, digital rectal examination (DRE) findings, and whether a prior prostate biopsy has been performed to assess the risk of PCa and the risk of high-grade PCa. (One such example is the PCa Prevention Trial PCa Risk Calculator [PCPTRC], available online at: http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp.)

Since the predictive value of an abnormal PSA on initial PSA testing is in the vicinity of 20-30%, a large number of men can be classified as increase-risk, but without evidence of PCa on biopsy and thus may be "at risk" candidates for prevention. It should be noted that despite negative prostate biopsies many men will still harbour PCa, which would be detected by subsequent or more extensive biopsies or removal and inspection of the whole prostate. Thus, these individuals are more likely accurately classified as "no evidence of disease" by the diagnostic criteria used. A small proportion of these men will have a high-grade prostatic intraepithelial neoplasia (HGPIN) as a histological finding, which could be a further indication of elevated risk. Although this illustrates a collaborative relationship between secondary prevention (screening) and primary prevention, these strategies for reducing PCa morbidity and mortality are competitive. Hypothetically, for example, a safe and perfectly effective chemopreventive agent that could be given to men at low- or high-risk would eliminate the need for screening. More realistically, if primary prevention tools become available, it will be necessary to design population approaches that effectively integrate these tools with screening efforts.

Another target population for preventive agents and interventions are men with localized and presumably indolent PCa, i.e., secondary prevention. This group of men is becoming increasingly common as more men undergo PSA screening, where lower thresholds to define abnormality are employed and more core biopsies specimens are obtained. The research community is attempting to develop techniques to discriminate these patients whose numbers have increased in conjunction with PSA testing from those with more aggressive tumours who therefore might benefit from

aggressive treatment. These patients and their physicians may accept widespread implementation of low-risk early interventions that effectively inhibit the growth and progression of early tumours to symptomatic disease. Such an approach may make more clinical sense as many adult men have histologic evidence of PCa even at a fairly young age. Thus, agents may be viewed not as true "preventive strategies" but actually growth inhibitory.

3.3 Defining Outcomes of Interest

The primary outcome of greatest importance in prevention studies is all-cause mortality. Does a prevention strategy increase length of life? The outcome is clear and unambiguous. However, because PCa results in only about 2-3% of all-deaths in men, identifying an impact due to prevention on all-cause mortality would require very large and long-term studies. Such studies are not feasible, though targeting higher PCa risk groups may make demonstrating changes on all-cause mortality possible. Reduction in PCa mortality is likely the next most important outcome as men (and their loved ones) place a great value on preventing death from PCa. However, ascertaining cause-specific death, especially PCa, is difficult, subject to ascertainment bias and may be unreliable even in randomized trials using rigorous blinded end-point adjudication committees. Other PCa specific outcomes could include stage of disease and development of metastatic disease. Additional outcomes could include PCa progression and intermediate (surrogate) markers such as PSA levels or rate of change and histological changes in detected cancers. Because preventive agents are given to many asymptomatic individuals and only benefit very few, major patient centered outcomes should include adverse effects, tolerability, and adherence.

The principal outcome in cancer prevention trials has been cancer incidence. Investigators have argued that a reduction in PCa incidence is sufficiently important to warrant clinical decision making regarding cancer prevention strategies. This is based, in part, on the rationale that a reduction in PCa incidence will be associated with future mortality reduction even if there is no reduction in mortality. However, PCa (like many diseases) is a heterogeneous condition. A preventive agent may have an impact on indolent tumours while promoting more aggressive disease. Therefore, in the absence of demonstrating a beneficial effect on all-cause or PCa mortality, studies should be sufficiently designed and powered to assess the impact of prevention on PCa incidence according to histologic categories. Reported outcomes should include the number of men with low-, intermediate-, and high-grade (Gleason 8-10) PCas, and the method of detection: PSA testing; DRE; for-cause or due to study-indicated prostate biopsy. Furthermore, because the natural history of men with PSA detected (and likely study-directed biopsy) cancers is much more favourable than patients with palpable disease or those detected for-cause, the impact on PCa morbidity and mortality is likely to be much smaller and require many more years to appear than observed for incidence. Therefore, a major rationale for using PCa incidence as a main outcome in prevention trials and by clinicians and policymakers implementing the results of these studies is that a reduction in PCa will result in fewer men undergoing treatment and associated harms. This is a relatively atypical rationale for initiating an intervention and suggests that any strategy that reduces the incidence of clinically insignificant PCa and decreases the associated harms related to overdiagnosis and overtreatment would be valuable and should be considered as prevention.
3.4 Findings from Randomized Controlled Trials

Three randomized controlled trials have specifically assessed the role of chemopreventive agents on the incidence of PCa. All have used PCa incidence as their primary outcome. Two mandated study biopsies (both assessing 5-alpha-reductase inhibitors [5ARIs]) to assess for PCa and used cancers detected on study biopsy as a main component of their primary outcome. Two evaluated 5ARIs (finasteride-PCPT and dutasteride-REDUCE), and one assessed selenium and Vitamin E, alone or in combination. The specific design and findings from these trials are reported in intervention-specific sections below. These three studies enrolled a total of approximately 60,000 men, followed for many years, and at study costs exceeding 200 million U.S. dollars. Despite the encouraging findings from preliminary studies that led to the initiation of these trials and the enormous effort and costs involved no clinically useful PCa preventive agents have been identified.

In summary, the findings from the two 5ARI studies indicate that 5ARI reduce the risk of being diagnosed with PCa among men who are screened regularly for PCa, many of whom undergo study directed prostate biopsies (**Figure 1**).

¹ PCa Prevention Trial

² REduction by DUtasteride of PCa Events

³ Selenium and Vitamin E Cancer Prevention Trial

FIGURE 1

5ARI for PCa Prevention According to Type of 5ARI, Study Duration and PCA risk (Average vs. Increased).

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1.9 BPH progression: Surgical interventions for treatment



It was found that 5ARI increased sexual and erectile dysfunction but improved bothersome lower urinary tract symptoms and reduced the need for surgical interventions for lower urinary tract symptoms and the incidence of acute urinary retention. Information was inadequate to assess the effect of 5ARI on PCa or all-cause mortality. Additionally, concern persists that they may increase the risk of high-grade (Gleason 8-10) tumours. Despite the large size and long duration of these studies few deaths occurred, highlighting the difficulty in designing and carrying out prevention trials with mortality as an outcome. Cost-effectiveness analyses of both the PCPT and REDUCE studies indicated that these agents are unlikely to be cost-effective when considering their impact on survival differences. They may be cost effective in high-risk populations assessing quality of life. (7,8) The U.S. Food and Drug Administration (FDA) recently denied a request for approval of these drugs for PCa prevention citing the failure to demonstrate a reduction on PCa mortality and an increase in high grade PCas and sexual adverse effects in patients randomized to 5ARI.

The SELECT study was a randomized, double-blind, placebo-controlled trial designed to test the efficacy of selenium (200 µg) and Vitamin E (400 mg) alone, and in combination for preventing PCa. This trial enrolled 32,400 men who were over age 55 (> age 50 for African-Americans), and had a normal DRE and PSA (\leq 4 ng/ml). (30) SELECT was terminated prior to the original follow-up date because interim analysis identified no possibility of a benefit with additional patient follow-up. Specifically, the authors found that selenium or Vitamin E, alone or in combination at the doses and formulations used, did not prevent PCa (there was a nonsignificant increased risk of PCa in the Vitamin E group: p=0.06, and Type 2 Diabetes in the selenium group). Recently updated findings with an additional 54,464 person-years of follow-up confirm that selenium did not reduce the risk of PCa alone or in combination with Vitamin E. Importantly, dietary supplementation with Vitamin E significantly increased the risk of PCa among healthy men (HR 1.17; 99% CI: 1.004-1.36; p=0.008).

Additional information comes from randomized trials of drugs evaluated for other indications but where PCa incidence or mortality was reported. Most have shown no reduction in PCa incidence but many have not been sufficiently sized to assess PCa outcomes. We discuss results from some of the larger trials or pooled findings.

Jiang and colleagues conducted a meta-analysis of randomized trials of antioxidant vitamins and selenium supplements published through January 2009 (Figure 2). (9) They found no significant effects of supplementation with beta-carotene, Vitamin C, Vitamin E, and selenium versus placebo on PCa incidence or mortality. In three randomized trials involving nearly 61,000 men, no reduction in PCa incidence occurred among men randomized to receive beta-carotene versus placebo. Similarly, in two studies involving 44,000 men, Vitamin C did not reduce PCa incidence (Jiang). (1) Figueiredo noted a 2.6 fold increase in the 10.8-year incidence of PCa among men assigned to folate (9.7%) compared to placebo (3.3%). (2) Bonovas assessed statin use and the risk of PCa. Among six randomized trials involving 40,178 men and followed for 7.4 years, there was no significant effect on PCa incidence (RR = 1.06; 95% CI: 0.93-1.20). (3) However, the included studies used lower potency statins than are currently available and thus additional research that includes these drugs would be of value. (4) Finally, Rothwell and colleagues conducted an individual patient data meta-analysis from randomized trials to assess the effect of daily aspirin on long-term risk of death due to cancer. (Figure 3) (5) Daily aspirin reduced deaths due to several cancers (especially gastrointestinal cancers). At 20 years aspirin reduced the risk of PCa mortality by 19% though findings were not statistically significant (p=0.12). The absolute effect at 15 years was less than 1%. While not specifically assessing cancer prevention the role of aspirin for reducing the incidence of other cancers has been previously demonstrated. Additionally, aspirin is recommended in higher risk individuals to prevent coronary heart disease events. The magnitude of potential benefit of aspirin for PCa incidence and mortality prevention appears to be small but may have marginal impact on clinical utilization. The results highlight the fact that to be an effective PCa preventive agent, the intervention must be well tolerated, low cost, and have positive impact on other health conditions.

FIGURE 2

Intervention effect of different antioxidant supplements versus placebo on incidence of PCa. From Jiang L, Yang K-h, Tian J-h, et al. Nutrition and Cancer. 2010;62:719-727.

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Study or Subgroup	Antioxic Events	lants Total	Placel Events	bo Total	Weight	Risk Ratio M-H, Random, 95%Cl	Risk Ratio M-H, Random, 95%Cl
2.1.1 beta-carotene							
ATBC 1994	80	7282	57	7287	9.4%	1.19 [0.87, 1.65]	<u></u>
Hennekens CH 1996	520	11036	527	11035	44.3%	0.99 [0.88, 1.11]	
Kirsh VA 2006 Subtotal (95% CI)	537	12203	601	12813	40.3%	0.94 [0.84, 1.05]	
Total events	1137	30521	1195	31135	100.0 /0	0.37 [0.30, 1.03]	1
Heterogeneity: $Tau^2 = 0.0$	00; Chi ² = 2	2.00 df =	= 2 (P = 0.	37); P =	0%		
Test for overall effect: Z	= 0.65 (P =	0.51)					
2.1.2 Vitamin C							
Gaziano JM 2009	508	7329	500	7312	46.5%	1.01 [0.90, 1.14]	- -
Kirsh VA 2008 Subtotal (95% CI)	672	15080 22400	666	14281 21502	53.5%		
Total events	1180	22403	1166	21555	100.0 /0	0.30 [0.31, 1.00]	T
Heterogeneity: Tau ² = 0.0	00; Chi ² = (0.53, df -	= 1 (P = 0	47); P =	0%		
Test for overall effect Z =	= 0.49 (P =	0.82)					
2.13 Vitamin E							
ATBC 1994	43	7286	67	7287	4.4%	0.64 [0.44, 0.94]	
Gaziano BIM 2009 Kirch VA 2009	493	/315	515	/326	28.1%	0.96 [0.85, 1.08]	
Lippman 6M 2008	200 472	8737	075 416	14206 8696	32.4% 25.7%	0.92 [0.83, 1.02] 1 13 [1 00 1 29]	
Lonn E 2005	116	4761	119	4780	9.3%	0.98 [0.76, 1.26]	_
Subtotal (95% CI)		43254		42295	100.0%	0.96 [0.85, 1.08]	•
Total events	1788		1792				
Heterogeneity: Tau ² = 0.0 Test of overall effect: Z =	01; Chi² = 0.65 (P =	11.02, di 0.51)	f = 4 (P =	0.03); l ² :	= 64%		
2.1.4 Selenium							
Duffield-Lillico AJ 2003	22	621	42	629	9.5%	0.53 [0.32, 0.88] —	
Lippman BM 2009	432	8752	416	8698	90.5%	1.03 [0.91, 1.18]	
Subtotal (95% CI)		9373		9327	100.0%	0.78 [0.41, 1.48]	
Total events	454	0.00 10	458		0.40/		
Test of overall effect: Z =	$19; Chl^2 = 0$ = 0.77 (P =	o 28, at : 0 44)	= I (P = 0	.01); p =	84%		
2.1.5 Vitamin E+ Seleniu	ım						
Lippman BM 2009	437	8703	417	8696	100.0%	1.05 [0.92, 1.18]	
Subtotal (95% CI)		8703		8696	100.0%	1.05 [0.92, 1.19]	•
Total events	437		417				
Test of overall effect: Z =	0.69 (P =	0.49)					
2.1.6 vitamin C, a-tocool	herol, Pca	arotene.	selenium	n and zir	ic		
Meyer F 2005	49	2522	54	2512	100.0%	0.90 [0.62, 1.33]	
Subtotal (95% CI)		2522		2512	100.0%	0.90 [0.62, 1.33]	
Total events	49		54				
Test of overall effect: 7 -	0 52 /P -	0 80)					
lest of overall effect. Z =	0.52 (1 =	0.00/					
2.1.7 a-tocopherol and P	-carotene	7007	67	7007	100 0%	0.94 [0.50, 1.10]	
Subtotal (95% CI)	00	7287	0/	7287	100.0%	0.84 [0.59, 1.19]	
Total events	56	1201	67	/20/	10010 /0		
Heterogeneity: Not appl	icable						
Test of overall effect: Z = 0.99 (P = 0.32)							
2.1.8 Pcarotene and ret	inyl palmi	tate					
CARET 2005	469	9420	432	8894	100.0%	1.03 [0.90, 1.16]	*
Suptotal (95% CI)	460	9420	122	8894	100.0%	1.03 [0.90, 1.16]	—
Heterogeneity: Not appli	409 icable		432				
Test of overall effect: Z =	= 0,38 (p =	0.70)					
		/					· · · · · ·
							0.5 0.7 1 1.5 2
						Favo	ours experimental Favours control

FIGURE 3

Effect of allocation to aspirin versus control on the 20-year risk of death due to the most common fatal cancers in 10,502 patients with scheduled treatment duration of 5 years or longer in the three trials with long-term follow-up. The eight most common cancer types are shown. (5).

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3.5 5-alpha Reductase Inhibitors

By the early 1990s, a considerable body of evidence was available to indicate that inhibition of 5ARI, which convert testosterone to the more potent androgen dihydrotestosterone (DHT) in the prostate and other organs such as liver and skin, was a possible means for chemoprevention of PCa. This evidence included studies of kindreds with a rare, inherited deficiency of Type II 5α –reductase, (6) pre-clinical studies, (7) and results of clinical trials evaluating the safety and efficacy of the Type II inhibitor finasteride as a treatment for BPH.

Two large randomized trials have been conducted specifically to assess the effect of 5ARI on the period prevalence of PCa. In 2003, the results of the PCPT were reported, marking the completion of the first full-scale Phase III trial for prevention of PCa. (8) The PCPT compared PCa occurrence among 18,882 men randomly assigned to either finasteride (5 mg/day) or placebo for seven years. At baseline, participants were age 55 years or older, and had a normal DRE and PSA \leq 3 ng/ml. Serum PSA and DRE were performed annually and after seven years of follow-up, remaining participants were asked to undergo an end-of-study (EOS) biopsy. The primary endpoint of the trial was the period prevalence of PCa, combining cancers diagnosed while on study and those discovered at the EOS biopsy. The overall prevalence of PCa was 24.8% lower in the finasteride group compared to placebo (95% CI: 18.6-30.4%). However, the prevalence of high-grade cancer was 25.5% higher in the finasteride group: 6.4% vs. 5.1% (p=0.005). The risk reduction for total PCa did not vary significantly by age, race, family history, or baseline PSA.

In contrast to PCPT, the dutasteride trial (REDUCE) enrolled 6,729 men considered at increased risk for PCa based primarily on age and PSA values. (2) Men were eligible if they were aged 50 to 75 years, had a PSA level of 2.5-10 ng/mL (for men aged 50-60 years) or 3.0-10 ng/mL (for men older than 60 years of age), and had a previous suspicion for PCa leading to a prostate biopsy within six months of study enrollment. Participants received biopsies, regardless of PSA, after two and four years of follow-up. Findings from the REDUCE trial indicated that dutasteride reduced the risk of incident PCa detected by biopsy by 23% (RR 0.77, 95% CI: 0.70-0.85); absolute reduction (16.1% vs. 20.8%) among men authors considered at greater risk for PCa (based on age, elevated PSA level, and having a previous suspicion of PCa leading to a prostate biopsy). Reductions were observed across age, family history of PCa, PSA level, and prostate volume subgroups. There were no differences between dutasteride and placebo in the number of men with Gleason score 7-10 tumours (p= 0.88). The authors concluded that 5ARI reduced the risk of being diagnosed with PCa among men who are screened regularly for PCa. Information was inadequate to assess the effect of 5ARI on PCa or all-cause mortality. It was noted that 5ARI increased sexual and erectile dysfunction. Similar to the PCPT, dutasteride improved outcomes related to BPH.

A recent meta-analysis evaluated randomized trials of 5ARI that provided PCa outcome published through June 2010 and lasting at least one year in duration (165). The authors estimated the benefits and harms of 5ARI in preventing PCa. Their primary outcome was PCa period-prevalence "for-cause". The authors identified eight studies that met the inclusion criteria but only the PCPT and the REDUCE study were designed primarily to assess the impact of 5ARI on PCa period-prevalence. None of the studies were designed to assess the impact of 5ARI on mortality.

The mean age of enrollees in all studies was 64 years, 92% were white, and the mean PSA was 3.1 ng/ mL. For-cause PCas comprised 54% of all cancers detected in placebo-controlled studies. Compared to placebo, 5ARI resulted in a 25% relative risk reduction in PCas detected for-cause (RR 0.75, 95% CI: 0.67-0.83), whereas, absolute risk reduction equaled 1.4% (3.5% vs. 4.9%). One BPH trial found the risk of PCas detected for-cause was significantly reduced with dutasteride and combined dutasteride plus tamsulosin compared to tamsulosin monotherapy. All-cause as well as PCa specific mortality was low (5.6% and 0.05% respectively). There were no differences in all-cause or PCa mortality between finasteride and placebo in any trial (relative risk all-cause mortality = 1.05 [95% CI: 0.94-1.18]). Six trials versus placebo assessed PCas detected overall. There was a 26% relative risk reduction favouring 5ARI (RR: 0.74, 95% CI: 0.55-1.00; 2.9% absolute reduction [6.3% vs. 9.2%]). Reductions were observed across categories of age, race, and family history of PCa, but not among men with baseline PSA > 4.0 ng/mL. Improvements were noted in outcomes related to BPH including symptom progression, risk of acute urinary retention, and need for surgical intervention.

Subsequent to that meta-analysis, the U.S. FDA reviewed data submitted by the manufacturers seeking a specific indication to use 5ARI for chemoprevention. Based on the presented findings the FDA did not approve finasteride and dutasteride for the prevention of PCa, concluding that the drugs do not possess a favourable risk-benefit profile for this indication. The FDA cited associated side effects, including loss of libido and erectile dysfunction, but most importantly, it noted that in both trials there was an absolute increase in the incidence of high-grade PCas in men randomized to finasteride or dutasteride, compared with controls. (21) The FDA was concerned that the greater absolute reduction in low risk and potentially clinically insignificant PCas due to 5ARI would be offset by an increase in potentially high-risk disease. Additional research would be useful to better understand the association of these drugs with the development of high-grade prostatic lesions, in order to determine the impact of 5ARI (or other potential preventive agents) on PCa mortality, and to identify the population of men that might benefit most from PCa prevention.

The excess of high-grade cancer detected in the 5ARI arms of these trials has generated considerable debate. The hypothesis that finasteride or dutasteride selectively promotes the growth of aggressive cancers has some plausibility; intraprostatic androgen suppression could provide a competitive advantage to clones that have acquired androgen-independent growth mechanisms. Some investigators have postulated that serum androgen deficiency increases risk of developing aggressive PCa, (9) and the pro-differentiating effect of androgens in the prostate under certain conditions is well established. (10) On the other hand, there are at least three possible explanations for the observation of excess high-grade cancer in PCPT that do not involve a pejorative effect of finasteride. First, it is possible that finasteride (and dutasteride) has effects on the cellular features and architecture of PCa that mimic or exaggerate the appearance of higher grade disease. (11) Second, finasteride reduced overall prostate gland volume by about 25%, based on ultrasound measurements obtained during the EOS biopsies. This means that finasteride-treated glands were more intensively sampled during blind biopsy compared to placebo, and that any given tumour had a higher probability of being detected. Since tumours received the highest Gleason score observed by the pathologist regardless of its prevalence in the biopsy sample, increased detection of high-grade tumours in the finasteride group should be expected. The apparent difference in the drug's effect on high- vs. low-grade tumours would be exacerbated if finasteride shrinks the volume of low-grade cancers more than the

high-grade ones. Third, the excess of high-grade cancer in the finasteride group was strongest in the first two years of follow-up. If finasteride promoted growth of aggressive cancers, we would expect a gradual increase in the number of excess high-grade cancers as follow-up continued.

The notable excess of high-grade disease early in follow-up suggests that in some men who had aggressive tumours that were present at baseline, finasteride decreased their serum PSA by substantially less than 50%, which in turn made them cross the PSA threshold of 4.0 as soon as their PSA was adjusted upward according to study protocol. In effect, these high-grade cancers could have been unmasked by "finasteride challenge". (12) A second controversy stemming from the PCPT concerns the clinical significance of the cancers prevented by finasteride in the trial. There were 387 fewer Gleason 2-6 tumours in the finasteride group, and 43 more Gleason 7-10 tumours. However, only 3.8% of all cancers detected in PCPT were Gleason 2-4; Gleason 6 cancers were the majority of those detected in both finasteride and placebo groups. The finasteride group had fewer Gleason 6 tumours both during follow-up and at EOS. Since most men with Gleason 6 cancers opt to undergo curative treatment, it can be argued that finasteride spares these men the cost and morbidity of such treatment. Although the prognosis for treated Gleason 6 cancers is generally quite good, an important subset of these patients will later develop recurrence and metastasis. Despite this information, the failure of the FDA to approve these drugs for PCa prevention and the specific warning label now required for these agents regarding the possibility of inducing higher grade cancers will severely limit their use, especially in the United States.

3.6 Anti-inflammatory Agents

There is strong evidence that inflammation plays a pathogenetic role in approximately 20% of all human cancers. (1) It is assumed to incite carcinogenesis by causing cell and genome damage, promoting cellular turnover, and creating a tissue micro-environment that can enhance cell replication, angiogenesis, and tissue repair. (2) Non-steroidal anti-inflammatory drugs (NSAIDs) can prevent the development of colon cancer (3), and possibly other cancers. (4) Proposed mechanisms for these effects, including induction of apoptosis and inhibition of cellular proliferation and angiogenesis, occur at least partly through the inhibition of the cyclooxygenase (COX) enzymes involved in prostaglandin synthesis.

3.6.1 Inflammation and prostate cancer

There is emerging evidence that inflammation is crucial for the aetiology of PCa. This evidence stems from molecular pathological, animal, histopathological, and epidemiological studies. (5,6) Proliferative inflammatory atrophy (PIA) delineates proliferative glandular epithelium with the morphological appearance of simple atrophy. (7) Areas of PIA show infiltration with CD3-positive T-lymphocytes and macrophages and are predominantly located in the peripheral zone of the prostate and adjacent to prostatic carcinoma. It has been postulated that PIA is a precursor of high grade prostatic intraepithelial neoplasia (PIN) and cancer. (8) Eicosanoids such as prostaglandins and other related compounds have been implicated in the inflammation process. The synthesis of prostaglandins and their metabolism in the prostate by a series of enzymatic reactions involving COX is

well recognized. (9) Three COX isoforms have been identified: the constitutively expressed COX-1, a housekeeping gene that has an important role in protecting the gastroduodenal mucosa, and the inducible COX-2 gene, an immediate early response gene that is rapidly induced in response to tumour promoters, cytokines and growth factors. (10) However, a functional role for COX-3 remains to be determined.

The role of prostaglandins in the development of PCa has been substantiated from several experimental studies in both human and animal models. The prostate has the highest level of COX-2 mRNA among human tissues. (11) Additionally, it was suggested that prostaglandins play a major role in the growth of PCa cells through the activation of COX-2 expression. (12) There is also evidence showing that COX-2 is over-expressed in PCa and that tumour grade is positively correlated to COX-2 levels. (13) Cumulatively, these findings suggest that inhibition of COX-2 may lead not only to inhibition of metastasis but also to inhibition of prostate carcinogenesis.

3.6.2 Non-steroidal anti-inflammatory drugs

NSAIDs are drugs with analgesic, antipyretic and – in higher doses – anti-inflammatory effects. The term "non-steroidal" is used to distinguish these drugs from steroids, specifically, glucocorticoids, which have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs can be classified based on their chemical structure or mechanism of action (Table 1).

Group	Examples
Salicylates	Aspirin (acetylsalicylic acid), Diflunisal, Salsalate
Propionic acid derivatives	Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Oxaprozin
Arylacetic acids	Diclofenac, Indomethacin, Sulindac, Etodolac
Enolic acid derivatives (Oxicam)	Piroxicam, Meloxicam
Fenamic acid derivatives (Fenamates)	Mefenamic acid, Flufenamic acid, Meclofenamic acid
Selective COX-2 inhibitors (Coxibs)	Celecoxib, Rofecoxib, Valdecoxib

TABLE 1. Classification of Non-steroidal Anti-inflammatory Drugs (NSAIDs)

x withdrawn from market

NSAIDs within a group will tend to have similar characteristics and tolerability. There is little difference in clinical efficacy among the NSAIDs when used at equivalent doses. However, there is a varying ability of specific NSAIDs to inhibit COX-1 and COX-2. Aspirin (acetylsalicylic acid) is a relatively selective inhibitor of COX-1 and is also used for the management of arterial thrombosis and prevention of adverse cardiovascular events by inhibiting the action of thromboxane A2.

The mechanism of action that defines the role of NSAIDs as potent agents for the chemoprevention of PCa is not clear. However, there is evidence that the inhibition of the biosynthesis of prostaglandins increases the susceptibility of cancer cells to apoptosis by down regulating the antiapoptotic protein Bcl-2. Selective inhibitors of COX-2 isoform have attracted considerable attention because of

their ability to selectively inhibit the inducible COX-2 isoform while allowing COX-1 to perform its "housekeeping" functions. By significantly reducing gastrointestinal side effects, these NSAIDs may have additional promise as chemopreventive agents. (14)

Celecoxib has been demonstrated to be effective in reducing colorectal cancer in patients with familial adenomatosis syndromes. (15) Development of selective COX-2 inhibitors as chemopreventive agents was effectively halted when the APPROVe trial, designed to test the efficacy of rofecoxib (Vioxx) for prevention of recurrent colorectal polyps, revealed that the rofecoxib group had a significant two-fold increase in serious cardiovascular events, an effect that emerged after 18 months of follow-up. (16)

3.7 Epidemiological and clinical studies

So far, there have been no published randomized trials for NSAID and PCa. The ViP trial, which was building towards enrolment of 15,000 men with borderline PSA elevation to test rofecoxib for prevention of PCa, was cancelled in September 2004 due to withdrawal of the drug (see above) (17). This again highlights the difficulty in assessing the effectiveness of a preventive agent if focused solely on its impact on PCa incidence. Two recent meta-analyses have included available data up to spring of 2008 (Table 2).

First author, year	Analyzed Studies (n)	Included Patients (n)	Odds Ratio (95% CI)	
			Aspirin	NA-NSAID
Jafari S, 2009 (18)	20	25,768	0.95 (0.91 – 1.00)	0.92 (0.85 – 1.00)
Mahmud SM, 2010 (19)	24	24,230	0.83 (0.77 – 0.89)	0.90 (0.80 - 1.01)

TABLE 2. Non-steroidal anti-inflammatory drugs (NSAIDs) and risk of PCa: results from recent meta-analysis

CI=confidence interval, NA=non-aspirin

Jafari and colleagues identified 20 eligible observational studies, of which seven were case-control, seven cohort, five nested case-control, and one cross-sectional. (18) Sixteen studies reported the effect of aspirin exposure with a pooled OR of 0.95 (95% CI: 0.91-1.00). Thirteen studies reported the effect of non-aspirin NSAIDs with a pooled OR of 0.92 (95% CI: 0.85-1.00). Pooled OR for PCa in patients exposed to all NSAIDs was 0.92 (95% CI: 0.86-0.97). Potential pitfalls with regard to methodology (publication, recall, screening, protopathic, referral biases) are discussed in Chapter 1. In most studies, use of NSAIDs was categorized as frequent, ever used, or never used, and the exact nature and duration of drug use was largely unknown. Therefore, a clinically meaningful recommendation about the optimal duration and dose is evasive.

Mahmud *et al.* included 10 case-control and 14 cohort studies in their meta-analysis. (19) Most studies measured exposure to more than one NSAID. Eighteen trials looked at aspirin alone and found a pooled OR of 0.83 (95% CI: 0.77-0.89). Eight studies reported on non-aspirin NSAID with a pooled OR of 0.90 (95% CI: 0.80-1.01).

In conclusion, the epidemiologic evidence for a protective effect of NSAID use against PCa is suggestive but not conclusive. Studies are limited by inadequate information on dose and duration of use and by methodological biases. Most studies also lack the statistical power to assess the effects of the less commonly used NSAID. Lastly, potential benefits of NSAID use should be weighed against known side effects of their long term use, especially because they would be used in older men who are at greater risk for gastrointestinal and renal adverse effects.

3.8 **Diet and Dietary Supplements**

Because of the large variation in PCa worldwide and migration studies showing that PCa rates increase in men who immigrate to the United States, dietary and environmental factors may play a role. Data on diet-related factors such as obesity show an association with PCa and overall outcomes. In particular, diets that were low in fat and animal products and those higher in soy or lycopenes and beta-carotenes, (found primarily in watermelon and tomatoes), appear to be associated with lower PCa incidence. As noted previously, pooled analysis of randomized trials have not shown a benefit on PCa incidence for either Vitamin C or beta-carotene. Van Patten and colleagues evaluated the literature on trials for the prevention of PCa recurrence. They identified a limited number of randomized trials in which diet and dietary supplements were used. Most assessed fortified margarine, phytoestrogen rich diets, plant based diet, lycopenes, and phytoestrogens. Results varied. Most used surrogate markers such as PSA doubling time to assess disease progression.

3.8.1 Soy (including isoflavones)

The low incidence of PCa in Asia compared to Western countries is well known. (1) Moreover, Japanese migrants to Hawaii have higher incidence of PCa. (2).

Thus, environmental factors, especially dietary style, may be related to the risk of PCa. Fat and calcium have also been reported to be risk factors for PCa. Conversely, lycopene, selenium, soy isoflavone, and Vitamin E were reported to be preventive factors. (3,4) However, the SELECT study, (5), a recent large-scale, double-blind study, was unable to demonstrate a preventive effect for selenium or Vitamin E on PCa and in fact demonstrated higher PCa incidence in men receiving Vitamin E.

In 1993, Adlercreutz *et al.* (6) reported that a soy diet was associated with a reduced risk of PCa, breast cancer, and cardiovascular diseases in the comparative study between Japanese and Swedish. Since then, the role of soy in reducing PCa risk has been considered. Hebert JR, *et al.*[7) reported a relation between amount of soy food consumption and PCa mortality. In the 42 countries, soy products were found to be protective (p=0.0001), with an effect size per kilocalorie at least four times as large as that of any other dietary factor.

A meta-analysis done by Yan and Spitznagel (8) demonstrated an association of soy food intake and PCa risk reduction. Included studies were two cohort studies and six case control studies .

Soy intake was associated with a 5-70% relative risk reduction in PCa incidence. The bioactive factors of soy are believed to be due to isoflavones, particularly daidzein, genistein, and equol. These agents have phyto-estrogenic and anti-oxidant effects, and especially, equol has an anti-androgenic action. (9)

A case-control study of the serum isoflavone levels in patients with PCa and healthy volunteers (10) found that some individuals were able to degrade daidzein into equol (equol producers), whereas others were not (non-producers). Akaza *et al.* found that the percentage of equol producers in patients with PCa was significantly lower than in the healthy controls (30.3% vs. 49.5%; p=0.013). (11) Those results suggest that equol or equol-producing ability may be deeply involved in PCa risk reduction.

Recently reported preliminary results from a pilot randomized trial of 158 Japanese men with a negative prostate biopsy suggest that oral isoflavone (60 mg/day) for 12 months may reduce PCa incidence (11).

Fujimoto *et al.* (12), conducted an age-stratified dietary survey of soybean food consumption and measured the serum isoflavone levels in healthy Japanese and Korean men. Significant differences in the daily intake of genistein and daidzein were found between the teenage group and the age group of \geq 30 years (p<0.05). In the Japanese cohort, the proportion of equol producers in the teenage group was only 10%, which was significantly the lowest among all age-strata. Decreased intake of isoflavones, a low serum level of equol, and the low incidence of equol production in the young generation may lead to an increase in the PCa incidence in Japan and Korea. While no Phase III randomized trials of soy for PCa prevention have been conducted, this remains an area for future study as the positive health effects of soy based diets across a wide range of conditions makes these potentially attractive.

Elucidating the mechanism of equol production may help in developing strategies for chemoprevention of PCa. Recently, the mechanism of biodegradation of daidzein into equol has been clarified by discovering a human intestinal bacteria. (13) It is important to investigate the potential of clinical intervention by changing equol non-producers to producers, as well as by ingesting equol-containing supplements.

3.9 Exercise and PCa Prevention

Exercise and maintaining ideal body weight has broad benefits for health including reducing heart disease risk, high blood pressure, obesity, and many other diseases. The thought of exercise being useful for preventing cancer is appealing. Interest in physical activity as a means for the primary prevention of cancer is increasing as the evidence for a protective effect is accumulating.

Cancer treatment, surgery, chemotherapy, immunotherapy, radiotherapy, and hormone deprivation have deleterious effects in otherwise healthy patients. It would seem logical that patients with better physical condition or who improve their physical condition with exercise would recover faster from any cancer therapy, tolerate it better, and overcome the side effects of any therapy easier.

Friedenreich, C. M in 2001 (1) analyzed the evidence for an etiological role of physical activity in the prevention of cancer of the colon, breast, prostate, testes, lung, endometrium, and ovary. The evidence for a causal association between physical activity and colon and breast cancers was found to be "convincing," for PCa to be "probable," for lung and endometrial cancers to be "possible," and for testicular and ovarian cancers to be "insufficient" (Table 3).

In that review, 15 of 30 studies found a reduction in PCa risk in men who were most physically active, with risk reductions averaging 10–30%. Two other studies found decreased risk only in subgroups of the population. No associations were found in nine studies, and increased risk was found in four studies.

Cancer Site	Consistency of Evidence for a Risk Reduction with Increased Physical Activity Levels		Strength of Risk Association		Dose- Response	Temporality (time period in life associated with risk reduction)	Biological Plausibility	Overall Level of Scientific Evidence	
	Cohort studies	Case- control studies	Total studies	Range of risk estimates	Average risk reduction				
Colon	15 of 20	23 of 26	39 of 46	0.3 to 1.0	40-50%	23 of 29	Activity throughout life?	Yes-several hypotheses	Convincing
Breast	8 of 14	16 of 22	24 of 36	0.3 to 1.6	30-40%	15 of 23	Early life? Adult life?	Yes-several hypotheses	Convincing
Prostate	10 of 16	5 of 10	15 of 26	0.5 to 2.2	10-30%	9 of 19	Early life ?	Yes-some hypotheses	Probable
Lung	6 of 6	0 of 2	6 of 8	0.4 to 1.3	30-40%	4 of 6	Unknown	Unclear	Possible
Endometrial	3 of 4	5 of 7	8 of 11	0.1 to 1.0	30-40%	4 of 7	Unknown	Yes-a few hypotheses	Possible
Testicular	0 of 2	3 of 6	3 of 8	0.5 to 3.3	20%	3 of 5	Unknown	Unclear	Insufficient
Ovarian	1 of 3	1 of 2	2 of 5	0.3 to 2.1	0%	2 of 3	Unknown	Yes-a few hypotheses	Insufficient

TABLE 3. Summary of Epidemiological Evidence on the Association between Physical Activity and Cancer by Criteria for Causality (1)

Furthermore, because negative studies are less likely to be published than positive studies (publication bias) it is possible that studies that failed to find an association were not published.

Liu *et al.* (2), in a literature review and meta-analysis, identified English-language articles through May 2011 that examined the effect of physical activity on PCa risk. This meta-analysis was conducted according to the guidelines for the meta-analysis of observational studies in epidemiology. (3) They included 43 studies that met the following criteria: (1) cohort or case-control studies addressing the association between physical activity and PCa risk; (2) studies that reported the effect estimates, such as relative risk (RR), hazard ratio (HR), and odds ratio (OR), with 95% confidence intervals (CIs) or that provided sufficient information to calculate these values; and (3) when multiple reports were published from the same population, the most recent or complete publications were included. The 19 prospective studies included 2,076,535 participants, with follow-up periods ranging from 2 to 26 years and 74,942 PCa cases. The 24 case-control studies included 13,352 cases and 33,957 controls, totaling 88,294 PCa cases. Fifteen and seven studies were categorized as high-quality studies. The pooled relative risk (RR) estimates for total, occupational, and recreational physical activity by study design are summarized in **Figure 4**.

FIGURE 4	Subgroups (Number of studies	Pooled RR (95% CI)	Р	I² (%)					
The Pooled Relative	ТРА								
Risk Estimates for	Cohort studies (24)	-	0.94 (0.91-0.98)	0.002	4.06				
Recreational Physical Activity	Case-Control studies (34)		0.86 (0.75-0.97)	0.02	69.82				
by Study Design (2).	Subtotal (58)	-	0.90 (0.84-0.95)	0.001	61.65				
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from Elsevier.	Cohort studies (9)	-	0.91 (0.87-0.95)	<0.001	0.00				
	Case-control studies (18)		o.73 (0.62-0.87)	<0.001	66.42				
	Subtotal (27)		0.81 (0.73-0.91)	<0.001	68.19				
	RPA								
	Cohort studies (19)	-	0.95 (0.90-1.00)	0.04	15.15				
	Case-control studies (15)		0.98 (0.85-1.14)	0.81	62.27				
	Subtotal (34)	-	0.95 (0.89-1.00)	0.07	43.43				
	I	Ι	Ι						
	0.5	1	2						

Abbreviations: RR = relative risk; CI = confidence interval; TPA = total physical activity

Physical Activity	No. of	Higher-quality Stud	Subtotal	Strength of Evidence	
	Increased Decreased	Decreased	No Association		
TPA	15 (52)	3 (10)	11 (38)	29	Indecisive
OPA	9 (69)	1 (8)	3 (23)	13	Strong
RPA	10 (48)	10 (48)	10 (48)	21	Indecisive

TABLE 4 Strength of Evidence for the Association between Physical Activity and PCa Risk

Abbreviations: TPA = total physical activity; OPA = occupational physical activity; RPA = recreational physical activity

Total physical activity (TPA) was associated with a decreased risk of PCa (pooled RR: 0.90; 95% CI: 0.84-0.95). The pooled RR for occupational physical activity (OPA) and recreational physical activity (RPA) were 0.81 (95% CI: 0.73-0.91) and 0.95 (95% CI: 0.89-1.00), respectively. For TPA, they observed a significant PCa risk reduction for individuals between 20 and 45 years of age (RR: 0.93, 95% CI: 0.89-0.97) and between 45 and 65 years of age (RR: 0.91; 95% CI: 0.86-0.97) who performed activities but not for individuals <20 years of age or >65 years of age.

The authors concluded that there appears to be an inverse association between physical activity and PCa risk, albeit a small one. It is not clear why occupational physical activity has a larger impact than recreational physical activity and the role for unmeasured confounding variables limits certainty about the role of diet on PCa risk reduction. Another recent study found that there is no correlation between the intensity of exercise or at what age it was done and the risk of PCa, advanced or PCa. (3) Given that increasing physical activity has numerous other health benefits, men should be encouraged to increase their physical activity in both occupational and recreational time to improve their overall health and potentially decrease their risk of PCa.

Several plausible hypothesized biological mechanisms exist for the potential association between physical activity and cancer, including changes in endogenous sexual and metabolic hormone levels and growth factors, decreased obesity and central adiposity, and possibly changes in immune function. Weight control may play a particularly important role because links between excess weight and increased cancer risk have been established for several sites, and central adiposity has been particularly implicated in promoting metabolic conditions amenable to carcinogenesis. Based on existing evidence, some public health organizations have issued physical activity guidelines for cancer prevention, generally recommending at least 30 minutes of moderate-to-vigorous intensity physical activity five or more days a week. Although most research has focused on the efficacy of physical activity in cancer prevention, evidence is increasing that demonstrates exercise also influences other aspects of the cancer experience, including cancer detection, coping, rehabilitation and survival, and survival after diagnosis.

Along with poor dietary intake and tobacco use, the lack of physical activity may be one of the main risk factors for cancer that can be modified through lifestyle/behavior change. (1) (**Figure 5**) Clear public health recommendations and health promotion campaigns have been established for diet and

tobacco that would, if adopted, result in a clear decreased incidence of cancer worldwide. A similar focus should now be directed to the role of physical activity as a means for reducing risk for some of the major cancer sites, such as prostate.

FIGURE 5 **Prospective Cohort Studies** Main Results for Sevenson et al., 1989 Epidemiological Studies of Thune et al., 1994 Lee et al., 1994 Physical Activity and PCa risk Steerland et al., 1995 by Type of Study Design. (1) Oliveria et al., 1996 Cerhan et al., 1997 Reprinted by permission from the Hartman et al., 1998 American Association of Cancer Glovamucci et al., 1998 Research (AACR): Friedenreich Liu et al., 2000 CM. Physical activity and cancer Lund Nilsen et al. 2000 prevention. Observational to Clarke et al., 2000 intervention research. Cancer Epidem Biomar. 2001;10:287-301. **Retrospective Cohort Studies** Paffenbarger et al., 1987 Vena et al., 1987 Hsing et al., 1994 Population-based Case-control Studies LeMarchand et all., 1991 West et all., 1991 Andersson et al., 1995 Whitemore et al., 1995 Villeneuve et al., 1999 Putnam et al., 2000 Hospital-based Case-control Studies Yu et al., 1998 Brownson et al., 1991 - 64 Dosemeci et al., 1993 Sung et al., 1999 Bairati et al., 2000 0.001 0.01 0.125 0.5 1 2 4 10

3.10 Clinically Meaningful Versus Indolent PCa

The success of PSA and promise of other markers for early detection of PCa has exacerbated concerns about the detection and treatment of indolent cancer that would not ordinarily have clinical consequences. The prevalence of latent, small foci of PCa is very high in autopsy studies, and the results of the PCPT — the first study to biopsy men regardless of PSA level — indicate that biopsy-detectable tumours are not uncommon even in men who have had serial negative PSA tests. This situation in itself strengthens the argument for the development of safe primary preventive strategies. However, on a more practical level, our difficulty in distinguishing threatening from non-threatening PCa creates a challenge in prevention research as well. Our current model for carcinogenesis assumes that tumours accumulate critical mutations and epigenetic traits as they progress, and that these characteristics render the tumour less vulnerable to both endogenous and exogenous defenses. Therefore, it

is reasonable to assume that the effectiveness of preventive agents will generally decrease as tumours progress, and that some agents might be effective in suppressing only the most indolent types. Until we have the ability to accurately distinguish PCas by their level of threat, it will be difficult to interpret the clinical significance of many preventive trials that rely on PCa incidence, and to know how many tumours that would have caused substantial morbidity or death have been prevented. On the other hand, particularly in the context of screened populations, it is clear that suppressing the growth of indolent tumours with non-toxic agents will have a beneficial effect on treatment-related morbidity. Alternatively, preventing the detection of clinically indolent, insignificant, cancers is an important part of PCa prevention strategies.

3.11 Effects of PSA Testing on Prevention Trials

When prevention trials are conducted in populations that have a high penetration of PSA testing, there is no way to avoid an effect of PSA on trial design, even if PSA testing is not part of the protocol. Exposure to PSA testing (and the threshold used to define abnormality and perform a prostate biopsy) is such a strong determinant of the likelihood of diagnosis, that it is naturally a very important potential confounder in any prevention study. More importantly, PSA testing, in trial design and in clinical practice markedly increases cancer detection, many of which are clinically significant. The overall impact on cancer prevention in the two 5ARI trials was greatest in the cancers detected by study directed biopsies or among men with low PSA values. Many of these would not progress in a man's life to be clinically noticeable. Therefore, the effect in non-study settings is likely less than observed in randomized trials where both PSA testing and study directed biopsies are mandated.

If PSA testing is not offered in a randomized trial protocol, there is a chance that active treatment could be associated with a different exposure to PSA testing, especially in studies in which participants can become unblinded or in those without blinding or placebo control such as dietary intervention studies. This bias would be very difficult to remove from intention-to-treat analyses. On the other hand, if PSA testing is offered in the protocol, the heavy exposure to repeated PSA testing in the trial arms will tend to exacerbate the influence of relatively indolent cancers on the trial results. On the whole, this seems preferable to introducing confounding by PSA testing.

A special situation arises when the preventive agent is capable of altering PSA, independent of its possible effect in suppressing tumours. We know that PSA is not cancer-specific, and that elevations are commonly associated with BPH. Finasteride is an obvious example of an agent that alters PSA independent of any cancer preventive effect. This raised complex design challenges in the PCPT and the REDUCE trial of dutasteride. The main options for dealing with this problem are blind adjustment of PSA values and mandatory biopsy of all participants. Both approaches are difficult, the former because improper adjustment of PSA can bias study results, and the latter because mandatory biopsy increases the potential influence of indolent cancers.

Unfortunately, the problem is not limited to drugs with obvious effects on PSA, such as 5ARI . PSA is a well-known androgen response gene. Several dietary compounds, such as Vitamin E (and especially the PMCol moiety of α -tocopherol) and lycopene have been shown to suppress androgen signaling in vitro, which could in theory affect PSA levels in men on trial and thus alter their probability of diagnosis. (33) Even dietary trials that involve potential weight loss face this problem, because weight loss is expected to alter hormone profiles and potentially could have effects on PSA values. Studies have reported an inverse association between obesity and PSA levels among men who are not believed to have PCa. (165) It appears essential to conduct careful preliminary studies to detect an effect of a preventive intervention on PSA in cancer-free men.

3.12 Pros and Cons of Various Phase II Designs

The difficulty in moving forward from Phase I, II or even smaller Phase III studies is evident in the findings from the three large PCa chemoprevention trials and pooled analysis of randomized trials of agents evaluated for other conditions that indicate at best a small benefit in the absolute risk reduction of PCa incidence that may be offset by harms. Even when results from smaller and alternative design studies are encouraging the failure of Phase III randomized trials to demonstrate a benefit or to be met with little clinical implementation are disappointing and suggest large randomized prevention trials may not be indicated or feasible at this time. Future PCa prevention trials should assess the impact on other health outcomes (e.g. coronary heart disease or other cancer risk that may positively alter the balance of benefits and harms). This will be a hard threshold to meet given the need to intervene on a large number of asymptomatic individuals for a long period of time. Instead, Phase II studies and smaller Phase III studies are more likely to provide insight into mechanisms of disease and lead to improved therapeutic regimens rather than being practical for true prevention. The previous guidance document offered potential design and intermediate endpoint biomarkers.

3.13 Choosing the Right Intervention: Whole Food Versus Isolated Compounds

Where dietary elements are involved, there is an obvious choice between testing specific compounds believed to carry important biological activity and testing whole foods or dietary patterns. Evidence is accumulating to support the contention that the effects of dietary factors or foods on cancer risk involve interactions among perhaps many specific elements in the food. A compelling example is provided by the unanticipated results of two Phase III trials of supplemental beta-carotene, in which supplements appeared to cause an increase in lung cancer risk among the participants, who were male smokers. (166) Numerous diet-history and serum-based observational studies had indicated that men with higher intake or higher blood levels of beta-carotene, due to consumption of certain fruits and vegetables, had reduced lung cancer risk. The aforementioned study in an animal model comparing the effects of tomato powder versus pure lycopene on inhibition of prostate tumour growth provides a similar note of caution. It is now recognized as a challenge for prevention researchers to use the power of focusing on single compounds for understanding mechanisms while also being aware of the potential importance of interactions when considering translational studies. Whole food or dietary intervention studies involve some tradeoff, as they often must give up the benefits of participant blinding and placebo control. Intermediate approaches, such as the use of capsules containing complex mixtures or extracts of foods, can offer an attractive alternative that retains blinding and placebo control. Research involving single compounds and whole foods are both necessary and should be viewed as complementary rather than competing strategies.

3.14 Preventing PCa Detection by Reducing the Use of the PSA Test and Altering the Threshold for Abnormality

The most effective method to reduce PCa incidence is to reduce PSA testing or alter the threshold used to define abnormal and initiate a prostate biopsy. For example, the introduction of PSA screening has resulted in more than 1 million additional men being diagnosed and treated for PCa in the United States. That growth was particularly dramatic for younger men. Most of this excess incidence represents overdiagnosis, i.e., the detection of tumours that would never cause a problem in a man's lifetime. But because almost all men undergo treatment, and treatment has harms, these men suffer those harms without any benefit (**Figures 6 and 7**). Raising PSA thresholds to denote abnormality and trigger a biopsy from the widely used level of 4 to a level of 8 would reduce by more than half the number of men being labeled as abnormal and possibly undergoing a biopsy. Based on findings from recent randomized screening and treatment trials such a strategy would markedly lower PCa detection (incidence), reduce overdiagnosis and treatment related harms, and have little to no negative impact on PCa mortality over at least a 10-15 year time frame.



The only PCa prevention strategies to date that have demonstrated a reduction in PCa incidence involve 5ARIs. As noted above, these agents have not received U.S. FDA approval for PCa prevention as concern has been raised about the potential harm related to increased number of high-risk cancers detected in men receiving 5ARIs as well as other adverse effects. Thus, the applicability of any current prevention strategy for general clinical use is doubtful. The magnitude of impact of altering PSA thresholds and its potential widespread benefit also should be compared to the relative reduction in the risk of being diagnosed with PCa in the 5ARI chemoprevention trials, which was approximately 25%. In contrast, regular screening with PSA testing at thresholds and frequencies currently employed (annual PSA testing with threshold of normality of 4 ng/mL) approximately doubles an individual's risk of being detected with PCa. Therefore, the relative reduction of approximately 25% in 5ARI studies must be interpreted in this context, yielding a net increase in PCa diagnoses of approximately 48% for the combined strategy of screening plus chemoprevention. The studies provide no information as to whether the magnitude of risk reduction for the diagnosis of PCa achieved by 5ARI would be the same, or considerably less in men who are not being actively screened for PCa. This is particularly important because the common perception that PSA-based early detection of PCa prolongs lives though at least 10 years is not supported by results of recent randomized PCa screening trials. The findings of the two largest trials highlight the uncertainty that remains about the precise effect that screening may have, but demonstrate that if any benefit does exist, it

is very small after 10 years. The European trial found a statistically insignificant 0.06% absolute reduction in PCa deaths for men age 50 to 74 years, while the United States trial found a statistically insignificant 0.03% absolute increase in PCa deaths. (6,7) A meta-analysis of all published screening trials found no statistically significant reduction in PCa deaths. (10)

Because most men with PCa diagnosed through PSA testing at thresholds of 4 ng/mL have indolent disease, the risk for over diagnosis and overtreatment is large. And, because the vast majority of men with PSA detected cancers undergo treatment they are subjected to treatment harms. Preliminary findings from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) found that PCa mortality 12 years after randomization was infrequent (approximately 7%) and did not differ between radical prostatectomy and observation among men diagnosed in the early PSA era. All-cause mortality, the primary endpoint in PIVOT, also did not differ between men randomized to surgery versus men randomized to observation. A mortality reduction may occur in men with baseline PSA levels of > 10 ng/mL but no reduction was seen in men with PSA < 10 ng/mL, men with T1c disease, or those having low tumour risk category characteristics. These findings strongly argue for reducing PSA testing and increasing thresholds that define abnormality in those who continue to undergo testing.

3.15 **Summary**

3.15.1 **5-alpha-reductase inhibitors (5ARIs)**

5ARIs reduce the risk of being diagnosed with PCa among men who are screened regularly for PCa. Information is inadequate to assess the effect of 5ARI on PCa or all-cause mortality. 5ARI increase sexual and erectile dysfunction but improve bothersome lower urinary tract symptoms and reduce the risk of acute urinary retention and the need for surgical intervention. Cost-effectiveness analyses of both the PCPT and REDUCE studies indicate that these agents are unlikely to be cost effective. New U.S. FDA warnings about the potential for an increase in the risk of high-grade PCa and the failure of these drugs to be approved for PCa chemoprevention limits their current clinical utility. Because of the uncertainty related to the risk of 5ARIs causing high grade PCas we recommend physicians discuss the benefits and harms of 5ARI treatment for PCa in men who express an interest in PCa prevention strategies.

3.15.2 Antioxidants

Selenium alone or in combination with Vitamin E, at the doses and preparations evaluated, are not effective at reducing PCa incidence. Vitamin E increases PCa risk. We recommend against the use of either Vitamin E or selenium, alone or in combination for PCa prevention. Beta-carotene and vitamin C do not reduce PCa incidence. We recommend against their use as supplements for PCa prevention. Tomato products containing lycopenes (another source of beta-carotene) have shown promise, but have not yet been tested in Phase III trials. Because of negative findings from RCTs of beta-carotene and the inability of large randomized trials of selenium and Vitamin E to confirm previous suggestive findings from smaller studies or studies using intermediate outcomes or epidemiological reports, we recommend against the use of lycopene supplements for PCa prevention.

3.15.3 **Diet**

Certain aspects of the traditional Asian diet, including soy foods, green tea, and fish deserve future research. The epidemiological evidence for an inverse association of this diet pattern, especially high soy intake on PCa incidence compared to the typical Western diet, is extensive. There is insufficient evidence to evaluate the effectiveness and harms of an "Asian diet" or specific soy intake for PCa prevention.

3.15.4 Weight control, energy balance

Weight control, exercise, and possibly cholesterol-lowering (through a combination of diet and physical activity modification) can be encouraged prudently and should be studied further as a means for PCa prevention. Statins are not effective in reducing PCa incidence but are indicated for cardiovascular risk reduction in many older men. Maintaining ideal body weight has positive health outcomes for other conditions and is recommended. Exercise is an important component for attaining ideal body weight and has widespread positive health effects, potentially including PCa risk reduction. However, there is insufficient evidence to recommend exercise and achieving ideal body weight specifically for PCa prevention.

3.15.5 Aspirin and Non-steroidal Anti-inflammatory Agents

Pooled data from randomized aspirin trials examining other primary outcomes suggest that aspirin may have a modest risk reduction in PCa incidence and a small absolute reduction (1%) in PCa mortality. Low-dose aspirin is indicated for vascular risk reduction in many older men. It is unlikely that PCa risk reductions would have a clinically meaningful impact on usage. Epidemiologic data from studies of NSAIDs are suggestive that these agents may reduce PCa risk. However, gastrointes-tinal and renal adverse effects of these agents would likely limit their widespread utilization as cancer prevention agents. We recommend against the use of NSAIDs or aspirin for PCa prevention.

3.15.6 **Preventing detection of clinically insignificant PCas**

PSA testing using widely studied and clinically implemented intervals and thresholds detects a large reservoir of tumours that would not cause problems in many men's lives, even if not treated (pseudodisease). These clinically insignificant tumours may exhibit histopathological criteria that appear clinically important and therefore most physicians recommend, and most men undergo, treatment. The benefits of PCa prevention are, in large part, due to preventing harms related to PCa treatment. Because almost all men who are diagnosed with PCa undergo treatment, preventing detection of clinically insignificant disease is important. The single most effective intervention to reduce the risk of a man being diagnosed with clinically insignificant PCa is to not undergo screening with the PSA blood test. Such action can reduce risk by half. Alternatively, if men are screened with PSA testing, then raising thresholds signaling abnormality or initiating a prostate biopsy or widening the testing frequency interval would lower the incidence of clinically insignificant cancers and have minimum, if any, impact on PCa mortality. Such a strategy would reduce harms associated with overdiagnosis and overtreatment. We recommend reducing PSA testing for prevention of detection of clinically insignificant setting for prevention of clinically insignificant setting for prevention of clinically insignificant setting for prevention of clinically insignificant for prevention of clinically insignificant setting for prevention of detection of clinically insignificant setting for prevention of detection of clinically insignificant for prevention of clinically insignificant for prevention of detection of clinically insignificant cancers and have minimum, if

nificant PCa and the associated harms related to overdiagnosis and overtreatment. Among men who undergo PSA testing, we recommend reducing the frequency of testing, and the age at which to end testing, as well as increasing the threshold to define abnormal, as methods to reduce PCa incidence.

3.15.7 Methodological recommendations

Risk stratification

Better risk stratification methods are needed to identify target populations for preventive interventions. Improvements may come through development of genetic testing, refinement, and validation of risk factors in epidemiological research and appropriate risk modeling, and through development of new techniques for early detection. More accurate characterization of individual risk — especially risk for more aggressive forms of PCa — will allow better decisions about balancing risk and benefit in preventive interventions.

Selecting agents for Phase III

International consensus on the optimal process for screening and selecting preventive interventions for Phase III trials would be useful. This would include establishing common methods regarding advantages and disadvantages of various pre-clinical (animal) models, and Phase I and Phase II studies. The problem with conducting Phase III studies is the need for very large long-term high-cost trials that include overall and PCa mortality. However, because three large-long term trials have been conducted that have not provided clinically important net benefits or led to U.S. FDA approval or widespread implementation, it is uncertain if trials powered to assess PCa incidence will be developed in the near future.

Intermediate biomarkers in Phase II

Given the number of agents and strategies that require testing, it is imperative to strengthen the array of tools available as intermediate biomarkers in Phase II trials. Incorporation of biomarker validation substudies into Phase III trials is an important way to accomplish this. Emerging technologies offer new opportunities to measure potentially relevant effects of preventive agents on tissue. These biomarkers are best used for assessing mechanisms of action and the role for potential future agents to be tested. We caution against extrapolating findings that indicate improvements in intermediate biomarkers to direct clinical benefits and implementation.

Integrating primary prevention and screening

Effective primary prevention approaches will affect secondary prevention (screening) efforts, and vice versa. The two approaches to reducing suffering and mortality due to PCa do not necessarily have to conflict. The Committee believes it is not too early to begin discussion of ways in which the two approaches can be integrated to maximize the benefit in populations of men at risk. As noted, all three randomized prevention trials have used PCa incidence as their primary outcome. The vast majority of detected cancers in these trials were PSA-detected disease, many of which would have a very favourable natural history. A primary argument for PCa prevention has been that it would reduce the need for PCa treatment and their associated harms. However, the single most effective method to reduce PCa incidence and thus the harms associated with overdiagnosis and overtreatment is to reduce PSA testing, lower the age to discontinue testing and extend intervals, and raise thresholds defining abnormality in individuals who undergo testing.



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Advances in Biomarkers

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4.1 Introduction

By definition, biomarkers serve as *in vivo*, measurable signals of biologic activity. Within the context of cancer, biomarkers can be utilized for cancer detection in normal or symptomatic patients, risk stratification in patients with known cancer, staging of disease, or monitoring of therapeutic response. Historically, proteins measured in blood, urine, or tissue have served as the classic biomarker. In contemporary medicine, there is a trend toward broader definitions of biomarkers to include genetic signals measured individually or in large panels, metabolic activity, and, in some cases, even imaging. This progressive trend serves to better individualize tumours, recognizing that tremendous tumour heterogeneity exists, particularly in the application of risk stratification. In this regard, biomarkers which are specific to the cancer, and not just the tissue from which the cancer is derived, not only offer the opportunity to reliably detect the presence of cancer, but to determine the threat that individual cancer poses to the individual patient.

In the case of prostate cancer, biomarkers have been utilized for detection and staging for many years. Serum acid phosphatase, while very non-specific, may have been among the first widely utilized biomarkers that strongly dictated therapeutic decisions. In this manner, urologists have always remained at the forefront of biomarker application in clinical practice.

Current clinical practice has been heavily driven by the utilization of serum prostate specific antigen (PSA). As discussed herein, although the test has several limitations, it remains a standard of care in the detection, staging, and monitoring of prostate cancer. Efforts to improve performance of PSA testing have had mixed results, but have made the test more interpretable in clinical practice. More recent efforts to improve the detection and risk stratification of prostate cancer have focused upon the identification of more cancer-specific markers, which may more specifically identify cancers and which also may tell us something about the cancer's behaviour.

4.2 Serum Markers

4.2.1 **Prostate-Specific Antigen (PSA)**

4.2.1.1 Clinical use

Prostate cancer (PCa) is the most common malignancy diagnosed in men in Europe and the USA and the second most frequent cause of cancer-related death in men. An estimated 200,000 men are diagnosed with PCa in the USA every year, with approximately 30,000 deaths annually (1,2). Current screening relies on a digital rectal examination in combination with a serum prostate-specific antigen test.

The overall survival rate for all stages combined has increased from 67% to 89% during the last two decades (3). Although controversial, this has been attributed to widespread PSA screening combined with high quality treatment. Prostate specific antigen-based screening has led to earlier detection,

which in turn enables earlier treatment and better treatment-related outcome for prostate cancer patients. There is now evidence from randomized trials confirming that PSA screening reduces metastatic disease and prostate cancer mortality (4).

Half a century ago, the identification of acid phosphatase gave rise to the age of tumour screening markers for prostate cancer. Consequently, determination of prostatic acid phosphatase (PAP) became the gold standard for detecting prostate cancer. However, a large number of false negative results limited the usefulness of this marker. Even after the development of radioimmunoassay, this problem could not be solved. Subsequently, PAP was replaced by another prostatic enzyme marker, PSA, which is more specific to prostatic tissue. Prostate specific antigen, which is encoded by an androgen-responsive gene located on chromosome 19q13.3-13.4 (4), is a serine protease which was originally referred to as human kallikrein 3 (hK3). It is secreted from prostate epithelial cells. During the past 15 years, PSA has become an indispensable marker for the diagnosis and follow up of prostate cancer patients. Prostate specific antigen remains the most clinically utilized tumour marker in human oncology in that it carries utility in detection, staging, risk stratification, and monitoring of therapeutic response.

4.2.1.2 **Detection**

For the detection of prostate cancer, the measurement of serum prostate specific antigen and digital rectal examination are standard procedures in clinical practice (**Figure 1**). When abnormal results are found in either test, a prostate biopsy is generally recommended to establish a histological diagnosis (5). A critical determinant of the sensitivity and specificity of PSA as a measure of prostate cancer risk is the cut-off utilized in men undergoing evaluation. Lowered cut-offs increases sensitivity, but reduces specificity, and may increase the risk of detecting clinically insignificant disease. A number of schemes have been proposed for the selection of cut-offs (see below), but in general the majority of historical series evaluating serum PSA have utilized a cut-off of 4.0 ng/ml for selection of biopsy, with several recent studies proposing a lower cut-off of 2.5 to 3.0 ng/ml.



PSA = prostate-specific antigen; DRE = digital rectal examination; BPH = benign prostatic hypertrophy

4.2.1.3 **PSA cutoffs**

As in any diagnostic test, the positive predicitve value (PPV) and specificity of PSA for prostate cancer detection are heavily influenced by the threshold chosen for biopsy. Using the historical cutoff of 4.0 ng/ml, cancer detection rates of 35%-42.3% have been reported on 10- to 12-core biopsy. At PSA levels over 10 ng/dl, the PPV improves to over 60% (6-8). Within the last decade, the conventional cut-off of 4.0 ng/ml has been challenged. An incidence of prostate cancer from 24% to 26.3% (mean 20.5%) was found when serum PSA levels were between 2.5 and 4.0 ng/ml (6-9). Furthermore, the European Randomized Study of Screening for Prostate Cancer (ERPSC) showed a significant mortality advantage with PSA screening using a cut-off of 3 ng/ml for biopsy at most centres. (4, 6-8)

Sensitivity is difficult to determine in a population of men with elevated PSA due to the difficulty of assessing the true histologic prevalence of prostate cancer in that cohort. The Prostate Cancer Prevention Trial (PCPT) employed empiric or for cause prostate biopsy in 9,060 men, and found

biopsy-detectable prostate cancer in 12.3% of men with PSA < 2.0 ng/ml (10,11). The sensitivity of cut-off 2.5 and 4.0 ng/dl in the placebo arm was 24.0% and 42.8%, respectively, with a specificity of 92% and 80% (12). Among cancers identified in men with PSA less than 2.0 ng/mL in the PCPT, 1.4.% had a Gleason score \geq 7, as compared to 6.7% of those with PSA in the range of 3.1-4.0 ng/dl (10-11). Clinically significant disease has been noted in 83% undergoing radical prostatectomy for PSA 2.5-4.0 ng/dl in historical series (9).

Prostate cancer risk is also influenced by factors such as age and race. This led to the introduction of age-specific reference ranges for PSA screening, first by Oesterling *et al.* (13) and subsequently by Morgan *et al.*, who also incorporated race (14). Similar race-specific age ranges have been documented in the Asian population.(15,16) Recently, genome analysis suggests a racial variation in prostate cancer phenotype, which may influence disease course.(17)

4.2.1.4 Limitations

While serum PSA testing is widely employed in medical practice, its use remains controversial in view of several fundamental limitations. Most criticism of serum PSA testing is derived from the concern that many detected cancers may not ultimately be lethal due to the prolonged lead time of the disease, the risk of death from competing co-morbidity, and the high prevalence of histologic cancer in autopsy series. Because prostate cancer is often slow growing, the widespread use of PSA testing may result in the detection of clinically insignificant tumours with resultant overtreatment. However, data from surgical series among patients with prostate cancer detected by PSA testing confirm that the cancer is organ-confined in only 60% of all PSA detected cancers, suggesting that many cancers detected in the clinical setting are indeed significant.

Prostate specific antigen has reduced specificity when used alone for optimal detection of prostate cancer, due to variable differences in the volume and composition of benign prostate hypertrophy (BPH) and other confounding conditions. However, PSA has improved performance characteristics for the detection of prostate cancer when combined with digital rectal examination (DRE), and this two-test combination has led to an improvement in the detection of early stage cancer. At present, the majority of prostate cancers are nonpalpable and are diagnosed through PSA screening, with an increased percentage of organ-confined tumours at surgery.

Another emerging concern is the risk of missing clinically relevant prostate cancers in patients with lower PSA serum levels (less than 4.0 ng/ml). An increased incidence of prostate cancer from 24% to 26.3% (mean 20.5%) was found when serum PSA levels were between 2.5 and 4.0 ng/ml (6–9). Catalona *et al.* found that 19% of detected prostate cancers with low PSA were no longer organ-confined. Among 42 specimens from patients who had radical prostatectomy with a serum PSA of 2.6 to 4.0 ng/ml, only 17% were clinically insignificant by conventional criteria (6). It is now recognized that clinically significant and insignificant cancers exist even at extremely low levels of serum PSA (6,7) showing that PSA levels reflect the spectrum of prostate cancer risk.

At the cut-off of 4.0 ng/ml, the general specificity of serum PSA is poor (18). Among patients in a PSA range between 4.0 and 10 ng/ml, the positive predictive value is 18% to 25% (mean 21%). (19-21) Thus, the ability of the total PSA level to distinguish prostate cancer from benign conditions, such as benign prostatic hyperplasia and prostatitis, is not robust. This may cause unnecessary anxiety and

morbidity of patients undergoing prostate biopsies. It should be recognized that poor specificity in prostate cancer detection is also potentially a function of undersampling due to the random nature of prostate biopsy. Increasing core number in prostate biopsy appears to reduce the false negative rate at any PSA cut-off. As such, the true specificity of PSA is not known in the absence of correlative autopsy series.

In summary, the major historical limitations of PSA in prostate cancer detection are the risk of underdetection of significant cancers, overdetection of insignificant cancers, and the resultant excess of negative biopsies incurred by relatively poor specificity. Taking these findings into account, there is a need for new tools to improve the specificity of screening, improved strategies for establishing optimal PSA cut-offs, and additional markers assessing disease risk. Currently it is not possible to noninvasively differentiate between clinically significant and insignificant prostate cancer reliably, even after prostate biopsy. Multiple attempts to refine PSA for these purposes and to establish new markers have been underway and are outlined in this chapter.

4.2.1.5 Improving specificity

PSA Isoforms

Free PSA (fPSA), percentage free/total PSA (%fPSA)

The majority of serum PSA circulates in complex with other proteins, including alpha-1 antichymotrypsin. The addition of free circulating PSA (fPSA) to complexed PSA is referred to as the total PSA (tPSA). Various studies have shown that ratio of the free to total PSA (f/t PSA) is lower in men with prostate cancer. The role of f/t PSA as a screening tool was reported by Catalona *et al.* (22). This multicentre study evaluated men with benign prostate hypertrophy and tPSA levels between 4 and 10 ng/ml. A f/t PSA of less than 25% showed a sensitivity of 95%, with a specificity improvement of 20% over tPSA alone. Djavan *et al.* presented a comprehensive review of the results of the different f/t PSA cut-off values. F/t PSA was found to be the most important predictor of prostate cancer in first and repeat biopsies if the volume of the entire prostate gland was less than 30cc (23,24). It was also found that an f/t PSA of 2.5 to 4.0 ng/ml (25). In an identical group of men with tPSA of 2.1 to 4.0 ng/ml, Catalona and coworkers found that 100% of non organ-confined or large volume tumours, and 80% of tumours deemed clinically significant, were identified with the use of a f/t PSA ratio of 10-15% (26).

Free PSA represents the most labile component of total PSA and as such, storage methods, delay to assay, and factors such as inflammation or infection may greatly influence the PSA level. This necessitates very strict sample handling, including separation of serum/plasma from the blood cells within a few hours of sample collection; otherwise, the sample has to be kept frozen (ideally –70°C for long-term storage) to provide optimal analysis (27). Another problem is that results of fPSA measured by different laboratories with kits from different manufacturers using the same specimen are not exactly reproducible. Finally, the optimal threshold for f/t PSA remains to be determined. For these reasons, f/t PSA has not been widely adopted as a primary screening tool and instead is primarily used as a reflex test among men being considered for repeat biopsy for persistently elevated PSA levels after an initial negative biopsy.

Intact PSA (iPSA) has been introduced as a molecular subfraction of free PSA that is not internally cleaved and has been suggested to be associated with prostate cancer (Figure 2). Nurmikko et al. developed a novel free PSA antibody, which failed to recognize free PSA that was internally cleaved at Lys145-Lys146. Thus, this antibody only measured intact single chain forms of free PSA (iPSA), such as mature inactive PSA and pro-PSA (proPSA) (28,29). This clinical trial on 178 men with benign prostate disease and 255 men with prostate cancer showed a significantly higher ratio of intact-to-free PSA in prostate cancer patients as compared to patients with benign prostatic disease. Conversely, a higher nicked-to-total PSA ratio in men without prostate cancer was seen (30). Multivariate logistic regression analysis revealed that tPSA, fPSA and iPSA each had independent predictive ability but the diagnostic accuracy of iPSA was not significantly better than the others. However, the nickedto-total PSA ratio proved to be useful to differentiate benign prostate disease from prostate cancer. The authors suggested using a combination of iPSA, fPSA and tPSA to more accurately detect prostate cancer. This test is hampered by its low specificity and the measurements are biased to some extent, since uncleaved PSA produced by benign lesions is also included in the calculation (31). The measurement of iPSA may help in prostate cancer detection, although further prospective studies are warranted to define cut-off values for percent intact-to-free PSA and percent nicked-to-total PSA to avoid unnecessary biopsies.





Benign PSA (bPSA) is a fraction of inactive fPSA with a characteristic clip at Lys182 (**Figure 3**). Mikolajczyk and co-workers first found an elevated tissue level of bPSA within the transition zone and also in the seminal plasma of patients with nodular BPH (32). Recently, an immunoassay for bPSA has been developed. A study by Linton *et al.* showed that bPSA represents a significant percentage (about 50%) of fPSA in BPH serum but not in control serum (31). Benign PSA was low or undetectable in the control group consisting of urologic patients not suspected to have BPH or prostate cancer, young and healthy men and women, and patients after radical prostatectomy. The median bPSA/tPSA values were significantly higher in the BPH group as compared to the cancer group. However, BPH may coexist in men with prostate cancer and this may explain the fact that the absolute level of serum bPSA was not significantly lower in the prostate cancer group in this study.

Complexed PSA (cPSA)

Once PSA gains access to the systemic circulation, the majority becomes complexed to protease inhibitors, including α 1-antichymotrypsin and α 2-macroglobulin. It has been recognized that the majority of PSA found in men with prostate cancer is complexed to α 1-antichymotrypsin (ACT). However, the accurate measurement of PSA-ACT is problematic due to non-specific binding, which has hampered research about the role of this complexed PSA (cPSA) (33,34). Eventually, a novel immunoassay (Bayer Diagnostics, New York) was developed allowing accurate measurement of all complexed forms (PSA-ACT and the minor forms) except for PSA complexed to α 2-macroglobulin. Most studies demonstrated the superiority of cPSA over tPSA in men with tPSA more than 4 ng/ ml, but results were similar when compared to f/t PSA ratio (18, 35-39). Djavan et al. found that cPSA cut-off values of 3.06 ng/ml and 2.52 ng/ml resulted in 90% and 95% sensitivity for detecting prostate cancer, and helped avoid unnecessary biopsies in 20.3% and 9.1% of cases, respectively (39). Complexed PSA volume-related parameters (cPSA density and transitional zone cPSA density) increased the ability of cPSA in a similar fashion like tPSA (39,40). In contrast, Okihara (41) and Stamey (42) were not able to show significant improvement in the specificity for cPSA relative to tPSA. A prospective study of 831 patients by Partin et al. revealed a significant enhancement in specificity of cPSA over tPSA of 6.2% to 7.9% within the tPSA range from 2.0 to 10.0 ng/ml (43). With a cPSA cut-off value of 2.1 ng/ml, Horninger et al. reported a sensitivity and specificity of 86% and 34.2%, respectively, for cancer detection in men with tPSA of 2.0 to 4.0 ng/ml (44). Complexed PSA appears to be a useful tool in the early detection of prostate cancer due to the marked improvement of specificity in patients with low tPSA levels in the range from 2.0 to 4.0 ng/ml. Complexed PSA is attractive as a single test, which provides information similar to that of f/t PSA ratio but offers the advantages of minimized test variability and stability. It is a potentially underutilized marker for prostate cancer screening and detection.

Pro-PSA (proPSA)

Pro-PSA (proPSA) is a precursor form of PSA enriched in tumour, as compared to benign, prostate tissues (45-48) (**Figure 3**). It comprises a native proPSA ([-7]proPSA) as well as truncated pro-leader peptides containing two or four amino acids, [-2]proPSA and [-4]proPSA, respectively. With the development of highly specific immunoassays for proPSA, multiple recent studies have been conducted to establish the clinical usefulness of proPSA in cancer detection compared to the currently used PSA assays (49,50). Catalona and colleagues showed that the ratio of proPSA to fPSA (%proPSA) had greater specificity for prostate cancer compared to fPSA and cPSA, at PSA levels from 2.0 to 10.0 ng/ml (51). Immunoassays for all three types of proPSA were studied and the [-2] proPSA assay outperformed the other two assays for cancer detection. Another interesting finding of this study was that proPSA had the highest relative specificity compared to other PSA forms at PSA 3.0 to 6.0 ng/ml. The authors of this study presented their findings in %proPSA, since normalizing proPSA in percentage of fPSA appeared to be more stable compared to single assay. ProPSA is an exciting tool that enhances the detection of prostate cancer in the tPSA range of 2.0 to 10.0 ng/ml.

FIGURE 3

PSA Isoforms



A study specifically concentrating on the precursor isoform of PSA containing two amino acids in the propeptide leader confirmed the presence of [-2]proPSA in the serum of men with prostate cancer, in which [-2]proPSA formed 25%-95% of the fPSA fraction, in contrast with 6%-19% in biopsy-negative men (52). Initial reports investigating the clinical value of [-2]proPSA in screening for prostate cancer showed that [-2]proPSA serum concentrations were generally higher in men with prostate cancer compared to men without cancer (53). Recently, reports by Sokoll *et al.* (54) and Stephan *et al.* (55) showed that [-2]proPSA can significantly improve prostate cancer detection. Jansen *et al.* reported that the PSA isoform, p2PSA (53) and, moreover, %p2PSA could have additional value beyond tPSA and %fPSA in prostate cancer detection within the tPSA range of 2.0-10.0 ng/ml by significantly increasing the predictive value and specificity for prostate cancer. By increasing the specificity of p2PSA relative to tPSA and fPSA, the use of p2PSA could potentially reduce the number of men undergoing unnecessary biopsy. The relationship of p2PSA with aggressive prostate cancer (Gleason score \geq 7) also requires further study (53).

PSA Velocity (PSAV)

Longitudinal kinetics of PSA over time can be expressed as PSA velocity (PSAV). It has been reported that an annual increase of 0.75 ng/ml/year in serum PSA can distinguish prostate cancer from benign conditions (56,57). More recent studies have demonstrated that even a PSAV of greater than 0.35 to 0.4 ng/ml/year is associated with a greater risk of prostate cancer, since men with BPH and those without known prostate disease have a PSAV of 0-0.15 ng/ml/year. Accordingly, the National Comprehensive Cancer Network recommends considering prostate biopsy for men with PSA \leq 2.5 ng/ml with a PSAV \geq 0.35 ng/ml/year. (58)

However, the use of PSAV continues to be controversial. (59) Some limitations of PSA kinetics include the significant individual (biologic) variability and interassay (analytic) variability, as well as confounding from conditions such as prostatitis (60,61). Furthermore, the accurate measurement of PSAV requires longitudinal evaluations, which are not always available. Some studies have failed to confirm incremental predictive value for PSAV beyond PSA alone. (62)

Notably, numerous studies have shown a relationship between PSAV and clinically significant and fatal prostate cancer. (63) In two hallmark studies, D'Amico *et al.* showed that men with a PSAV >2 ng/ml/year had a significantly greater risk of disease-specific mortality after radical prostatectomy and radiation therapy. (64,65) Others have shown that PSAV, many years prior to a prostate cancer diagnosis, predicts fatal disease in the future. (66) It is possible that PSAV is more specific for

the presence of life-threatening disease than for overall prostate cancer detection. (67) Well-designed prospective studies are necessary to better evaluate the role of PSA velocity in the early identification of significant prostate cancer.

PSA Density (PSAD)

Since much of serum PSA is produced in benign prostatic hyperplasia, correction of the PSA for gland volume can, in theory, improve the specificity of serum PSA for cancer detection. Prostate specific antigen density (PSAD), the quotient of serum PSA level divided by prostate volume, and PSA density of transition zone (PSAD-TZ) have been reported to offer significant enhancement in cancer detection since 1992. The concept of PSAD-TZ is derived from the observation that the majority of gland enlargement seen in benign prostatic hypertrophy is located in the transition zone (68-70). The specificity of PSAD was reported to be 20% to 37% at sensitivity rates greater than 90% using a cut-off of 0.10 ng/ml/cc. Evaluating the PSA density avoided 20% to 37% of negative biopsies with a maximum undetected cancer rate of 10% (71-73). Djavan *et al.* demonstrated improvement in the effectiveness of PSAD-TZ cut-off of 0.25 ng/ml/cc resulted in a specificity of 47% with sensitivity of 95%. Multivariate analysis showed that PSAD-TZ and percent-free PSA were the most powerful and highly significant predictors of prostate cancer. Taneja *et al.* demonstrated further improvements in PSAD-TZ when applying volume specific cut-offs and when utilizing complexed PSA rather than total PSA. (74)

The wide implementation of PSAD in screening is hampered by several practical issues. The most prominent problem is the requirement for an invasive test (transrectal ultrasound), which is infrequently done prior to the time of biopsy, as well as inter-examiner differences in ultrasound measurement. Additionally, it carries reduced specificity in men with a prostate volume of less than 30 cc (23,75). Therefore, PSAD and PSAD-TZ may be most useful to determine the need for repeat biopsy. Indeed, Djavan *et al.* found that PSAD-TZ was an important predictor on repeat biopsy in a prospective study of 1051 cases (24). Repeat biopsies may be considered for men with PSA levels between 4.0 and 10.0 ng/ml if the PSAD-TZ is more than 0.26ng/ml/cc or free PSA less than 30%. PSAD-TZ also proved to be useful in a PSA range between 2.5 and 4.0 ng/ml.

PSAD has also been shown to be associated with prostate cancer aggressiveness. It has also been used to help identify men with potentially insignificant prostate cancer who are candidates for active surveillance.

4.2.1.6 **PSA for staging of prostate cancer**

The application of PSA for determining the extent of disease has been the focus of numerous investigations. With serum PSA levels less than 4.0 ng/ml, patients are more likely to have prostate-confined cancer compared to those with significantly elevated PSA levels. However, despite direct correlation between PSA and pathologic tumour stage, studies have shown that PSA cannot accurately predict the final pathologic stage for the individual patient. Some modest improvement in staging has been noted when using f/t PSA, complexed PSA, and PSA density. Despite this, the use of PSA alone is not sufficiently sensitive or specific to use for the determination of tumour stage. Because of this, several investigators have combined PSA level, clinical stage, and biopsy Gleason score to improve the predictive value for estimating pathological stage. The combination of PSA, clinical stage, and Gleason score may be used by the urologist as a guide to better predict pathologic stage and to counsel patients who are likely to benefit from definitive local therapy (**Table 1**) (1). They may also aid in selecting patients at risk for metastatic disease, who may initially benefit from pelvic lymph node dissection or alternatively, those patients at low risk for disease outside the prostate that may avoid the potential complications of a lymph node dissection. Many staging nomograms have been developed. The most familiar nomogram is derived from the work of Partin *et al.*, from the Johns Hopkins Medical Center, to predict extent of prostate cancer. It uses prostate-specific antigen level, clinical stage, and biopsy Gleason score. The most recent "Partin Tables," based on cases from 2000 to 2005, are available from the Johns Hopkins website at: http:// urology.jhu.edu/prostate/partintables.php (1).

TABLE 1

Modified from: Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (partin tables) for the new millennium. Urology 2001;58(6):843-848.

Clinical Stage T1c (nonpalpable, PSA elevated)

PSA				Gleason Score		
(ng/mL)	Pathologic Stage	2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10
0-2.5	Organ-confined	95 (89-99)	90 (88-93)	79 (74-85)	71 (62-79)	66 (54-76)
	Extraprostatic extension	5 (1-11)	9 (7-12)	17 (13-23)	25 (18-34)	28 (20-38)
	Seminal vesicle (+)	_	0 (0-1)	2 (1-5)	2 (1-5)	4 (1-10)
	Lymph node (+)	_	_	1 (0-2)	1 (0-4)	1 (0-4)
2.6-4.0	Organ-confined	92 (82-98)	84 (81-86)	68 (62-74)	58 (48-67)	52 (41-63)
	Extraprostatic extension	8 (2-18)	15 (13-18)	27 (22-33)	37 (29-46)	40 (31-50)
	Seminal vesicle (+)	_	1 (0-1)	4 (2-7)	4 (1-7)	6 (3-12)
	Lymph node (+	_	_	1 (0-2)	1 (0-3)	1 (0-4)
4.1-6.0	Organ-confined	90 (78-98)	80 (78-83)	63 (58-68)	52 (43-60)	46 (36-56)
	Extraprostatic extension	10 (2-22)	19 (16-21)	32 (27-36)	42 (35-50)	45 (36-54)
	Seminal vesicle (+)	_	1 (0-1)	3 (2-5)	3 (1-6)	5 (3-9)
	Lymph node (+)	_	0 (0-1)	2 (1-3)	3 (1-5)	3 (1-6)
6.1-10.0	Organ-confined	87 (73-97)	75 (72-77)	54 (49-59)	43 (35-51)	37 (28-46)
	Extraprostatic extension	13 (3-27)	23 (21-25)	36 (32-40)	47 (40-54)	48 (39-57)
	Seminal vesicle (+)	_	2 (2-3)	8 (6-11)	8 (4-12)	13 (8-19)
	Lymph node (+)	_	0 (0-1)	2 (1-3)	2 (1-4)	3 (1-5)
10.0	Organ-confined	80 (61-95)	62 (58-64)	37 (32-42)	27 (21-34)	22 (16-30)
	Extraprostatic extension	20 (5-39)	33 (30-36)	43 (38-48)	51 (44-59)	50 (42-59)
	Seminal vesicle (+)	_	4 (3-5)	12 (9-17)	11 (6-17)	17 (10-25)
	Lymph node (+)	_	2 (1-3)	8 (5-11)	10 (5-7)	11 (5-18)
Key: PSA: Pro	state-specific antigen					

PSA		Gleason Score						
(ng/mL)	Pathologic Stage	2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10		
0-2.5	Organ-confined	91 (79-98)	81 (77-85)	64 (56-71)	53 (43-63)	47 (35-59)		
	Extraprostatic extension	9 (2-21)	17 (13-21)	29 (23-36)	40 (30-49)	42 (32-53)		
	Seminal vesicle (+)	_	1 (0-2)	5 (1-9)	4 (1-9)	7 (2-16)		
	Lymph node (+)	_	0 (0-1)	2 (0-5)	3 (0-8)	3 (0-9)		
2.6-4.0	Organ-confined	85 (69-96)	71 (66-75)	50 (43-57)	39 (30-48)	33 (24-44)		
	Extraprostatic extension	15 (4-31)	27 (23-31)	41 (35-48)	52 (43-61)	53 (44-63)		
	Seminal vesicle (+)	_	2 (1-3)	7 (3-12)	6 (2-12)	10 (4-18)		
	Lymph node (+)	_	0 (0-1)	2 (0-4)	2 (0-6)	3 (0-8)		
4.1-6.0	Organ-confined	81 (63-95)	66 (62-70)	44 (39-50)	33 (25-41)	28 (20-37)		
	Extraprostatic extension	19 (5-37)	32 (28-36)	46 (40-52)	56 (48-64)	58 (49-66)		
	Seminal vesicle (+)	_	1 (1-2)	5 (3-8)	5 (2-8)	8 (4-13)		
	Lymph node (+)	_	1 (0-2)	4 (2-7)	6 (3-11)	6 (2-12)		
6.1-10.0	Organ-confined	76 (56-94)	58 (54-61)	35 (30-40)	25 (19-32)	21 (15-28)		
	Extraprostatic extension	24 (6-44)	37 (34-41)	49 (43-54)	58 (51-66)	57 (48-65)		
	Seminal vesicle (+)	_	4 (3-5)	13 (9-18)	11 (6-17)	17 (11-26)		
	Lymph node (+)	_	1 (0-2)	3 (2-6)	5 (2-8)	5 (2-10)		
10.0	Organ-confined	65 (43-89)	42 (38-46)	20 (17-24)	14 (10-18)	11 (7-15)		
	Extraprostatic extension	35 (11-57)	47 (43-52)	49 (43-55)	55 (46-64)	52 (41-62)		
	Seminal vesicle (+)	_	6 (4-8)	16 (11-22)	13 (7-20)	19 (12-29)		
	Lymph node (+)	_	4 (3-7)	14 (9-21)	18 (10-27)	17 (9-29)		
Key: PSA: Pro	state-specific antigen							

TABLE 1 (CONT'D)

Modified from: Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (partin tables) for the new millennium. Urology 2001;58(6):843-848.

PSA				Gleason Score		
Range (ng/mL)	Pathologic Stage	2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10
0-2.5	Organ-confined	88 (73-97)	75 (69-81)	54 (46-63)	43 (33-54)	37 (26-49)
	Extraprostatic extension	12 (3-27)	22 (17-28)	35 (28-43)	45 (35-56)	46 (35-58)
	Seminal vesicle (+)	-	2 (0-3)	6 (2-12)	5 (1-11)	9 (2-20)
	Lymph node (+)	-	1 (0-2)	4 (0-10)	6 (0-14)	6 (0-16)
2.6-4.0	Organ-confined	80 (61-95)	63 (57-69)	41 (33-48)	30 (22-39)	25 (17-34)
	Extraprostatic extension	20 (5-39)	34 (28-40)	47 (40-55)	57 (47-67)	57 (46-68)
	Seminal vesicle (+)	-	2 (1-4)	9 (4-15)	7 (3-14)	12 (5-22)
	Lymph node (+	-	1 (0-2)	3 (0-8)	4 (0-12)	5 (0-14)
4.1-6.0	Organ-confined	75 (55-93)	57 (52-63)	35 (29-40)	25 (18-32)	21 (14-29)
	Extraprostatic extension	25 (7-45)	39 (33-44)	51 (44-57)	60 (50-68)	59 (49-69)
	Seminal vesicle (+)	-	2 (1-3)	7 (4-11)	5 (3-9)	9 (4-16)
	Lymph node (+)	-	2 (1-3)	7 (4-13)	10 (5-18)	10 (4-20)
6.1-10.0	Organ-confined	69 (47-91)	49 (43-54)	26 (22-31)	19 (14-25)	15 (10-21)
	Extraprostatic extension	31 (9-53)	44 (39-49)	52 (46-58)	60 (52-68)	57 (48-67)
	Seminal vesicle (+)	-	5 (3-8)	16 (10-22)	13 (7-20)	19 (11-29)
	Lymph node (+)	-	2 (1-3)	6 (4-10)	8 (5-14)	8 (4-16)
10.0	Organ-confined	57 (35-86)	33 (28-38)	14 (11-17)	9 (6-13)	7 (4-10)
	Extraprostatic extension	43 (14-65)	52 (46-56)	47 (40-53)	50 (40-60)	46 (36-59)
	Seminal vesicle (+)	-	8 (5-11)	17 (12-24)	13 (8-21)	19 (12-29)
	Lymph node (+)	-	8 (5-12)	22 (15-30)	27 (16-39)	27 (14-40)
Key: PSA: Pro	state-specific antigen					

Clinical Stage T2b (palpable >½ of one lobe, not on both lobes)

PSA		Gleason Score						
(ng/mL)	Pathologic Stage	2-4	5-6	3 + 4 = 7	4 + 3 = 7	8-10		
0-2.5	Organ-confined	86 (71-97)	73 (63-81)	51 (38-63)	39 (26-54)	34 (21-48)		
	Extraprostatic extension	14 (3-29)	24 (17-33)	36 (26-48)	45 (32-59)	47 (33-61)		
	Seminal vesicle (+)	-	1 (0-4)	5 (1-13)	5 (1-12)	8 (2-19)		
	Lymph node (+)	-	1 (0-4)	6 (0-18)	9 (0-26)	10 (0-27)		
2.6-4.0	Organ-confined	78 (58-94)	61 (50-70)	38 (27-50)	27 (18-40)	23 (14-34)		
	Extraprostatic extension	22 (6-42)	36 (27-45)	48 (37-59)	57 (44-70)	57 (44-70)		
	Seminal vesicle (+)	-	2 (1-5)	8 (2-17)	6 (2-16)	10 (3-22)		
	Lymph node (+)	-	1 (0-4)	5 (0-15)	7 (0-21)	8 (0-22)		
4.1-6.0	Organ-confined	73 (52-93)	55 (44-64)	31 (23-41)	21 (14-31)	18 (11-28)		
	Extraprostatic extension	27 (7-48)	40 (32-50)	50 (40-60)	57 (43-68)	57 (43-70)		
	Seminal vesicle (+)	-	2 (1-4)	6 (2-11)	4 (1-10)	7 (2-15)		
	Lymph node (+)	-	3 (1-7)	12 (5-23)	16 (6-32)	16 (6-33)		
6.1-10.0	Organ-confined	67 (45-91)	46 (36-56)	24 (17-32)	16 (10-24)	13 (8-20)		
	Extraprostatic extension	33 (9-55)	46 (37-55)	52 (42-61)	58 (46-69)	56 (43-69)		
	Seminal vesicle (+)	-	5 (2-9)	13 (6-23)	11 (4-21)	16 (6-29)		
	Lymph node (+)	-	3 (1-6)	10 (5-18)	13 (6-25)	13 (5-26)		
10.0	Organ-confined	54 (32-85)	30 (21-38)	11 (7-17)	7 (4-12)	6 (3-10)		
	Extraprostatic extension	46 (15-68)	51 (42-60)	42 (30-55)	43 (29-59)	41 (27-57)		
	Seminal vesicle (+)	-	6 (2-12)	13 (6-24)	10 (3-20)	15 (5-28)		
	Lymph node (+)	_	13 (6-22)	33 (18-49)	38 (20-58)	38 (20-59)		

4.2.1.7 Monitoring of therapeutic response with PSA

In addition to its use in screening and prognostication, a critical role for PSA is in monitoring the course of disease and therapeutic response. Following radical prostatectomy (RP), PSA levels should become undetectable by conventional assays. The subset of patients with a persistently detectable PSA after RP has been studied and shown to have a high risk of metastatic progression. For example, Rogers *et al.* reported a 10-year distant metastasis-free survival rate of only 22% in 160 men who failed to achieve an undetectable PSA level after RP. (1)

Of note, in rare cases spurious PSA elevations may be seen following RP due to interference with the PSA assay by antibodies (*e.g.*, human anti-mouse antibodies). (2, 3) In cases where the clinical picture seems inconsistent (for example, a low-risk patient with organ-confined disease and an elevated postoperative PSA), repeat testing with a different assay and other specialized laboratory studies may be pursued to rule out assay interference.

For the majority of patients with an initially undetectable PSA after RP, subsequent PSA rises are used to assess for biochemical recurrence (BCR). BCR itself is a heterogeneous phenomenon, with varying biologic aggressiveness. Pound *et al.* reported a median time of eight years from BCR to metastasis and five more years from metastasis to death. However, only 34% of men with BCR in their series developed metastatic disease during follow-up. (4)

In this regard, longitudinal changes in PSA over time are a useful predictor of prognosis among men with BCR after RP. For example, in 379 men with biochemical failure after radical prostatectomy, Freedland *et al.* showed that PSA doubling time was a significant predictor of prostate cancer-specific mortality. (5) Time to PSA recurrence is also an important predictor of prostate cancer-specific mortality. (5, 6) Indeed, BCR that occurs more than 5 to 10 years after RP has been shown to have a more favourable prognosis than early BCR. (7, 8)

It is noteworthy that many different definitions have been used to report on BCR after RP. In a literature review of 145 articles by the American Urological Association (AUA) Guidelines Panel, 53 different BCR definitions were used after RP. (9) The most common definition was a PSA level >0.2 ng/ml. Because recurrence-free probability estimates will vary based upon the definition that is used (10), the AUA panel recommended using a standard criteria of a PSA level ≥0.2 ng/ml confirmed by a second measurement to define BCR after RP. (9)

It is noteworthy that the definition for BCR itself may influence the prognostic significance. The AUA Guidelines Panel chose the aforementioned threshold in order to maximize sensitivity and provide a standard for outcomes reporting, with the acknowledgement that other definitions have greater specificity for clinically significant BCR. (9) Indeed, Stephenson *et al.* subsequently compared 10 different BCR definitions in 3,125 patients treated by RP, and showed that a PSA >0.4 ng/ml with a confirmatory increase had the best fit for prediction of metastatic progression. (11)

For men at high risk for BCR on the basis of adverse pathology features at radical prostatectomy, several randomized trials have examined the role of adjuvant radiation therapy versus observation. These include the SWOG, EORTC and German ARO trials. (12-14) There is agreement among these studies that adjuvant treatment is associated with a reduced risk of BCR compared to observation, although the benefit may be confined to specific subgroups (*e.g.*, positive surgical margins). (15)

Nevertheless, adverse pathology features are an imperfect predictor for BCR and many men never experience recurrence despite the presence of non organ-confined disease at RP. As such, adjuvant radiation therapy will lead to overtreatment in a proportion of patients not destined to have recurrence. An alternative strategy is to give salvage radiation therapy to men with BCR, thereby avoiding the cost and side effects of secondary therapy for those who do not have recurrence. (16, 17) There is currently no randomized evidence comparing adjuvant radiation therapy to early salvage therapy.

However, long-term studies of the salvage radiotherapy approach suggest that it is most beneficial when initiated at low PSA levels. (18) In this regard, it is noteworthy that bone metastases are seen at much lower PSA levels in the post-RP population than in men with an intact prostate. (19) In a recent study of hormone-naïve patients with bone metastases after RP, 25.9% occurred at PSA levels <10 ng/ml. (19)

In light of these issues, there has been investigation into more sensitive PSA assays that might facilitate the earlier identification of BCR. To this end, "ultrasensitive" PSA assays have been developed with a lower limit of detection of <0.1 ng/ml (the limit for conventional assays). Indeed, some of these assays can detect levels in the range of 0.001 ng/ml. Although these assays are relatively new, several studies have examined their use in the post-RP population. Shen et al. evaluated ultrasensitive PSA levels in 545 men following RP to assess the ability of ultrasensitive PSA nadir to predict biochemical relapse. Biochemical relapse was defined as two consecutive increasing post-nadir measurements of 0.1 ng/ml or greater. At a mean follow up of 3.1 yrs, they demonstrated that men with a nadir of less than 0.01 ng/ml had a significantly lower rate of biochemical relapse. Furthermore, ultrasensitive PSA nadir levels of 0.01, 0.02 or 0.04 or greater ng/ml independently predicted biochemical relapse on multivariate analysis. These findings suggest that ultrasensitive PSA nadir point may assist in identifying candidates for early adjuvant or salvage therapies. (20) For example, Malik et al. measured ultrasensitive PSA levels in 801 recurrence-free men at three years after RP to predict the risk of delayed BCR. (21) They found that the majority of patients had a three-year ultrasensitive PSA ≤0.04 ng/ml, with a 7-year BCR-free cumulative survival rate of 95.7%. By contrast, in the minority of patients with a three-year ultrasensitive PSA >0.04 ng/ml (but undetectable by conventional assays), the seven-year BCR-free survival rate was significantly lower at 65.4% ($p \le 0.01$). Thus, the authors identified a majority of men at low risk for delayed BCR on the basis of an ultrasensitive PSA ≤ 0.04 ng/ml at three years after RP. It is possible that this information could be used to reassure patients or to guide the subsequent follow-up protocol, although additional clinical studies would be necessary to evaluate this.

More recently, a novel nanoparticle-based bio-barcode assay was developed, with approximately 300 times greater sensitivity than commercial immunoassays. (22) In the preliminary study, the bio-barcode assay was applied to banked serum samples from 18 post-RP patients. Based upon their data, the authors suggested that a PSA nadir <5 pg/ml represents a "normal" postoperative level, and that a rising bio-barcode level may provide lead-time in detecting BCR. Nevertheless, as yet there is no evidence that initiating secondary therapy for a PSA in the range of 5-100 pg/ml, for example, would improve clinical outcomes. Overall, additional prospective studies will be necessary for the ultrasensitive and bio-barcode assays before any clinical recommendations can be made.

In contrast to the post-RP setting, monitoring for recurrence after radiation therapy is more complex, since PSA-producing prostatic tissue remains in situ. In 1996, the American Society for Therapeutic Radiology and Oncology (ASTRO) met to create a consensus criteria for relapse after radiation therapy. (23) The resultant "ASTRO" definition for BCR is three consecutive rises in PSA after the post-radiation nadir value. The date of failure is then backdated to the midpoint between the nadir value and the first PSA rise.

As with RP, the AUA Guidelines Panel similarly noted a high degree of heterogeneity between studies in the definition used for BCR after radiation therapy. (9) In 208 articles published through 2004, they found 99 different definitions for BCR after radiation therapy. Because the ASTRO criteria was the most commonly used, it was also recommended by the AUA Guidelines Panel to standardize outcomes reporting in clinical studies of radiation therapy.

However, some limitations of the ASTRO critieria engendered controversy, including the lengthy follow-up interval necessary for 3 PSA determinations from which to make the call, the bias introduced by backdating, and the difficulty of comparisons with BCR after RP. (23) Additionally, the ASTRO criteria were developed from data of patients who received external beam radiation therapy alone (without concomitant hormonal therapy) and it was not linked to subsequent survival outcomes. (24)

Accordingly, another consensus conference was held in Phoenix in 2005 to reconsider the criteria for BCR after radiation therapy. (24) This conference led to the establishment of the "Phoenix criteria," in which BCR is instead defined as a PSA rise by ≥ 2 ng/ml above the post-treatment nadir value, with the date of failure assigned "at call" (no backdating). Unlike the 1996 ASTRO criteria, this definition is associated with the risk of subsequent clinical progression and it also may be used for patients receiving concomitant hormonal therapy.

4.2.1.8 Risk calculator/nomograms and artificial neural networks (ANN)

Predictive algorithms and nomograms combine multiple variables to provide information that is statistically more robust than any individual variable. A nomogram is "an objective tool that uses an algorithm or mathematical formula to predict the probability of an outcome". These tools can give probabilities of cancer location or of treatment success, based on scientific studies done in large patient populations. Algorithms/nomograms may be valuable for evaluating the potential extent of disease and risk of recurrence.

Many nomograms have been published in the peer-reviewed literature. The University of California San Francisco developed the Cancer of the Prostate Risk Assessment (CAPRA) score, which is intended to combine the accuracy of nomograms with the ease of calculation of risk. The Johns Hopkins website (http://urology.jhu.edu/prostate/hanTables.php) also has the Han Tables which provide two models:

- 1. Preoperative prediction of recurrence probability following surgery using the available information before surgery (PSA level, biopsy Gleason score, and clinical stage)
- 2. Postoperative prediction of recurrence probability following surgery using the available information before and after the surgery (PSA level, surgical Gleason score, and pathological stage)

The Memorial Sloan-Kettering Cancer Center (MSKCC) nomograms (at http://www.mskcc.org/ mskcc/html/10088.cfm) developed by Kattan *et al.* (1) are based on Cox proportional hazards regression analysis modified by restricted cubic splines. The application of cubic splines imparts flexibility to the nomogram that allows continuous variables to maintain nonlinear relations. The MSKCC nomograms use actuarial survival analysis (*e.g.*, Kaplan-Meier), which is appropriate for calculating time-to-event predictions. An important stance incorporated into these nomograms is that patients receiving secondary treatment before demonstrating disease progression are classified as treatment failures. This approach is used because the secondary treatment was potentially prompted by some evidence of recurrence, so the time of secondary treatment is assumed to be shortly before the recurrence would have been demonstrated. Lastly, these nomograms are calibrated and validated to evaluate their accuracy (2).

Several nomograms have been published utilizing large cohort data in order to assist clinicians and patients to understand the clinical impact of prostate cancer diagnosis. For example, Thompson *et al.* (3,4) used prostate biopsy data from participants in the Prostate Cancer Prevention Trial (PCPT) to develop the Prostate Cancer Risk Calculator, a predictive model of prostate cancer. They used logistic regression to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA, PSA velocity, DRE result, and previous prostate biopsy. From this, they created a predictive model which allows an individualized assessment of prostate cancer risk and risk of high-grade disease for men undergoing prostate biopsy.

In a recent study by Ngo and Presti *et al.* (5), this prostate cancer risk calculator was evaluated in men from the Stanford Prostate Needle Biopsy Database who underwent an initial 12-core prostate biopsy. They concluded that caution should be used when applying the prostate cancer risk calculator to counsel patients referred for suspicion of prostate cancer since it underestimates the risk of high grade disease. In another study Nguyen *et al.* (6) assessed PCPT risk calculator performance in a large contemporary cohort of patients sampled by extended biopsy schemes. They concluded that the current calculator remains predictive but does not maintain initial accuracy in contemporary patients sampled by more extensive biopsy schemes. Instead, they suggested that revising the calculator, by modeling contemporary data and/or incorporating additional prognostic variables, might improve its utility in current clinical practice.

Based on data from the ERSPC, Kranse-Roobol *et al.* used multivariable logistic regression to create a different risk estimation tool known as the Prostate Cancer Risk Calculator (7-10) (http://www. prostatecancer-riskcalculator.com/). In this indicator, six different logistic regression models have been used (**Table 2**) and the contributions of the different predictors were graphically translated via rotation (**Figure 4**). Different versions of the Risk indicator are available for the prediction of biopsydetectable prostate cancer as well as potentially indolent disease. Since its description, this predictive tool has been validated in external populations with more extended biopsy schemes.

FIGURE 4

One of the Prostate Cancer Risk Calculators: Risk Calculator 3: Predicting the likelihood of a positive sextant biopsy in a man who has never been screened.

Source: http://www.prostatecancerriskcalculator.com/seven-prostatecancer-risk-calculators.



Select Risk Calculator: You Res Calculator (1 2 6 Res Calculators for motical use prior 1 5 + 1011 4 4 + 1011 5

Risk Calculator 3

Previously unscreened men - is biopsy needed?

Hek Calculator 3 allows a more precise prediction of a positive biopoy than the PBA Risk Calculater because it includes the results of the rectal excenses on, atmostregenetry indicating the presence of hyposchogenic leators, and also the hyposchogenic leators, and also the volume of the prestate (determined at utmanography). Each personale has its own value in predicting topony outcome (Richol et al., Prostate 2008). Please rule that a large proclate volume is an important negative predictor of prostate concerve.

TABLE 2 Description of the variables used in the SWOP Prostate Cancer Risk indicator

Modified from: Kranse R, Roobol MJ, Schröder FH. A graphical device to represent the outcomes of a logistic regression analysis, an illustration of its possible use in prostate cancer screening, and prostate cancer treatment counselling. *Prostate 2008;68:1674–80.*

PCa Risk Calculators	Variables used in the model
1	Age, family history of prostate cancer, AUA seven-symptom score
2	Serum PSA value
3	Serum PSA value, ultrasound-assessed prostate volume, outcome of DRE (1/0), outcome of TRUS (ie, a hyopechoic lesion, 1/0)
4	Serum PSA value, ultrasound-assessed prostate volume, biopsy Gleason score, cancerous tissue length of total of prostate biopsies, noncancerous tissue length of total of biopsies
5	Serum PSA value, ultrasound-assessed prostate volume, outcome of DRE (1/0), outcome of TRUS (ie, a hyopechoic lesion, 1/0)
6	Serum PSA value, ultrasound-assessed prostate volume, outcome of DRE (1/0), outcome of TRUS (ie, a hyopechoic lesion, 1/0), having had a previous negative biopsy (1/0)

AUA = American Urological Association; PSA = prostate-specific antigen; PC = prostate cancer; DRE = digital rectal examination; TRUS = transrectal ultrasound.

Artificial neural networks (ANNs) are a computational methodology used to perform multifactorial analyses, inspired by networks of biological neurons (**Figure 5**). Like neural networks, ANNs contain layers of simple points (nodes) of data that interact through carefully weighted connection lines. The use of ANNs in prostate cancer is ideal because of:

Djavan *et al.* (9) showed that artificial neural networks (ANNs) increase the predictive accuracy to predict the results initial prostate biopsy compared with PSA-related parameters. (9)

- 1. multiple predicting factors that influence outcome;
- 2. the desire to offer individual consulting based on various tests;
- **3.** the fact that prior logistic regression analysis results have had serious limitations in application; and
- **4**. the need for an up-to-date tool with wide-spread applicability.



FIGURE 5

ANN architecture for diagnosis of prostate cancer on repeat biopsy

(Stephan C, Xu C, Cammann H et al. Assay-specific artificial neural networks for five different PSA assays and populations with PSA 2-10 ng/ ml in 4,480 men. World J Urol. 2007 Mar,25(1):95-103) Reprinted with permission.

4.2.2 Human glandular kallikrein 2 (hK2)

Human glandular kallikrein 2 (hK2) has 80% sequence homology with PSA and they both belong to the human tissue kallikrein family (1). It has been found that hK2 expression increases incrementally during the development from benign prostate epithelium to primary cancer and lymph node metastasis (2). This is in contrast to the low PSA serum levels that are often seen in some patients with poorly differentiated prostate cancers. These findings suggest that compared to PSA, hK2 has a higher ability to distinguish between BPH and prostate cancer. Partin *et al.* proposed that hK2 measurements in combination with f/t PSA could improve the sensitivity and specificity of cancer detection, and avoid unnecessary biopsies in the tPSA levels from 2.5 to 4.0 ng/ml (3). A screening study in Goteborg using a PSA cut-off of 3 ng/ml showed a significantly higher hK2 levels in men with prostate cancer (4). In the bloodstream, hK2 seems to be present in concentrations of 1–2% compared with PSA (5,6)

However, the covariance of hK2 and PSA concentrations is generally less than 60%, suggesting that hK2 might function as an independent tumour marker. Similar to PSA, hK2 can also be found in different molecular forms. It has been shown *in vitro* to form a complex with several protease inhibitors, including 2-antiplasmin, ACT, antithrombin III, 2-macroglobulin, C1-inactivator, and plasminogen activator inhibitor-1 (PAI-1) (7,8). Both free and complexed forms of hK2 have also been found in biological fluids. In the bloodstream, gel-filtration studies have suggested that 80–95% of hK2 is in the uncomplexed, free form (5, 9, 10) and up to 20% can be complexed with ACT in sera from patients with PCa that contain high concentrations of hK2 (11). Because circulating hK2 is present in very low concentrations, the immunoassays used to measure hK2 must have low detection limits and excellent reproducibility. For the PSA "gray zone" of 2–10 μ g/L, respective hK2 values will be 0.02–0.5 μ g/L. In testing with the first published hK2 assay, up to 57% of samples had hK2 concentrations below the detection limit (5). The utility of serum hK2 measurements and its value in combination and/or versus f/t PSA still need to be confirmed on larger studies. hK2 seems to offer complementary information to PSA when included in a panel of kallikrein markers (12). In this validation of the ERSPC study, the diagnostic accuracy for detection of prostate cancer, as measured by area under the ROC curve, was improved from 63% to 78% with the panel.

4.2.3 **Prostatic acid phosphatase (PAP)**

The discovery of prostatic acid phosphatase (PAP) by Kutscher and Wolbers in 1935, and additional early work by Gutman *et al.*, uncovered the association of PAP with metastatic prostate cancer, making it the original biomarker for prostate cancer (PCa). (1-5) Normally secreted by mature prostatic glandular and ductal epithelial cells, PAP is the most abundant phosphatase in human prostate tissue and seminal fluid. (6) Malignant disruption of the normal epithelial barriers leads to elevated serum levels of PAP, allowing the serial monitoring of PAP to assess efficacy of hormonal therapy and predict clinical outcomes. (7-9) However, initial studies of its utility as a diagnostic tool were unsuccessful due to poor sensitivity. (10) Ultimately, the discovery of prostate-specific antigen (PSA) significantly diminished the clinical role of PAP. (11)

Despite the increase in early detection of PCa associated with PSA screening, approximately 30% of patients develop biochemical recurrence (BCR) following primary local therapy. (12,13) Preoperative features such as elevated PSA levels and higher Gleason scores fail to optimally identify candidates for adjuvant therapy. (14-16) These findings have prompted several groups to assess the use of serum PAP as a marker for PCa stratification and prognosis. Moul *et al.* reported that pretreatment PAP levels serve as an independent predictor of biochemical recurrence. (17) Han *et al.* also found that serum PAP levels independently predicted tumour recurrence following prostatectomy; and they also reported that lower PAP levels were associated with improved biochemical recurrence-free survival. (18) More recently, Dattoli *et al.* and Fang *et al.* reported that PAP levels were the strongest predictor of long-term biochemical failure and cause-specific survival in a cohort of men with a Gleason score of \geq 7, and PSA \geq 10 ng/mL following external beam radiotherapy (EBRT), and brachytherapy, respectively. (6,19,20) As local control of prostate cancer improves, PAP may have a potential role in identifying patients at higher risk for late failure or development of systemic disease. (21)

Recent investigations on PAP have identified a distinct form of the phosphatase, labeled cellular PAP (cPAP). These studies indicate that cellular PAP (cPAP) levels regulate prostate epithelial growth and may play a role in the progression of hormone refractory PCa. (22) In contrast to serum PAP, cPAP levels and corresponding cPAP mRNA levels are lower in PCa tissue relative to normal or hyperplastic prostate tissue. (23) Additionally, cPAP and serum PAP have differing biochemical profiles. (24-28) Through its role as a prostate-specific protein tyrosine phosphatase, cPAP may function as a negative growth regulator of prostate cancer. (29,30) Specifically, cPAP dephosphorylates human EGF receptor-2 (HER-2) and consequently decreases cell proliferation. (31) Conversely, decreased cPAP levels results in elevated HER-2 activity, correlating with PCa progression and androgenindependent growth of PCa cells. (32) Furthering these findings, Chuang et al. have shown that cPAP levels inversely correlate with tyrosyl phosphorylation and activation of ErbB-2 expression. (22) Increased expression of ErbB-2 has been associated with PCa growth and PSA secretion in androgenreduced conditions, supporting a role for cPAP as a negative growth regulator of PCa and progression to hormone refractory disease. (19,33,34) Despite these findings, work remains to identify the direct interaction between cPAP and ErbB-2 as well as the specific dephosphorylation site of ErbB-2 by cPAP.(22)

Finally, the United States Food and Drug Administration (FDA) recently approved a novel immunotherapy for hormone refractory PCa that was developed using PAP as the antigen. (35) Via a recombinant DNA fusion technique, PAP is linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), creating an immune stimulatory protein known as PA2024. (35) This fusion protein is combined with dendritic cells obtained via leukophoresis from an individual patient and then re-infused into this patient to elicit an immune response. The final infusion product is known as Sipuleucel-T (Provenge®, or APC8015). (35,36) Sipuleucel-T has extended overall survival by approximately four months and reduced risk of death by 22% in men with asymptomatic or minimally symptomatic metastatic hormone refractory PCa in Phase III randomized controlled clinical trials, while maintaining an acceptable side-effect profile. Sipuleucel-T did not result in a significant effect on radiographic progression-free survival or PSA levels. (35)

In conclusion, PAP has experienced a dramatic evolution from a diagnostic marker to a treatment target since its discovery in 1938. Developing work with cPAP and immunotherapy offer promise that PAP's role in PCa diagnois and therapy may continue to expand.

4.2.4 Alkaline phosphatase

Alkaline phosphatase is an enzyme produced naturally within the body. It is mostly made in the liver and bones. When there is a breakdown of bone within the body, more alkaline phosphatase is sent into the bloodstream where it can be measured with a simple blood test. Because prostate cancer has a strong preference for spreading to the bones, alkaline phosphatase could theoretically be used to determine bone metastasis. Lorente *et al.* (1) investigated the usefulness of bone alkaline phosphatase isoenzyme and prostate specific antigen (PSA) determined by radioimmunoassay to predict bone scan evidence of metastasis in newly diagnosed untreated and treated prostate cancer. They showed that a bone alkaline phosphatase enzyme level that becomes greater than 30 ng/ml indicates the need to perform a bone scan. They recommend the clinical use of bone alkaline phosphatase enzyme, determined by radioimmunoassay and PSA measurement, for the diagnosis of bone metastases and progression of prostate cancer because of the good sensitivity and specificity.

In a recent study, Sonpavde *et al.* (2) evaluated the association of a change in serum alkaline phosphatase with overall survival in men with metastatic castration-resistant prostate cancer (CRPC) receiving chemotherapy. They reported that for men with CRPC, bone metastasis and high baseline alkaline phosphatase, receiving docetaxel or mitoxantrone chemotherapy, normalization of alkaline phosphatase was predictive of better survival. An increase in alkaline phosphatase was also predictive of poor survival independent of PSA increase. In another study, Yigitbasi *et al.* (3) evaluated the prognostic value of serum alkaline phosphatase is important and was among one of the statistically significant prognostic factors that affects time to progression and survival of metastatic prostate cancer. Xie *et al.* (4) reported that alkaline phosphatase significantly predicted survival in men with CRPC who had bone metastases. They evaluated 224 men who had CRPC with bone metastases, and who were receiving chemotherapy. In this study, patients with normal alkaline phosphatase levels and higher PSA levels have improved survival.

The clinical use of alkaline phosphatase may thus be limited to those individuals at risk of bone metastasis, under consideration for bone imaging, or receiving systemic therapy for known bone disease. The lack of prostate cancer specificity for this marker makes it unlikely to be widely employed in the majority of prostate cancer patients.

4.2.5 Early prostate cancer antigen (ePCA)

Utilizing a focused proteomic approach, a series of novel prostate cancer-associated biomarkers has been identified. One of the hallmarks of a cancer cell is alterations in the shape, size, and morphometry of the nucleus. Since nuclear changes are one of the key features the pathologist uses to identify cancer cells, the goal of these studies was to find molecular correlate of what the pathologist is seeing under the microscope.

The initial studies examining composition of the nuclear structure associated with prostate cancer evaluated normal rat prostate tissue in comparison with a rat model of prostate cancer (Dunning tumour). This study compared how the nuclear matrix was altered in cancer cells and if these matrix protein patterns could distinguish closely related sublines of the same Dunning tumour (1). The nuclear matrix proteins in several Dunning cell lines were examined and compared with the nuclear matrix protein composition of the dorsal prostate, the original tissue from which this tumour was derived. Using high-resolution two-dimensional gel electrophoresis, the NMPs of the Dunning cell lines were found to be significantly different from the rat dorsal prostate. In addition, using the same technique, the study was able to differentiate metastastic and non-metastatic lines. The NMP composition in human prostate tissue was then examined (2). The NMP patterns for fresh prostate, benign prostatic hyperplasia (BPH), and prostate cancer from 21 men undergoing surgery for clinically localized prostate cancer or BPH were compared using the high-resolution gel electrophoresis. Fourteen different proteins, by molecular weight and isoelectric point, were consistently present or

absent among the various tissues. One of the identified NMPs, ePCA (Early Prostate Cancer Antigen), was expressed in prostate cancer samples and in normal adjacent tissue, but not in prostates from unaffected individuals.

Antibodies directed against ePCA positively stain the negative biopsies of men who, as much as five years later, were diagnosed with prostate cancer (3). A significant difference exists in ePCA staining intensity between tumour tissue from the prostate cancer population and tissue from donor controls. At the same time, normal adjacent prostate tissue from cancer patients also has significantly higher ePCA staining when compared with the donor controls, indicating the presence of a field effect (3). These studies were further supported by additional studies using distinct types and sets of samples but which likewise also identified the field effect changes associated with ePCA expression.

With the interesting findings observed regarding the tissue expression of the protein, studies were performed to determine if ePCA could be detected in the blood of men with prostate cancer. The initial studies on a very small sample set revealed that plasma ePCA levels above 1.7 OD could detect prostate cancer in 11 out of 12 prostate cancer patients, demonstrating a sensitivity of 92%. None of the healthy donors had plasma ePCA levels above the cut-off level. Furthermore, when considering the entire study population, only two bladder cancer patients presented with plasma-ePCA levels above the cut-off, resulting in an overall specificity of 94% (4). Recent studies examining the expression of EPCA in the serum have demonstrated that ePCA levels can be helpful in predicting the future detection of prostate cancer (5,6), as well as provide prognostic information about the disease (7, 8) (**Table 3**). Further studies are clearly needed in order to determine the potential clinical utility of ePCA. The biggest challenge is the development of a robust clinical assay that can detect this protein in the blood.

TABLE 3 The AUC Values, Specificity, Sensitivity, PPV, and NPV at the Thresholds for tPSA, PSAD, and Preoperative ePCA for the Discrimination of BPH and IPCa

Modified from: Zhao Z, Zeng G, Zhong W. Serum early prostate cancer antigen (EPCA) as a significant predictor of incidental prostate cancer in patients undergoing transurethral resection of the prostate for benign prostatic hyperplasia. *Prostate. 2010;70:1788-98.*

Test	AUCs	95% CI	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
tPSA	0.524	0.404 - 0.632	38.7	42.6	30.2	67.7
PSAD	0.615	0.558 - 0.738	53.1	44.3	36.4	70.1
ePCA	0.952	0.912 - 0.981	98.0	100	85.7	100

PSA, prostate specific antigen; PSAD, PSA density; ePCA, early prostate cancer antigen; IPCa, incidental prostate cancer; BPH, benign prostatic hyperplasia; PPV, positive predictive values; NPV, negative predictive values. AUC, area under the curve; 95% Cl, 95% confidence intervals; ROC, receiver operating characteristic curves.

4.2.6 Growth factors

4.2.6.1 Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3)

The tissue-expressed insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) has been shown to be associated with tumour grade, progression, pathologic stage, and clinical recurrence in a variety of cancers, including prostate cancer (1).

Stattin et al. (2) measured levels of IGF-1, IGFBP-1, IGFBP-2, IGFBP-3, and insulin in plasma samples from 149 men who had a diagnosis of prostate cancer between 1 month and 10 years after blood collection, and among 298 control men. They found that patients with prostate cancer had statistically significantly higher mean levels of IGF-I than control subjects (229 ng/ml; 95% confidence interval [CI] = 218-240 ng/ml versus 214 ng/ml [95% CI = 208-221 ng/ml]; p=0.02) and IGFBP-3 (2611 ng/ml [95% CI = 2518–2704 ng/ml] versus 2498 ng/ml [95% CI = 2437–2560 ng/ml]; p=0.04). Also, they reported that association between prostate cancer risk and increased IGF-1 was particularly strong in younger men in their study, suggesting that circulating IGF-1 may be specifically involved in the early pathogenesis of prostate cancer (2). In a prospective study, higher levels of acid-labile subunit (ALS) - which modulated IGF-1 levels - associated with a 40-60% increased risk of prostate cancer have been described. Higher levels of ALS also correlated with a 2-fold risk of advanced stage PCa that persisted for more than nine years after blood testing. Still, the origin and role of circulating levels of IGFs and IGFBPs and its potential implications for prevention strategies remain to be further elucidated in subsequent studies. (3) Future research may focus on the manipulation of IGF in the management of prostate cancer or on its chemoprevention either by therapeutic regulation of IGF-1 levels in the upper quartile or by dietary modification. (4)

In a meta-analysis, Rowlands *et al.* (5) reported that, even though we observed a modest increase in the risk of prostate cancer associated with higher levels of IGF-1, and a slight reduced risk with higher levels of IGFBP-3, neither of these peptides are likely to be useful as additional measurements in prostate cancer PSA screening. The strength of the associations are too weak to have any value as a screening test because at these odds ratios, the detection rate (sensitivity) is less than 8% for a 95% specificity (5% false positive rate). (6,7)

This issue has been investigated by Oliver *et al.* (8) who found no evidence that measurement of IGFs or IGFBPs enhanced the specificity of prostate cancer detection beyond that achievable by the currently used free/total PSA index.

Although IGF-1 measurement is unlikely to increase the discriminatory accuracy of current prostate cancer screening methods (serum prostate specific antigen or digital rectal examination), it does represent a potentially modifiable risk factor for prostate cancer, and this could be achieved through dietary or lifestyle interventions which may alter IGF-1 levels. (9)

4.2.6.2 Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR) has been found to be able to translocate to the nucleus upon stimulation with epidermal growth factor (EGF) (10). Once in the nucleus, it has been shown to be involved in several different cellular processes that are important in cancer progression. Lin *et al.*

(10-11) have previously shown that nuclear EGFR is able to activate the transcription of genes, such as the cell cycle regulator cyclin D1, through association with its promoter (12-13). Nuclear EGFR was also found to be involved in the activation of the inducible nitric oxide synthase (iNOS) pathway through its interaction with signal transducers and activators of transcription 3 (STAT3) (14). Furthermore, it has also been found to be involved in DNA synthesis (8) and repair (15-17) through interaction with the proliferating cell nuclear antigen (PCNA) and DNA-dependent protein kinase. As the functions of nuclear EGFR continue to be elucidated, it is becoming more apparent that nuclear expression of EGFR plays a significant role in prostate cancer development and progression.

Activation of EGFR has been implicated in the progression of normal prostatic epithelium to androgen-dependent cancer and, eventually, hormone-refractory prostate cancer. Marks *et al.* (18) investigated both amplification of EGFR gene by fluorescence *in situ* hybridization (FISH) and over-expression of EGFR by immunohistochemical staining in prostate tissue from 71 patients treated by hormonal therapy. They reported that EGFR gene amplification was present in 1 of 71 tumours. Immunohistochemically, EGFR expression was demonstrable in 57 of 71 tumours and membranous immunostaining for EGFR was observed in >75% of tumour cells in 11% of cases. In their study, there was no correlation between EGFR protein expression and gene amplification, or EGFR expression and clinicopathological characteristics or clinical outcome. Marks and coworkers found that EGFR gene expression was detectable in 35% of a large series of hormone-treated prostate cancer, and that EGFR protein is frequently expressed in tissues from these patients. EGFR overexpression may serve as a reasonable target for therapeutic intervention in this otherwise difficult-to-treat subset of prostate cancer. (18)

In another study, Shuch *et al.* (19) investigated EGFR expression in a well-characterized cohort of PCa patients to determine the association between EGFR expression and race. Tumour tissues from 202 radical prostatectomies were studied (142 African Americans, 60 whites; median age, 67 years; stage T2, n = 130; stage > or = T3, n = 72; Gleason score < 7, n = 110; Gleason score > or = 7, n = 92). They reported that EGFR overexpression, defined as complete membrane staining in more than 10% of tumour cells, was observed in 75 of 202 patients (37%). There was a significant association between EGFR overexpression and African American race (p=0.0006), higher pretreatment prostate-specific antigen (PSA; p=0.02), and stage (p=0.02), but not Gleason score (p=0.33). The association between African American race and EGFR overexpression remained significant in a multivariate model after controlling for grade, stage, and pretreatment PSA simultaneously (p=0.003). (19)

HER2/neu (also known as ErbB-2) stands for "Human Epidermal growth factor Receptor 2" and is a protein that confers higher aggressiveness in some cancers. It is a member of the ErbB protein family, more commonly known as the epidermal growth factor receptor family. Osman *et al.* (20) determined the association between serum levels of shed Her-2/neu protein and disease progression in men with prostate cancer. In this study, of 279 patients, 37 (13.3%) had increased serum Her-2/neu. They concluded that increased serum Her-2/neu correlates with the presence of metastatic disease and it may indicate an increased risk of death in patients with castrate, metastatic prostate cancer. The detection of serum Her-2/neu is a minimally invasive alternative to tumour sampling for identifying potential candidates for anti-Her-2/neu treatment strategies. (20)

4.3 Urine Markers

Urine biomarkers are promising since they are readily available and obtainable noninvasively. Screening markers of urine samples can be used to detect either exfoliated cancer cells or secreted prostatic products that could indicate the presence of prostate cancer. Prostatic products are released directly into the genitourinary tract, and may be useful for early detection of prostatic cancer. DNA, RNA and protein markers have all been proposed as suitable diagnostic agents.

A promising approach to improve the diagnostic accuracy of tumour markers is to identify the prostate cancer-specific genes. Novel approaches in molecular technology seem to overcome hurdles in detecting prostate cancer cells in urinary samples. Thus prostate cancer detection by means of urine samples is coming into the realm of clinical practice.

4.3.1 Prostate cancer antigen 3 (PCA3)

Prostate-specific antigen (PSA) has clear but limited ability to detect prostate cancer. In fact, the Prostate Cancer Prevention Trial (PCPT) detected prostate cancer in 6.6%, 10.1%, 17%, 23.9% and 26.9% of subjects with "normal" PSA values of <0.5, 0.6-1.0, 1.1-2.0, 2.1-3.0 and 3.1-4.0 ng/ml respectively. Since the majority of men between the ages of 45 and 75 had PSA values of <4.0 ng/ml, it has been suggested that 15% of high-grade cancer cases are routinely missed with a PSA-driven evaluation. (1-3) To refine risk stratification, derivative measurements such as percent free PSA3, age-specific PSA ranges (4), and PSA velocity (5) have been proposed, but are constrained by the same limitations as PSA itself; namely, non-malignant conditions such as benign prostatic hyperplasia (BPH) and prostatitis are common confounding conditions. These limitations of PSA as a clinical tool have led to an intensive search for other prostate cancer biomarkers.

While many promising biomarkers for the early detection of prostate cancer, have been described, few make it past the initial discovery phases and fewer yet are ever translated into a clinical assay. One of the most promising biomarkers for prostate cancer is prostate cancer antigen 3 (PCA3, also known as Differential Display Code 3 or DD3). (6) PCA3 is a prostate-specific gene that was found in 95% of prostate cancer samples initially studied (6), and significantly overexpressed in cancer versus benign tissue (7). It is known to be a non-coding messenger ribonucleic acid (mRNA) with no resultant protein; thus its biologic role remains uncertain.

Clinically, PCA3 mRNA is detectable in the urine and prostatic fluid of men with prostate cancer. This fact led to the development of a precise molecular urinary assay with a good sensitivity and specificity for predicting prostate cancer on needle biopsy (69% and 79%, respectively). In contrast, specificity of PSA was only 28% in the same sample. (8) Other studies have shown that urine and prostatic fluid PCA3 assays produce comparable results. (9) The same study found that the informative rate for the PCA3 assay improved from 74.4% to 96.7% with an attentive DRE. (8) This led to the recommendation that urine should be collected after an attentive DRE to increase the number of prostate cells shed into the urine.

Currently, several urinary PCA3 assays exist, with initial feasibility studies in Europe relying upon a time-resolved fluorescence-based, quantitative RT-PCR-based methodology. The only commercially available PCA3 assay in the United States uses whole urine rather than sediment, and relies upon magnetic microparticle capture, transcription-mediated RNA amplification and hybridization protection assay detection of PSA and PCA3 mRNA. All versions of this assay are reported as a ratio of PCA3 mRNA/PSA mRNA. (8) PCA3 is currently the only urinary prostate cancer biomarker to have progressed past the initial discovery phases and be translated into a commercial assay.

Subsequently, a number of multicentre studies have evaluated the diagnostic ability of urine PCA3 compared to a biopsy; (10-12) diagnostic accuracies ranged from 66-81% (10-12) and were superior to that of PSA (p<0.05). (10-12) In addition, PCA3 scores correlated with the risk of prostate cancer detected on biopsy such that a PCA3 value >100 was associated with a 50% chance of a positive prostate cancer diagnosis. (11) Deras *et al.* in a separate study analyzed data on 190 prostate cancer cases and 346 controls. (13) (**Table 4**) Both PCA3 (p<0.0001) and history of at least one biopsy (p<0.0001), but not the interaction of these two variables predicted prostate cancer on biopsy. The PCA3 receiver operating characteristic curve did not differ in its ability to detect prostate cancer amongst first, repeat and all biopsies. Likewise, predictability curves were similar in shape amongst the three biopsy groups. The only noted difference was at the beginning of the predictability curve (14) where prostate cancer prevalence was higher for first biopsy. This would suggest that PCA3 may be useful for men with prior negative prostate biopsies, a clinical situation where PSA has little diagnostic value.

PCA3 Cut-off	Sensitivity (%)	Specificity (%)
5	96	14
20	71	56
35	54	74
50	40	83
65	32	91
90	20	95

TABLE 4 PCA3 Assay Sensitivity and Specificity in various cut-offs

Modified from: Deras IL, Aubin SM, Blase A, et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. J Urol. 2008;179:1587-92.

N= 570 men undergoing prostate biopsy, 36% biopsy positive PCA3: prostate cancer antigen 3

PCA3 mRNA levels are independent of prostate volume and serum PSA. (15) The independence from PSA suggests that it has the ability to add significantly more diagnostic information compared to PSA derivatives, which are all correlated with PSA. Assuming that PSA is still used as a screening test, this offers significant advantages. In one study by Haese, PCA3 urinary levels were independent of prostate size as measured by transrectal ultrasound; thus, eliminating confounding by prostate size and BPH. (16) Moreover, in the same sample he was able to show that PCA3 was independent of PSA. (16) Thus, PCA3 may potentially be used for additional risk stratification across all PSA ranges.

There is a suggestion that PCA3 may significantly refine the pre-test probability for men considered for a repeat biopsy. Repeat prostate biopsy is indicated for patients who have a prior negative biopsy but continue to have an elevated serum PSA or abnormal DRE, or for follow-up of previous pathologic diagnoses of pre-malignant high-grade prostate intraepithelial neoplasia (HGPIN) or ASAP. (17) It remains unclear when and how often to repeat a prostate biopsy as there is a documented decline in cancer detection with each successive biopsy. (18,19). Among men with persistently elevated PSA who are undergoing repeat biopsy, Marks and colleagues demonstrated limited reliability of PSA in prostate cancer prediction and a significant superiority of the urine PCA3 assay in 226 men undergoing repeat biopsy (AUC 0.68 for PCA3 versus 0.52 for serum PSA, p<0.01). (11) Others have found as a sub-analysis that the diagnostic accuracy of PCA3 was similar between men undergoing first versus repeat biopsy. (13,20)

PCA3 may be significantly higher among more aggressive, higher grade, and larger tumours relative to more indolent or lower grade tumours. On prostate biopsy, PCA3 has been variably found to be associated with Gleason grade. (21,22) In the REDUCE trial, PCA3 was measured in the control group and among those with cancer, the PCA3 level was associated with increasing grade. (22) However, several smaller studies have not demonstrated this association. (21) It is conceivable that the 40% estimated undergrading of cancer with a needle biopsy relative to a radical prostatectomy, may explain why this association is hard to confirm on a biopsy. (23) More convincing evidence for a grade association comes from radical prostatectomy pathologic findings. (15) In such a study, the PCA3 level was measured in the urine prior to surgery and found to be correlated with the final pathologic grade. (15)

Despite promising initial studies, the clinical utility of PCA3 has only been intensely studied in the setting of prostate cancer detection after a screening PSA test has been performed. (24) PCA3 has not been rigorously evaluated in other context for which PSA is otherwise commonly used and thus caution should be exercised in this regard. To date, other untested clinical applications for PCA3 include prostate cancer screening, either independently or as adjunct with PSA; post-prostate cancer treatment follow-up; and active surveillance of low-grade PCA. Future work is clearly needed in these areas.

While PCA3 appears to improve prostate cancer detection, it has inherent limitations. There are no standards for the urinary assay and all methods rely upon urine obtained immediately after an attentive DRE. This is similar to PSA for which there are several assays; and reported values vary based upon the assay method of PSA measurement used (25). Specimen informative rates are generally high, but a small proportion of men will have to provide repeat urine samples after an inadequate DRE, to express a sufficient number of prostate cells. Furthermore, it is unclear if a suboptimal DRE or a small peripheral tumour producing a minimal shed cells into the urine can result in a falsely negative PCA3 score. A recent report noted that PCA3 RNA can be detected in HGPIN and benign tissue proximal to neoplastic glands, raising the possibility of confounding by some HGPIN lesions. (26) Lastly, this assay, while approved in Europe and Canada, has not been FDA-approved.

There is mounting evidence that suggest a combination of urine PCA3 and serum PSA is superior to PSA alone for detection of prostate cancer, though these studies are limited to pre-screened patients with elevated or rising PSA levels. PCA3 may serve as a useful adjunct for risk stratification for prostate biopsy, and in particular, for counselling men contemplating repeat biopsy where PSA is of much less diagnostic value.

4.3.2 **Survivin**

Survivin mRNA expression in voided urine from patients with bladder, prostate, and renal cancer was evaluated and revealed 100% specificity but no sensitivity. (1) Fisker *et al.* have investigated the effects of different locked nucleic acid modified antisense mRNA antagonists against survivin in a prostate cancer model. These mRNA antagonists were found to be potent inhibitors of survivin expression at low nanomolar concentrations indicating the high potential of locked nucleic acid for therapeutic use. (2)

4.3.3 **TERT**

Telomerase is coded for by the TERT gene and is important in maintaining the telomeric ends of chromosomes. Telomere activity has been identified in cell senescence and malignancy, capping and protecting the ends of the eukaryotic chromosomes and thus, protecting them from degradation and fusion with other chromosomes. In a recent study by Bantis *et al.* (3), positive telomerase expression was detected in 67.8% of prostate carcinomas.

4.3.4 **MCM-5**

Two monoclonal antibodies to detect mini-chromosome maintenance-5 (MCM-5) in urinary sediments have been developed and tested in urine samples of patients with prostate cancer. MCM-5 was not elevated in patients with BPH. A recent study by Dudderidge *et al.* reported that urinary MCM-5 test detects prostate cancer with 82% sensitivity and with a specificity ranging from 73 to 93%. They concluded that urinary MCM-5 detection seems to be a simple, accurate, and noninvasive method for identifying patients with prostate cancer. (4)

4.3.5 **OHDG**

Urinary 8-hydroxydeoxyguanosine (8-OHdG) is considered as a biomarker of generalized cellular oxidative stress and has been linked to cancers. Increased urinary concentrations of 8-OHdG were detected by the enzyme-linked immunosorbent assay (ELISA) in the urine of patients with prostate and bladder cancer. (5) But a recent study by Richardson *et al.* (6) reported that in prostate cancer, 8-OHdG was not significantly elevated in the acini or stroma of cancer-containing prostatic tissue compared with age-matched benign prostatic tissue. Although 8-OHdG was significantly elevated in the acini nuclei compared with the surrounding stroma nuclei in both cancer-containing and benign prostatic tissue, it, by itself, was not a strong biomarker for prostate cancer risk assessment. (6)

4.3.6 Sarcosine

Sarcosine is an amino acid derivative of N-methylglycine and is involved in the amino acid metabolism and methylation processes that are enriched during prostate cancer progression (see Metabolomics section). It could also serve as a new target to be measured during therapeutic interventions and help in the identification of aggressive tumours for radical treatment. Cavaliere *et al.* (7) presented a new urine test that can help in early diagnosis of prostate cancer. Their method for the quantification of sarcosine in urine consists of a solid-phase microextraction (SPME) step followed by gas chromatography-triple quadrupole mass spectrometry analysis. The accuracy and precision of their method were evaluated at concentrations of 70, 250, and 800 ng/ml, and were found to be acceptable. Very satisfactory values (0.10 and 0.16 ng/ml, respectively) were also achieved for the limit of detection and the limit of quantification. This protocol represents a rapid, simple, selective, and sensitive tool to quantify sarcosine in urine samples for prostate cancer diagnosis and for a screening test. (7)

4.4 Tissue Markers

Identification of prostate cancer within tissue is generally performed through the observation of glandular patterns upon microscopic exam. As pathologists became more able to survey prostate tissues through immunohistochemical methods, several characteristic proteins were identified which might allow more specific assessment of prostate cancer within small amounts of tissue. Additionally, immunohistochemistry allowed assessment of the predictive ability of candidate proteins in determining disease prognosis.

Investigations into the genetic origins of prostate cancer have provided the most significant recent advances in biomarker development. High-throughput microarray and sequencing technologies have enabled numerous gene expression studies exploring the differences between benign and malignant prostate tissue. Building on these initial findings, work has expanded further into defining additional neoplastic molecular changes, such as genetic polymorphisms and epigenetic modifications. This section aims to summarize the clinically relevant findings within these areas and their potential for novel biomarkers. (1)

4.4.1 Alpha-methyl CoA racemase (AMACR)

Utilizing subtractive hybridization and differential display techniques, several genes were initially identified as possible cancer markers. The Corixa Corporation combined these techniques with DNA microarrays and identified the gene P504S, which was found to express the protein α -methylacyl-CoA racemase (AMACR). (1,2) This protein is overexpressed in the prostate cancer epithelium, allowing for its use as a highly specific tissue diagnostic tool. (3,4). Several studies have recently reported utilizing urine detection of AMACR as part of prostate cancer-specific urine panels and may ultimately outperform current serum biomarkers. (5) Barry *et al.* (6) conducted a prospective cohort study among 920 men aged 47 to 84 years, who were diagnosed with prostate cancer in order to evaluate the association of AMACR expression with lethal prostate cancer over a 20-year follow-up period. They found that lower AMACR intensity was associated with higher prostate-specific antigen levels

(p=0.003), and more advanced clinical stage (p=0.06) at diagnosis, and a nonsignificant trend for higher risk of lethal outcomes. The hazard ratio (HR) comparing the lowest to the highest quartile of AMACR expression intensity was 1.53 ((95% CI: 0.86-2.73), *p*-for-trend across quartiles=0.07); this trend was further attenuated after adjustment for age, Gleason score, stage, and cohort with an HR of 1.24 (95% CI: 0.69-2.22), *p*-for-trend =0.23. They concluded that low AMACR expression in primary tumour specimens was not independently associated with the development of metastatic and lethal prostate cancer after treatment over a 20-year follow-up period, after adjustment for important clinical covariates at diagnosis. (6)

4.4.2 Hepsin

Hepsin is a type II serine protease that has been shown to be overexpressed in multiple studies. (1,2). Analysis of tissue microarrays from over 700 clinically stratified prostate cancer specimens demonstrated that hepsin expression correlates significantly with measures of clinical outcome (3). In a study by Stephan *et al.* (4), matched prostate tissue samples from the cancerous and noncancerous parts of the same prostates were obtained from 90 patients with prostate cancer who underwent radical prostatectomy. They found that hepsin overexpression in cancerous compared with noncancerous tissue was found in 81 of the 90 patient samples (90%, p<0.001). In 48 patients (53%), hepsin overexpression was more than 10-fold in cancerous tissue. The ratio of cancerous-to-noncancerous hepsin expression was significantly higher in the 39 patients with grade 3 tumours compared with the 51 with grade 2 tumours (median 15.5 vs 9.6, p=0.031). For the prognosis, a cut-off at the 75th percentile provided a significant difference between patients at lower risk (pT2, G2 and Gleason score less than 7) and higher risk (pT3/4, G3 and Gleason score 7 or greater) for relapse. Their report of the quantitative analysis of hepsin expression showed a strong and significant overexpression in prostate cancer tissue. (4) Multiple studies have shown overexpression of hepsin gene that expresses the protein hepsin in prostate tumours. However, the lack of detection of hepsin in serum or urine currently limits its role as a biomarker. (5)

4.5 Prostate-specific Membrane Antigen (PSMA)

Prostate-specific membrane antigen (PSMA) is a type II membrane protein with folate hydrolase activity produced by the prostatic epithelium. The expression of this molecule has also been documented in extraprostatic tissues, including small bowel and brain. Silver *et al.* (1) performed an extensive immunohistochemical analysis on a panel of well-characterized normal and malignant human tissues to further define the pattern of prostate-specific membrane antigen (PSMA) expression. Detectable PSMA levels were identified in prostatic epithelium and other organs. They found that 33 of 35 primary prostate adenocarcinomas and 7 of 8 lymph node metastases displayed tumour cell PSMA immunostaining. Eight of 18 prostate tumours metastatic to bone expressed PSMA. Extraprostatic PSMA expression appears to be highly restricted. Also, the decrease in PSMA immunoreactivity noted in advanced prostate cancer suggests that expression of this molecule may be linked to the degree of tumour differentiation. (1) Another study by Ben Jemaa *et al.* (2) was undertaken to relate the co-expression of PSMA and PSA with the degree of vascularization in normal and pathologic prostate tissue to elucidate their possible role in tumour progression. The study was carried out in 6 normal, 44 benign prostatic hyperplastic and 39 cancerous human prostates. They found that in normal prostate tissue, PSMA and PSA were equally expressed $(3.7 \pm 0.18 \text{ and } 3.07 \pm 0.11)$. A significant difference in their expression was seen in hyperplastic and neoplastic prostate tissues (16.14 ± 0.17 and 30.72 ± 0.85, respectively) for PSMA and (34.39 ± 0.53 and 17.85 ± 1.21, respectively) for PSA. A study of prostate tumour profiles showed that the profile [PSA+, PSMA-] expression levels decreased between normal prostate, benign prostatic tissue, and primary prostate cancer. On the other hand, the profile [PSA-, PSMA+] expression levels increased from normal to prostate tumour tissues. PSMA overexpression was associated with high intratumoural angiogenesis activity. By contrast, high PSA expression was associated with low angiogenesis activity. These data suggest that these markers are regulated differentially and the difference in their expression showed a correlation with malignant transformation. (2)

Mhawech-Fauceglia *et al.* (3) measured PSMA expression in normal tissues and in 3,161 benign and malignant tumours, in order to define sensitivity and specificity in prostatic adenocarcinoma using multiple tissue microarray sections with a monoclonal antibody to PSMA. Prostate cancer was positive in 93/141 cases (66.0%); all 846 benign tumours were negative for PSMA. The sensitivity and specificity of PSMA in distinguishing prostate cancer from any other type of malignancy was 65.9% and 94.5%, respectively. They concluded that, despite its expression by subsets of various types of malignancies, PSMA is still considered to be fairly sensitive and highly specific for prostate cancer. (3)

4.6 Neuroendocrine Markers in Prostate Cancer

Pretl first described neuroendocrine cells (NE) in the prostate in 1944. (1) Believed to stem from neurogenic origin, these cells are found within both normal and malignant prostate tissue, do not express androgen receptors, and are considered androgen insensitive. (2-7) Consequently, the neuro-endocrine differentiation (NED) of prostate cancer may have a role in the development of hormone-refractory PCa. (8)

Prostatic NE cells store peptide hormones within cytoplasmic granules, containing products such as chromogrannin A (CGA), neuron-specific enolase (NSE), chromogrannin B, somatostatin, human chorionic gonadotropin, thyroid-stimulating hormone, parathyroid hormone-related protein, bombesin, and members of the *calcitonin* gene family (*e.g.* calcitonin, katacalcin, calcitonin gene-related peptide). (2, 9-14).

While NED is not strictly defined, it is most frequently characterized by the presence of NE cells throughout adenocarcinoma cells. These NE cells do not appear to be different from NE cells present in the benign prostate tissue. However, they do have the potential for malignant transformation, as

seen in small cell carcinoma, a highly malignant variant of NED. Given that these cells lack androgen receptors, conversion to a malignant form of NED represents a potential transition towards androgen-independent PCa. (15-21)

The precise origin of NED in prostate cancer remains unclear. Previous studies identified a role for interleukin-6 (IL-6) in the development of NED in LNPCa cells. (22-25) Recent studies have revealed that activation of the phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (PI3K-AKT-mTOR) is required for NED in PCa cell lines. In addition, androgen deprivation has been shown to induce NED in LNCaP. (26)

Immunohistochemical studies (IHS) of PCa tissue have yielded conflicting results regarding the prognostic potential of NED. Higher levels of CGA have been associated with poorly differentiated PCa, but were not correlated with Gleason scores. (27-30) However, CGA levels have been shown in several studies to correlate with worsening tumour differentiation, bone metastases, decreased time to recurrence, and biochemical recurrence, but not disease-specific survival. (30-32) More recently, strong staining of NE markers by IHS in patients with D2 PCa was associated with a greater risk of death on multivariate analysis. In addition, this study also found poorer cause-specific survival in D2 PCa with strong CGA staining. (10)

Most secretory products of NE cells are secreted into the bloodstream and are measurable by immunoassay. Elevated pretreatment serum levels of CGA, NSA and pro-gastrin releasing peptide (Pro-GRP) have all been significantly correlated with poor prognosis in patients undergoing hormonal treatment. (9,10,12,33-35) More recently, increased CGA velocity was associated with androgen-deprivation in men with pT3 PCa and PSA progression, and serum CGA levels increase as intervals of hormone therapy increase. (14,36) These findings suggest that NED progression is increased with hormonal therapy. (37)

Recently, Dizeyi *et al.* reported that the NE product, serotonin (5-HT), dose-dependently activated the Akt/PI3K and MAPK/Erk pathways in PCa cell lines, further strengthening the association between NED and hormone-resistance in PCa. This work also suggests possible novel targets based upon t-HTR antagonists. (38)

In addition, Nishikawa *et al.* explored the role of a novel 40-amino acid neuropeptide called manserin in PCa progression. They reported a significant correlation between manserin-positive rates and Gleason score. Manserin expression was associated with a decreased median time to progression, and was significantly associated with progression on univariate, and multivariate analysis. They concluded that manserin may serve as a novel marker of PCa progression. (39)

Currently, serum and tissue CGA levels represent a valid serum marker for NED. Furthermore, CGA levels add prognostic information, with elevated CGA velocities correlating with developing hormone-resistance. Novel NE markers, such as manserin, may also offer the potential to provide additional information, not only for disease prognosis and staging, but also as therapeutic agents.

4.7 ETS Rearranged Prostate Cancer: A New Class of Cancer-Specific Biomarkers

In 2005, a novel bioinformatics approach helped identify recurrent gene fusions in PCa involving the 5' untranslated region of the androgen-regulated gene *TMPRSS2* with *ERG* or *ETV1*, two members of the ETS transcription factor family (1) (**Figure 6**). Fusion of *TMPRSS2* with *ERG* or *ETV1* occurred only in cases with overexpression of the respective *ETS* gene, and fusions were not detectable in benign prostate tissues. Using FISH, more than half of a PSA-screened cohort of prostatectomy samples had *ETS* rearrangements, confirming their existence at the chromosomal level (DNA). Over 200 published studies have confirmed the existence of *ETS* gene fusions in approximately 50% of over 2,000 PSA-screened PCas, with 15-35% of non-PSA screened cancers having *ETS* fusions (2,3). These studies have demonstrated that fusion at the genomic level (as detected by FISH), and subsequent overexpression of the *ETS* gene fusion transcripts is essentially 100% specific for prostate cancer in tissue studies. (4-21).



Analysis of TMPRSS2-ERG positive and negative PCa cell lines showed that the *TMPRSS2-ERG* fusion resulted in androgen-regulated expression of ERG. Thus, the androgen-responsive elements that normally restrict the expression of *TMPRSS2* to the prostate now drive the aberrant overexpression of 5' truncated *ETS* oncogenes (1,14). This discovery represented a paradigm shift in our understanding of common epithelial cancer development, as recurrent chromosomal rearrangements and gene fusions had not been described in common epithelial cancers. Such gene fusions are common in leukemias, lymphomas and sarcomas (22), with the prototypic example being a rearrangement between chromosomes 9 and 22, which results in fusion of the *BCR* and *ABL* genes, and characterizes chronic myelogenous leukemia (CML). Importantly, the [9-22] rearrangement is a pathognomonic biomarker for CML (9-22), and this finding led to the development of imatinib, which inhibits the *BCR-ABL* gene fusions as pathogenomic biomarkers of PCa has the potential to revolutionize the early diagnosis of PCa.

4.7.1 **Prevalence of ETS fusions in prostate cancer**

Determining the prevalence of ETS fusions is complicated by a lack of completeness of the 5' and 3' partners, the detection method, and the characteristics of the clinical cohort assessed. For example, RT-PCR can only detect specific fusion isoforms with known 5' partners. As TMPRSS2-ERG is by far the most common subtype of ETS fusions (~85% of all ETS fusion positive samples [15]), it is often the only subtype examined, and can be used to estimate ETS fusion prevalence. A recent review assessing over 25 published studies with ~1,500 cases, found that TMPRSS2-ERG fusions have been reported in ~50% of prostate cancers, reflecting the prevalence in PSA-screened cohorts from North America, Europe and Asia (3). Since that time, additional studies (24-32) with over 1,200 cases representing similar cohorts have reported a TMPRSS2-ERG prevalence of 45%, consistent with previous results. Similarly, a multi-institution study of "for cause" needle biopsies (elevated PSA or abnormal DRE) found that 46/100 biopsies with cancer had TMPRSS2-ERG rearrangements (33). Results from three population-based cohorts with over 750 cases have been published, with TMPRSS-ERG prevalences of 15% (clinical stage T1a-b) (17), 30% (T1-3) (34), and 35.5% (T1-3) (35) (Table 5). At present, the reason for the different prevalence in population- and PSA-screened cohorts is unclear, although clinical T1 stage cancers in all population-based cohorts have the lowest TMPRSS2-ERG prevalence (15% and 17%) (17,34).

Assessing *ETV1*, *ETV4* and *ETV5* fusions is best accomplished by FISH, given the multiple 5' partners. The largest studies suggest that together, they account for approximately 5-10% of PSA-screened prostate cancers (10,15,36). For example, Attard *et al.* identified *ETV1* gene rearrangements in 5.4% of the population-based cohort of 429 patients with approximately 30% *TMPRSS2-ERG* prevalence (36).

TABLE 5 Prevalence of ETS Fusions

Modified from: Fitzgerald LM, Agalliu I, Johnson K, Miller MA, Kwon EM, Hurtado-Coll A, et al. Association of TMPRSS2-ERG gene fusion with clinical characteristics and outcomes: Results from a population-based study of prostate cancer. BMC Cancer. 2008;8:230.

Clinical Stage	TMPRSS2-ERG prevalence
T1a-b	15%
T1-3	30%
T1-3	35.5%

4.7.1.1 **Detection of the** *TMPRSS2-ERG* **gene fusion using immunohistochemistry**

Recently Park *et al.*, reported the identification of a rabbit anti-ERG monoclonal antibody (clone EPR 3864; Epitomics, Burlingame, CA) using immunoblot analysis on prostate cancer cell lines, synthetic TMPRSS2-ERG constructs, chromatin immunoprecipitation, and immunofluorescence (37) They correlated ERG protein expression with the presence of *ERG* gene rearrangements in prostate cancer tissues using a combined immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) analysis. They independently evaluated two patient cohorts and observed *ERG* expression confined to prostate cancer cells and high-grade prostatic intraepithelial neoplasia associated with ERG-positive cancer, as well as vessels and lymphocytes (where ERG has a known biologic role). The combined pathology evaluation of 207 patient tumours for ERG protein expression had 95.7% sensitivity and 96.5% specificity for determining *ERG* rearrangement prostate cancer. Given the ease of performing IHC versus FISH, ERG protein expression may be useful for molecularly subtyping prostate cancer based on *ERG* rearrangement status and suggests clinical utility in prostate needle biopsy evaluation.

4.7.2 **Diagnostic implications of gene fusions**

The fusion of *TMPRSS2* and *ERG* loci at the chromosomal level and subsequent overexpression of the TMPRSS2:ERG transcript and truncated ERG protein product is essentially 100% specific for the presence of PCa in tissue studies (1-4). The protein product of the *TMPRSS2:ERG* fusion is not chimeric, nor known to be secreted, limiting antibody-based detection in serum (as for PSA). However, a clinical-grade, urine-based assay for the non-coding transcript PCA3 (a prostate-specific gene overexpressed in > 95% of prostate cancers [15]) has been developed that has shown utility for adding to serum PSA for PCa detection (6,7), and previous studies using research grade RT-PCR based assays have shown that TMPRSS2:ERG mRNA is also detectable in urine (8-12).

Tomlins *et al.* have recently reported the results of a clinical-grade, transcription-mediated amplification (TMA) assay for quantifying TMPRSS2:ERG mRNA based on the same technology as the PCA3 assay (13). TMPRSS2:ERG transcript was quantitatively measured in prospectively collected whole-urine from multiple cohorts, including 218 men undergoing prostatectomy at the University of Michigan, and 1,094 men undergoing biopsy at 10 academic and community clinics. Urine TMPRSS2:ERG was associated with indicators of clinically significant PCa at biopsy and prostatectomy, including tumour size, high prostatectomy Gleason score and upgrading at prostatectomy (13). *TMPRSS2:ERG*, in combination with urine PCA3, improved the multivariate PCPT risk calculator performance for predicting cancer on biopsy (AUC in test set, 0.79 vs. 0.64, *p*<0.001). In the biopsy
cohorts, using a three-class stratification system, men in the highest and lowest *TMPRSS2:ERG*+PCA3 score groups had markedly different rates of cancer (69% vs. 21%, p<0.001), clinically significant cancer by Epstein criteria (61% vs. 15%, p<0.001) and high-grade cancer (40% vs. 7%, p<0.001) on biopsy. They demonstrated that urine *TMPRSS2:ERG*, in combination with urine PCA3, enhances the utility of serum PSA for predicting PCa and clinically relevant cancer on biopsy.

Based on associations with the presence of cancer and significant pathology, they explored several clinically applicable models for demonstrating the value of urine *TMPRSS2:ERG* for individualizing PCa risk in PSA-screened men presenting for biopsy. Through ROC analysis, they found that *TMPRSS2:ERG* had significantly increased AUC compared to serum PSA in both the academic- and community-biopsy cohort (0.71 vs. 0.61, p=0.002 and 0.65 vs. 0.59, p<0.13, respectively). Previous studies using research grade assays have demonstrated that measuring both PCA3 and *TMPRSS2:ERG* in urine outperforms either marker alone for predicting the presence of PCa on biopsy (8,9). Mertz *et al.* showed that amongst informative men with *TMPRSS2:ERG*, PCA3 and serum PSA measured, *TMPRSS2:ERG*+PCA3 score had significantly increased AUC compared to serum PSA in both the academic (n=606, 0.77 vs. 0.61, p<0.001) and community-biopsy cohorts (n=456, 0.71 vs. 0.60, p=0.001), which also improved upon the AUC of TMPRSS2:ERG alone in both cohorts (academic: 0.77 vs. 0.71, p<0.001; community: 0.71 vs. 0.65, p=0.002). These results are highly encouraging and represent a pathway for the development and expansion of cancer-specific tests that can be multiplexed with *TMPRSS2:ERG* and PCA3. Specifically, the inclusion of *TMPRSS2:ETV1* or *SPOP* mutations (see below) would improve the sensitivity of the assay without compromising cancer specificity.

4.7.3 **Clinical therapy implications of gene fusions**

The androgen receptor (AR) has been, and still remains the main target for pharmacologic treatment of PCa. Recent novel approaches have been developed to target even the lowest levels of androgens by blocking steroid synthesis. For example, Abiraterone acetate (Zytiga™, Centocor Ortho Biotech, Inc.) is a selective small molecule inhibitor of cytochrome (CYP) 17, which effectively blocks the production of androgen (1). It has recently been approved by the FDA in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. In the initial phase I clinical trial, abiraterone demonstrated a decrease in PSA following treatment in 50% of all men with castration-independent prostate cancer (2,3). In that study, 83% of men (5/6) with TMPRSS2:ERG fusion PCa had a decrease in PSA following abiraterone treatment. This study was not designed to test the potential role of abiraterone with respect to TMPRSS2:ERG fusion status, and these findings have yet to be validated. However, the possibility that TMPRSS2:ERG fusion status or other molecular characteristics could predict response to therapy warrants further study. The further rationale for exploring differential response of ETS rearrangement PCa in trials targeting AR relates to the five prime partners of most ETS gene fusions, which are usually highly androgen-regulated genes (e.g. TMPRSS2, SCL45A3 and NDRG1). In vitro experiments demonstrate that by increasing androgen levels, one also increases the production of ETS gene-fusion transcripts. Therefore, it is theoretically possible that ETS rearrangement PCa might respond to anti-androgen therapy in a manner distinct from non-ETS PCa.

Another intriguing avenue of clinical research is the potential to target "actionable" gene fusions in PCa. To date, there are no drugs that target *TMPRSS2:ERG* specifically. RAF kinase fusions, although rare, are of immediate therapeutic significance given the numerous approved and investigational agents. Palanisamy *et al.* (4) demonstrated that the RAF kinase fusions were sensitive to sorafenib, an orally active FDA-approved agent that inhibits multiple kinases, including RAF (5). This suggests that screening patients for RAF fusions may identify a subset of PCa patients that may benefit from existing targeted therapies, similar to the current clinical application of ALK inhibitors for *EML:ALK4* non-small-cell lung carcinoma patients (6,7). We envision that other targetable gene fusions and driving mutations will be discovered in the coming years.

There are other PCa molecular classes that may offer distinct targets for therapy. For example, Ateeq *et al.* recently demonstrated proof of principle that SPINK1 overexpressing PCa can be targeted using cetuximab, an EGFR inhibitor (8). SPINK1 harbors a high homology with EGF. Preclinical models using recombinant SPINK1 support targeting the extracellular domain of SPINK1. This early work provides a rationale for both the development of humanized monoclonal antibodies to SPINK1 and evaluation of EGFR inhibition in SPINK1(+)/ETS(-) PCas.

4.8 Molecular Profiling

While serum PSA evaluation has ushered in an era of earlier prostate cancer detection, the positive predictive value of a serum PSA between 4.0 and 10.0 ng/ml in a patient with a normal DRE remains approximately 30%. The poor specificity of this test essentially states that 70% of men with "elevated" PSA levels do not have evidence of prostate cancer on biopsy. As a result, many groups have developed manipulations of PSA evaluation to improve the test characteristics and performance of this test. (See Section 4.2)

Molecular profiling strives to improve upon PSA through identification of novel markers of prostate cancer that provide enhanced test characteristics for prostate cancer diagnosis and outcome. Once identified, such novel markers also harbour the potential to serve as therapeutic targets. One excellent example of this is the development of sipuleucel-T, a novel immunotherapy based upon the original prostate cancer biomarker, prostatic acid phosphatase (PAP).

The molecular biology of prostate cancer involves complex interactions amongst several pathways, including androgen receptor signaling, apoptosis, cell-cycle regulation, signal transduction and angiogenesis. Given this complexity, the search for potential markers of prostate cancer involves investigation of these pathways from the level of DNA to the final array of metabolites being produced by the neoplastic environment. At this point, strategies in PCa early detection primarily rely on surrogate biomarkers that are prostate-specific, and not intrinsically prostate cancer-specific. An alternative strategy is to develop clinically robust assays for biomarkers identified through genomic and transcriptomic studies that are not only cancer-specific (1), but also predictive for non-indolent prostate cancer.

The following sections describe an example of utilization of techniques aimed at identifying novel markers for prostate disease through analysis of genomic, transcriptomic, proteomic and metabolomic profiles.

4.8.1 **Genome sequencing of PCA suggest hidden** genomic complexity

To gain initial insights into genomic alterations that may underpin high-risk PCa, the complete genome characterization of seven prostate tumour samples and their matched normal counterparts (from whole blood obtained from the same patient) was performed. In the initial study, all patients harboured Gleason 7-9 tumours of stage T2c or greater. Three tumours harboured *TMPRSS2:ERG* chromosomal rearrangements.

The average coverage in these first experiments was more than 30 times, yielding a fraction of the genome deemed "callable" for somatic mutations that exceeded 80% in all cases. Most PCa genomes harboured between 2,527 and 3,659 somatic base mutations, with a mean mutation frequency of approximately 1.3 x 10⁻⁶. A median of 14 non-synonymous base mutations per sample resided within the protein coding gene. Analysis of the non-synonymous coding mutations revealed several intriguing candidate cancer genes. Two genes (*SPTA1* and *ADAM18*) were found mutated in 2/7 tumours. *ADAM18* encodes a disintegrin and metalloprotease domain family member involved in sperm function (1). ADAM proteins exert key cell-cell and cell-matrix interactions, and members of this family have been postulated to have roles in cancer (2). In addition, members of the HSP-1 stress response complex (*HSPA2, HSPA5,* and *HSP90AB1*) were mutated in 3/7 PCas. These genes encode Hsp70 and Hsp90 isoforms, which form a chaperone complex (3,4) targeted by several anticancer drugs in development. Interestingly, 2/7 PCas harbour nonsense mutations in potassium channel genes (*KCNQ3* and *KCNT1*). Accumulating evidence suggests that several potassium channels may negatively regulate tumour cell growth. Additional studies will be required to determine the functional importance of these mutations.

All prostate genomes also harboured a large number of rearrangements. This result is one of the major surprises in this study. Detailed examination of the spectrum of chromosomal rearrangements revealed a striking recurrent pattern that encompassed both inter- and intrachromosomal events. Several genomes contained complex rearrangements consisting of multiple loci that exchanged "breakpoint arms", thereby creating a mix of chimeric chromosomes without concomitant loss of associated genetic material (*e.g.*, all breakpoints produce balanced translocations). This "twinned" pattern of breakage and rejoining was particularly manifested in the *TMPRSS2:ERG* fusion-positive PCas: indeed, each such tumour harboured at least one set of "twinned breakpoint" chromosomal groups.

Interestingly, closer inspection of the sites at which the breakpoints occurred revealed that several breakpoints were situated in close proximity to genes known to play oncogenic roles in other cancers. For example, in one "chain" of "twinned breakpoints", the pairs of breaks occurred as follows: (1) 60bp from exon 5 of TANK binding kinase 1 (*TBK1* or "NK-kB-activating kinase); (2) within the 5'UTR of *TP53* (7kb away from exon 1); (3), ~51Kb from *MAP2K4* (a kinase that directly activates several MAP kinases); and (4), ~3kb from the *ABL1* protooncogene. The mechanisms by which these

breaks occur and chimeric chromosomes emerge, as well as the functional implications, are still unknown. However, this striking observation raises the possibility that "twinned" translocations dysregulate multiple genes in parallel to promote prostate tumourigenesis.

Genomic rearrangements appear to be nonrandom, locus-specific and depend, in part, on the proximity of chromosomal regions in the nucleus (5). Moreover, there is mounting evidence suggesting that transcription factors are associated with DNA double-strand breaks, thus predisposing transcribed regions to genomic rearrangements. For example, both androgen and estrogen signaling recruits the enzyme topoisomerase 2B (TOP2B) to target gene promoters, which creates DNA double-strand breaks and facilitates transcription (6,7). The androgen receptor and TOP2B are co-expressed in human PCa precursor lesions in which TMPRSS2:ERG rearrangements are known to occur, suggesting a critical role of TOP2B in the recurrent ETS rearrangements. Three recent studies have also shown that androgen signaling promotes TMPRSS2:ERG fusion formation (8-10), in part, by recruiting DNA break-inducing enzymes (e.g. activation of induced cytidine deaminase (AID)) to translocation breakpoint sites (9). More recently, we demonstrated that rearrangement breakpoints were enriched near open chromatin, AR and tERG DNA-binding sites in the setting of the ETS gene fusion TMPRSS2:ERG, but inversely correlated with these regions in tumours lacking ETS fusions (11). Hence, transcription factors can contribute to the formation of genomic rearrangements by facilitating the juxtaposition of chromosomal loci and recruiting enzymatic machinery involved in DNA breaks to these target loci. This work also suggests that inhibitors of repair enzymes such as PARP1 and DNA-PK decrease the susceptibility to gene fusions. It also raises concerns that TOP2B inhibitors such as etoposide or doxorubicin might facilitate gene fusions and rearrangements by enhancing double-stranded DNA breaks. Ongoing research is exploring the clinical implications of these observations.

A broader analysis of the structural rearrangements identified 20 genes containing an intragenic breakpoint in more than one prostate tumour. Two tumours contained breakpoints situated within *PTEN* (at different nucleotide positions), a well established PCa tumour suppressor gene (12). In one case, *PTEN* rearrangement co-occurred with a dinucleotide deletion within the *PTEN* coding sequence.

Interestingly, two additional tumours carry rearrangements predicted to disrupt the *MAGI2* gene, which encodes a protein known to interact with, and stabilize PTEN (13,14). Thus, four out of seven tumours harboured rearrangements predicted to inactivate *PTEN* or *MAGI2*. Importantly, three of these tumours were *TMPRSS2:ERG*-positive. A follow-up array based analysis performed by the Demichelis lab has identified at least one additional tumour that harbours a focal deletion involving the *MAGI2* locus. Recent studies have shown a statistically significant co-occurrence of *TMPRSS2:ERG* and *PTEN* loss in human tumours (15). In addition, mouse PCa models suggest that *TMPRSS2:ERG* promotes PCa progression when co-occurring with PTEN loss or PI3K pathway activation (16,17). Given that MAGI2 has been shown to bind and stabilize the PTEN protein, and to enhance the ability of PTEN to suppress Akt activation, the discovery of intragenic *MAGI2* breakpoints in PCa tumours, raises the possibility that MAGI2 disruption might also cooperate with TMPRSS2:ERG in prostate tumourigenesis.

As a subsequent analysis of significantly more genomes demonstrates, there are only a few truly recurrent non-synonymous mutations in PCa (Barbieri/Rubin/Garraway submitted). The most common recurrent non-synonymous mutation in PCa involves SPOP. The *SPOP* gene encodes the substraterecognition component of a Cullin3-based E3-ubiquitin ligase (18,19). Mutations in *SPOP* in PCa were originally reported in two systematic sequencing studies (11,20). We have now identified the presence of recurrent mutations in *SPOP* in 6-13% of human PCas in multiple independent patient cohorts (Barbieri and Rubin, unpublished). Recurrent missense mutations are found exclusively in the structurally-defined substrate-binding cleft of SPOP, and structural analysis suggests that these mutations will inactivate SPOP function by disrupting SPOP-substrate interaction (21). Further, we found that loss of SPOP function in prostate cell lines resulted in increased invasion, and altered gene expression; evidence of this expression signature was identified in primary tumours harbouring SPOP mutation. Importantly, all *SPOP* mutations occurred in tumours that were negative for *ERG* rearrangement and *PTEN* deletion; these tumours displayed characteristic somatic copy-number aberrations. Taken together, these findings support a distinct molecular class of PCa.

4.8.2 Inherited genetic variants and prostate cancer

We also recognize that in addition to these somatic alterations, there are important modifying risk factors that are heritable. These germ-line risk factors may predispose to PCa or even more importantly, to an aggressive PCa. As demonstrated in a large Scandinavian Twin Registry Study (1), PCa, more so than for any other common tumour types, is significantly attributable to hereditary factors. Specifically, the proportion of susceptibility accounted for by genetic defects was estimated as 42%. As the individual genetic makeup plays a role in PCa susceptibility, we anticipate that germline variants also modulate PCa progression.

A series of independent studies, both genome-wide association studies (GWAS) and family linkage analyses, reported on multiple independent Single Nucleotide Polymorphisms (SNPs) as PCa risk markers. In 2006, Amundadottir *et al.* (2) and Freedman *et al.* (3) detected PCa risk SNPs in three regions of 8q24 using linkage analysis, followed by fine-mapping in an Icelandic family (54), and using an admixture scan approach in West African ancestry men. Multiple other loci have subsequently been identified (4-6) and replicated (7).

On the one hand, the data clearly reflect the strong genetic component involved in PCa incidence. On the other hand, the modest reported effects of the risk SNPs diminish their suitability in diseasedetection applications. In addition, it has been extremely challenging to demonstrate a functional role for these risk SNPs, which are most often outside of gene coding areas.

Of relevance, some GWAS studies investigated SNPs as risk markers for aggressive or more advanced PCa (8,9). Hypothesis-driven studies focused on variants associated with disease progression and adverse outcome (10-16), or cancer-specific death (11,12,15-17). For the first time, Lin *et al.* (18) reported on the discovery and independent validation of five SNPs associated with PCa-specific mortality involving *ARVCF*, *LEPR*, *CRY1*, *RNASEL*, and *IL4* genes.

The second most common source of variation among human individuals (SNPs are the first) is Copy Number Variants (CNVs) (19,20), defined as copy-number changes-gains or losses-of stretches of DNA between few hundred bases to several megabases wide. Similar to SNPs, CNVs commonly seen in the genome of healthy individuals (21,22), confer susceptibility to diseases like Alzheimer's disease, Parkinson's disease, mental retardation, autism, bipolar disorder and schizophrenia (23,24), and exert functional impact (25-28). Emerging studies reveal germline CNVs to confer risk to cancers such as neuroblastoma (29) and to be enriched in Li-Fraumeni syndrome (30). Interestingly it has been ascertained that the occurrence rates of SNPs and CNVs are different, where CNVs have higher rates of occurrences, suggesting that these two types of polymorphisms potentially carry different information (31). To date, studies of germline CNVs and PCa risk have mainly used a candidate gene approach (32-37). One example of a CNV investigated as a PCa risk biomarker involves the UGT2B17 gene, a member of the uridine diphospho-glucuronosyltransferase (UGT) gene family that plays a central role in the catabolism of testosterone and dihydrotestosterone. UGT2B17 maps to a highly polymorphic locus on 4q13.2, which is completely deleted (homozygous deletion) in about 10% of Caucasian individuals. This variant is known to exert a dosage effect of UGT2B17 transcript levels. To systematically investigate the role of CNVs in PCa, our group characterized over 5,000 variants in about 2,000 men from the Tyrol Early Prostate Cancer Detection Program cohort (38), and identified low frequency, transcriptionally active CNVs associated with PCa risk and more aggressive disease (Demichelis, Rubin, submitted).

Overall, we envision that further characterization of inherited genetic variants associated with PCa risk and progression can help unravel the mechanisms behind the disease etiology and the disease dynamics. In addition, PCa progression or cancer-specific death risk markers could eventually be exploited in combination with PCa-specific somatic markers like *TMPRSS2:ERG*, and PCA3, as part of a highly-sensitive and specific non-invasive test to identify, at the time of diagnosis, which men will benefit from treatment.

4.8.3 **Epigenetic changes in prostate cancer**

Changes in gene expression may occur as a result of alterations in DNA. Alterations known as epigenetic modifications include changes in DNA methylation and histone acetylation status, as well as the previously described changes in nuclear structure. Segments within the gene promoter that are composed of GC-rich regions are termed CpG islands. Alterations in the methylation status of these regions may affect gene expression and have been shown to play a role in carcinogenesis (1). Perhaps the most studied gene with a methylation change associated with prostate cancer is that of the *glutathione S-transferase P1 (GSTP1)*. GSTP1 belongs to a family of detoxifying enzymes that are involved in metabolic reduction of electrophilic carcinogens. These enzymes have been suggested to be involved in the development of prostate cancer. Elevated levels of GSTP1 CpG hypermethylation have been detected in tissues from precancerous lesions (atypia and prostatic intraepithelial neuplasia [PIN]) and within ejaculates, urine, and plasma from men with prostate cancer (2). A large number of studies have evaluated these hypermethylated CpG islands of GSTP1 as prostate cancer tumour markers (3-6).

Many of these initial studies of prostate cancer DNA methylation markers have exhibited high sensitivity and specificity (7, 8), and improved upon the sensitivity of histology alone (9). Bastian and colleagues (10), utilized a restriction endonuclease, QMSP (RE-MSP), to detect abnormalities in the CpG islands found in serum *GSTP1* DNA. No men with a negative biopsy had *GSTP1* DNA detected in their sera, compared to 12% of men with clinically localized PCa and 28% with metastatic disease.

With the success of demonstrating the strong association of *GSTP1* methylation and prostate cancer, additional efforts have focused on examination of the whole genome methylation status and its association with prostate cancer. Other DNA methylation changes have been demonstrated to be indicators of prostate cancer and correlate with the aggressive nature of the disease (11-12). It is clear that we are now just hitting the tip of the iceberg in our understanding of the importance of methylation changes and prostate cancer and furthermore, the potential of these changes to serve as biomarkers of the disease.

4.8.4 **Studies of gene expression**

After the completion of the Human Genome Project, information regarding the annotation of approximately 30,000 genes became available for evaluation. (1) Of particular research interest has been the investigation of genetic alterations in cancer. Multiple tools have evolved for evaluation of the available genetic information. One way of investigating this data is through the use of expressed sequence tags (ESTs). ESTs are short (400-800 base pairs) "tags" of mRNA representing the expressed components of complementary DNA (cDNA). The collection of ESTs derived from a library of cDNA represents a static overview of the active genome being utilized by the cell, tissue or organism that has been catalogued. The frequency of a specific set of ESTs correlates to the rate of transcription, and thus, proportionally represents the gene expression level. The collection of human ESTs is available for evaluation (http://www.ncbi.nlm.nih.gove/dbEST) and allows for mining of this database for the identification of overexpressed genes involved in prostate cancer. (2,3)

Analysis of the EST database by Asmann *et al.*(3) and by Ernst *et al.*(5) provided early evidence of a link between the overexpression of cysteine rich secretory protein-3 (CRISP3) and prostate cancer. The CRISP protein family is highly conserved amongst vertebrates, and is primarily expressed by exocrine glands. (6) Animal studies have also revealed that CRISP has a role in sperm function and fertilization, and exhibits strong androgen dependence. (7-8). In human tissue, CRISP3 proteins are expressed by neutrophils, salivary glands, pancreas, as well as prostate, and these proteins may have a role in male fertility. (9-14) The exact role for CRISP3 remains unclear. However, its presence in the secretory granules of neutrophils suggests a role in proteolysis and cellular matrix remodeling, similar to other seminal plasma proteases such as TMPRSS2 and PSA. (14)

Additionally, Bjartell *et al.* have shown that elevated CRISP3 expression in tissue microarrays is associated with a slight increase in risk of recurrence after radical prostatectomy (HR=1.53, p= 0.010). (15) However, the use of CRISP3 did not improve performance of existing prediction models. (15) Additional studies have provided further support for CRISP3 as a potential prostate cancer-specific biomarker. (4, 16-17).

More recently, Ribeiro *et al.* discovered that CRISP3 overexpression is associated with pT3 disease (p=0.006) and that CRISP3 expression correlates with the levels of the transcription factor, ERG. This study further provided evidence for the direct regulation of CRISP3 expression by ERG, suggesting a role of ERG and CRISP3 in locally advanced prostate cancer and links this role to TMPRSS2-ERG-positive prostate cancer (14). Future work is needed to further characterize the role of CRISP3 and prostate cancer, but this early work serves as an example of the emerging potential for these genetic analyses.

4.8.5 **Proteomic profiling**

Multiple, complex molecular events characterize cancer development and progression. Deciphering the molecular networks that distinguish organ-confined disease from metastatic disease may lead to the identification of biomarkers of cancer invasion and disease aggressiveness. Although alterations in gene expression have been extensively quantified during neoplastic progression, complementary analyses of proteomic changes have been limited (1).

Proteomics involve the use of mass spectometry to study differences in patterns of protein expression (1). While patterns of protein expression have been proposed to yield more biologically relevant and clinically useful information than assays of single proteins, many limitations in the use of proteomics exist. In contrast to genomics, in which amplification techniques like polymerase chain reaction (PCR) allow for the investigation of single cells, no technology is available at the protein level. Other issues between studies have been the lack of uniform patient inclusion and exclusion criteria, small patient numbers, absence of standardized sample preparations, and limited analytical reproducibility (2).

Artificial intelligence-based pattern recognition algorithms have been developed and successfully used to analyze complex serum proteomic data streams generated by surface enhanced, laser desorption ionization time-of-flight mass spectroscopy. Ornstein *et al.* (3) used a high performance, hybrid quadrupole time-of-flight mass spectrometer to generate discriminatory serum proteomic profiles to determine if this technology could be used to evaluate the need for prostate biopsy in men with elevated prostate specific antigen (PSA). They collected serum samples from 154 men with serum PSA 2.5 to 15.0 ng/ml and/or abnormal DRE prior to transrectal ultrasound guided biopsy. They concluded that testing with this model yielded 100% sensitivity and 67% specificity. In other words, if the proteomic pattern had been used to determine the need for prostate biopsy, men with PSA between 2.5 and 15.0 ng/ml, 67% (42 of 63) with negative biopsies would have avoided unnecessary biopsy, while no cancers would have been missed (3).

To study the fluctuating state of the proteome, Grubb *et al.* (4) applied reverse-phase protein array technology to analyze the status of key points in cell signalling involved in pro-survival, mitogenic, apoptotic and growth regulation pathways in the progression from normal prostate epithelium to invasive prostate cancer. They found that, focused analysis of phospho-specific endpoints revealed changes in cellular signalling events through disease progression and between patients.

4.8.6 Metabolomic profiling

Genomic and proteomic studies provide insights into the myriad of genetic alterations. Aberrant transcription processes play a role in the development and progression of prostate cancer. Metabolomics aims to build from this foundation to profile the end-product of these aberrant processes in order to identify markers characteristic of the neoplastic process.

Utilizing high-throughput evaluation of 42 tissue and 220 urine or plasma prostate cancer-related samples with liquid-and-gas-chromatography coupled with mass spectrometry, Chinnaiyan *et al.* recently reported preliminary findings of evidence for a prognostic prostate cancer metabolite. (1) From over 1,126 metabolites, an N-methyl derivative of glycine known as sarcosine was uniquely associated with prostate cancer and metastatic progression. Furthermore, sarcosine was identified as measurable in urine samples, making it an attractive biomarker target.

Recently, attempts to validate the use of urinary sarcosine have yielded negative results. Jentzmik *et al.* evaluated urinary sarcosine levels in a cohort of men with prostate cancer, men with negative prostate biopsy results, and healthy volunteers using sarcosine measured by gas chromatographymass spectroscopy, with normalization to serum creatinine. The authors revealed that sarcosine levels were lower in patients with prostate cancer and were not associated with prostate cancer grade or stage. They further found no influence of DRE on urinary sarcosine level. (2,3)

While these studies offer conflicting results regarding the use of urinary sarcosine levels, they represent preliminary evaluations. However, they do signal promise for the use of metabolomic evaluations.

4.8.7 **Molecular signature of prostate cancer**

While there is tremendous work in characterizing the heterogeneous molecular aberrations responsible for the initiation and progression of prostate cancer, the bulk of the current understanding of the disease stems from small cohorts of patient tissue and through differing methodology. Several groups are now expanding this work through the use of onco-mining and oncogenomic analysis to evaluate wider sets of tissue. (1,2). Working from comparative transcriptomic and oncogenic pathway analysis, Ding *et al.* recently demonstrated that loss of the TGF- β /BMP-SMAD4 in mice leads to the reproducible emergence of invasive, metastatic and lethal prostate cancers. They further confirmed that four gene signature of PTEN, SMAD4, cyclin D1 and SPP1 represent key mediators of the biological process leading to the transformation from poorly progressive prostate cancer to metastatic disease. (1) Similarly, Taylor et al. performed an integrative analysis of DNA copy number alterations, aberrant expression and focused exon resequencing in 218 well-defined prostate cancer tumour. They identified the nuclear receptor coactivator, NCOA2, as an oncogene in approximately 11% of tumours. They further identified a novel chromosomal deletion at 3p14 associated with TMPRSS2-ERG fusion-positive prostate cancers, suggesting a tumour suppressor role for the genes FOXP1, RYBP, and SHQ1. (2). In addition, the database utilized in this study is publicly available for additional analysis. With continued access to larger datasets, additional elucidation of the molecular pathways involved in the development of clinically progressive prostate cancer will propel future development of panels of mutated genes and the identification of molecular signatures to assist in the differentiation between indolent and aggressive disease.



4.9 References

Serum Markers:

PSA

i. Clinical use

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AMACR

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C5

New Developments in Screening and Early Detection of Prostate Cancer

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5.1 Introduction

The dramatic growth in scientific research focused on prostate cancer continues to challenge healthcare professionals and public health authorities worldwide. Recent publications concerning the efficacy of prostate cancer screening have fueled public debate concerning appropriate testing policies. Improvements in healthcare and an aging population in many Western countries suggest that the management of prostate cancer will pose increasing demands on already strained health care systems.

Unfortunately, widespread geographic variations in the incidence and mortality of this disease preclude a single unified policy concerning screening and treatment. Differences in the incidence of this disease have been attributed to both environmental factors — such as dietary habits, lifestyle and sun exposure — and genetic factors including both racial and familial traits. The intensity of testing for prostate-specific antigen (PSA) also affects prostate cancer incidence and mortality statistics. Ideally, a common European strategy concerning prostate cancer screening should be developed. Barring specific recommendations, this strategy should focus on providing accurate information on the efficacy and effectiveness of prostate-cancer screening as well as providing equal access and quality of care to those men who seek treatment for this disease, as suggested by the 2009 manifest of Europa Uomo (1), the umbrella organization of patient representatives for prostate cancer.

The 2009 publication of the European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrating that population-based screening of men aged 55-75 years can reduce prostate cancer mortality has generated increased urgency among member states of the European Union to develop appropriate screening policies (2). To date, no country has embraced population-based testing because the target population remains undefined and the relative benefits and harms associated with screening continue to be debated. In Scandinavia, Sweden has pursued regional screening studies designed to optimize screening protocols (3), while Norway and Denmark discourage population-based testing. In The Netherlands, discussion has focused on the possible inclusion of new imaging tools and risk-based protocols, while in Belgium, health authorities have asked health care professionals to compose a "balanced guideline." The United Kingdom awaits the results of the ProtecT trial expected in 2015 before making any further revisions to its policies (4), while France and Germany support individual patient testing. In North America, annual PSA testing is widely practiced, but guidelines developed by different medical organizations concerning the appropriate target population are often contradictory.

This chapter reviews the current medical literature surrounding prostate cancer screening. Our understanding of the incidence and natural history of this disease has grown substantially during the past decade and has altered our perspective concerning how to conduct population-based screening. The initial enthusiasm associated with the ability of PSA testing to identify localized disease has given way to the realization that annual PSA testing may lead to a decline in prostate cancer mortality but can also lead to the diagnosis of and treatment of a large number of indolent tumours. From a public-health perspective, the associated morbidity may or may not be balanced by net health care benefits. To date, prostate cancer screening has yet to satisfy public health criteria for population-based testing, leading many researchers to explore the efficacy of individual risk assessment for early detection of this disease.

5.2 Screening

5.2.1 Arguments for and against population-based screening

Prostate cancer (PCa) is the most commonly diagnosed malignancy (excluding non-melanoma skin cancer) and the third leading cause of death from cancer in men in Western countries (after lung and colorectal cancer)(5, 6) . The lifetime risk of a PCa diagnosis is 15.8% for an individual man in the United States, and approximately 9% for a man in Western Europe (7, 8, 9). The lifetime risk of dying from PCa is low relative to the lifetime risk of a PCa diagnosi(ie, 2.8% in the United States and 3.1% in Western Europe) (7, 8, 9). The risk of being diagnosed with PCa under age 55 is unknown, but very low (10). The incidence rates may be influenced by diverse genetic and environmental factors, such as lifestyle, air quality, diet, nutrition, chemicals, and of course, screening activity (11). Overall, these incidence and mortality rates give PCa important public health relevance (12).

Before the 1980s, even studies of series of locally confined prostate cancer reported rapid development of metastases and death. One of the earliest studies by Hanash *et al.* (13) reported 10-year survival rates of 52% and 4% for stage A and B disease, respectively. Nowadays, many of these patients would very likely have been classified as M+. In the 1980s with the digital rectal examination (DRE) as the only method of diagnosis, 30-35% of men had bone metastases, and 45-50% had nodal disease (14). The mortality-incidence ratio in the pre- PSA era showed that on average one out of each two to three prostate cancer patients died of their disease (15).

In 1994 Catalona *et al.* showed that with DRE- and PSA-based screening, the rate of organ-confined disease was 70-85% as compared to 30% in unscreened men (16). After the introduction of the PSA test in the US in the mid-80s, the incidence of PCa increased and peaked in 1992 to 179 per 100,000 in white men, and in 1993 to 250 per 100,000 in black men (17). Contemporary data show that in countries where PSA testing is not common, like Japan, 60-70% of the prostate cancers diagnosed have extended beyond the prostate (15), while in the US, where already in the year 2000, 56.8% of men aged \geq 50 reported ever having a PSA test (18), an estimated 4% of prostate cancer patients present with metastatic disease at the time of diagnosis (7).

The changes in PCa incidence and death over time in Europe showed that relative to the steep increase in incidence, the PCa-specific death has remained relatively stable. Nevertheless, a decrease of disease-specific mortality has been reported in numerous countries over the last ten years (19). It has been disputed whether this is the result of early detection and treatment, and so far it appears to be a mixed effect of screening of asymptomatic cancers, as well as improved quality of care of localized disease with radical prostatectomy and combined radiotherapy with endocrine treatment in higher risk disease.

The objective of screening is to identify a disease at a stage in its natural history where treatment can be applied to prevent death or suffering (20). Screening aims to avoid deaths from cancer by preventing the development of advanced disease. Therefore, effective treatment of early-staged disease is essential to attain the aims of screening. Although screening may lead to earlier diagnosis, screening tests will not always benefit the person being screened. Overdetection (detected cancers that would not have been diagnosed in the absence of screening) may result in overtreatment (treatment of cancers that would not have been diagnosed in the absence of screening), with its associated increased costs, and potential side effects (20, 21).

The final endpoint of a cancer-screening trial is cancer-specific mortality. However, there are more criteria that have to be fulfilled before screening can be adopted in a public health program. A total of 10 WHO criteria for appraising the validity of a screening program were developed by Wilson and Jungner, Table 1 (22). These criteria were created in 1968 and still apply today as the traditional, and "the gold standard" of screening assessment (2002). Nevertheless, these criteria have been found to be too vague or theoretical, and an exchange of views regarding screening policies has occurred over the last two decades (23, 24). This has resulted in several adaptations to the classic criteria, which led to 10 new criteria, Table 2 (24). The majority of the more recent criteria overlap with the classic criteria, particularly with regard to screening for health conditions at an early stage, where there exist effective interventions to improve outcomes compared to clinical care.

For PCa screening, criteria 3 and 6 of Andermann *et al.* (24) are currently not met, while criteria 9 and 10 are at least subject to intense discussion. There is no consensus regarding the target population at which age to start and stop screening (see further), and the risk of overdetection of indolent cancers needs to be minimized. The balance between benefit and harms will conclude this chapter.

TABLE 1 The 10 Criteria by Wilson and Junger, 1968 (22)

- 1. Condition sought should be an important health problem.
- 2. There should be an accepted treatment for patients with recognized disease.
- 3. Facilities for diagnosis and treatment should be available.
- 4. There should be a recognizable latent or early symptomatic stage.
- 5. There should be a suitable test or examination.
- 6. The test should be acceptable to the population.
- 7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- 8. There should be an agreed policy on whom to treat as patients.
- 9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

10. Case finding should be a continuing process and not a "once-and-for-all" project

TABLE 2 The 10 updated criteria by Andermann et al. (24)

1. The screening programme should respond to a recognized need.

2. The objectives of screening should be defined at the outset.

3. There should be a defined target population.

4. There should be scientific evidence of screening programme effectiveness.

5. The programme should integrate education, testing, clinical services and programme management.

6. There should be quality assurance, with mechanisms to minimize potential risks of screening.

7. The programme should ensure informed choice, confidentially and respect for autonomy.

8. The programme should promote equity and access to screening for the entire target population.

9. Programme evaluation should be planned from the outset.

10. The overall benefits of screening should outweigh the harm.

5.2.2 Available data on population-based screening

The information on screening in the general population has been obtained from both observational cohort studies and randomized controlled trials (RCTs).

5.3 Case-control and Observational Studies

Various studies analyzed historical or prospective data from population based cohorts in a variety of screening protocols in order to assess the diagnostic instruments like DRE and PSA.

Richert-Boe *et al.* examined the effect of previous DRE on prostate cancer mortality and found that compared to a group without DRE, a similar number of fatal prostate cancer patients had had a screening DRE during the 10-year study period (OR = 0.84; 95% CI, 0.48-1.46) (25). Jacobsen *et al.* conducted a similar study and found that control subjects had had more DREs between years 2 and 10 before diagnosis than case subjects (OR = 0.51; 95% CI, 0.31-0.84), indicating a protective effect of DRE (26). Two case-control studies assessing the effect of both PSA testing and DRE on prostate cancer mortality also showed contradictory results (27, 28).

Incidence data from the Surveillance, Epidemiology, and End Results (SEER) system, together with mortality data from the National Center for Health Statistics showed that age-adjusted prostate cancer mortality rates gradually increased for both whites and African Americans from 1969 to 1991. Subsequently, starting in 1991, a 16.1% decline of prostate cancer mortality for white men and, starting in 1993, a 10.9% decrease occurred for African American men through 1997 (29). One explanation for these observations is PSA-based screening at the same time as an increasing prostate cancer incidence was seen. One problem with ascribing the ecologic trends to screening is the timing of the decline in mortality. An expected prostate cancer mortality reduction takes many years, whereas in this case, a decline in mortality was seen only two to three years after widespread screening occurred. Another ecologic analysis from Austria found that prostate cancer mortality in Tyrol, an area with a free screening program, began to drop below that of the rest of the country a few years after screening began. This finding could be attributed to the screening program and/or preceding changes in treatment (30).

5.4 Randomized Controlled Trials

One of the first studies that had been initiated according to a randomized design was a study in the Quebec area in 1988. However, as a result of the low adherence, and of fact that data were not analyzed in an intent-to-treat fashion, the trial could not contribute to an answer to the question of whether screening reduces mortality (31).

The Norrköping screening study was originally designed as a feasibility trial to study organizational, psychological and economic consequences of screening (32). The sample size was calculated to primarily investigate these clinical questions, and there was no mention of randomization, or the intention to conduct repeat-screening visits. In a 2004 publication (33), the trial, for the first time, was described as a randomized controlled clinical trial.

It is however questionable whether the applied screening algorithm, with screening every third year and a biopsy indication on the basis of a digital rectal examination (DRE) initially, and using a PSA-cut-off of 4 ng/mL later on, is an effective strategy. This is reflected by the number and characteristics of interval cancers in the latest publication (34). The number of interval cancers appears to be equal to the number of screen-detected cancers. Furthermore, the tumour characteristics of the interval prostate cancer cases, of which 1/3 were M1 at the time of diagnosis and 71.4% were advanced tumours, highlight a highly ineffective screening strategy. When this first prerequisite is not met by the chosen algorithm (i.e. a reduced incidence of advanced and metastatic disease), it is highly unlikely to find a disease-specific mortality reduction.

In 1993, two large RCTs were initiated with prostate cancer mortality reduction as an endpoint, one in the US, as part of the Prostate Lung Colorectal and Ovary screening trial (PLCO) (35), and one in Europe called the European Randomised Study of Screening for Prostate Cancer (ERSPC) (36).

The PLCO is a trial in the United States that enrolled 155,000 women and men, 55-74 years of age, in 10 screening centres. All men with a prior diagnosis of PCa, but not with previous PSA screening, were excluded. In the prostate section of the PLCO trial, men in the intervention arm received screening once each year by DRE and PSA for a period of four years, and by PSA alone for two additional years. A sextant biopsy was recommended for PSA values greater than 4.0 ng/ml and/or an abnormal DRE. The regional healthcare providers made final decisions on whether to take a biopsy and on the biopsy technique used.

The ERSPC is conducted in eight European countries (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, and Switzerland) and enrolled 267,994 men 55-74 years of age. All men with a prior diagnosis of PCa were excluded. In the ERSPC trial, men were screened in most countries with an interval of four years, except in Sweden, where a two-year interval screening was used. Biopsy indications were performed according to the screening algorithm, which differed slightly for each centre, but in general were triggered by a PSA level \geq 3.0 ng/ml (214).

In March 2009, both trials presented their apparently contradictory results with respect to the main endpoint (2,37). In the ERSPC trial, a 20% mortality reduction was shown after a median follow-up of nine years. By contrast, the PLCO trial showed no effect of screening on disease-specific mortality with seven years of follow-up. After these two long-awaited publications, a plethora of reviews and editorials appeared, trying to explain these apparently contradictory results and speculating what might be the truth. Detailed comparisons between the trials (38, 39) showed that in reality, the two trials were fundamentally distinct, with respect to design, algorithm, and follow-up that the differences in outcome can be explained on that basis. Within PLCO screening, the indication for biopsy (according to judgment of the physician) is compared with less screening (opportunistic PSA testing in more than 50% of men in control arm), while in ERSPC screening, biopsy (according to a strict defined protocol) is compared to routine clinical practice with a much lower percentage of PSA testing in the control arm. Thus, when comparing protocol-based screening with no screening, at least a 20% prostate cancer mortality reduction was achieved. After correction for non-compliance, the reduction was 27% (40) and increased to 29-31%, if also a correction for contamination in the control arm was applied.

Recently a 44% prostate cancer mortality reduction was reported by the Goteborg Screening Trial (part of ERSPC) after 14 years of follow-up (3). These data point towards a considerable reduction of prostate cancer mortality due to PSA-driven early detection in combination with effective treatment of locally confined disease.

The occurrence of metastatic disease is a very important contributor to the suffering related to prostate cancer. Prevention or delay of metastatic disease therefore, can be considered as another critical endpoint of screening studies. Several studies have reported that early diagnosis by PSA testing result in an absolute reduction of the number of men with metastatic disease at diagnosis. The Goteborg Screening Trial reported, after 10 years of follow-up, a reduction in metastatic disease at the time of diagnosis 48.9% in favour of the screening arm (41). Etzioni *et al.* quantified the link between PSA screening and the decline in distant stage incidence in the US using a fixed-cohort stimulation model (42). The model results indicated that PSA screening accounted for approximately 80% of the observed decline in distant-stage incidence. The ERSPC study has shown a 41% decrease of metastatic disease in the screen arm at the time of first diagnosis.

5.5 Overdetection and Overtreatment

The achieved reduction in prostate cancer mortality within ERSPC after nine years of follow-up coincided with a considerable number of men that needed to be screened (NNS = 1,410) and treated (NNT = 48) to avoid one death from prostate cancer. (2) The most important factors influencing these numbers were the potentially unnecessary PSA tests at re-screening in men with very low PSA values who are at very low risk of developing a clinically significant prostate cancer (i.e. a cancer that will cause symptoms and/or death) during their life time. Potentially indolent cancers detected in such men increase the incidence in the screening arm and thereby increase the NNT. Another closely related factor is age, as the NNT increases dramatically with it, likely due to this detection of cancers remaining asymptomatic during the remainder of life.

Next to this the positive predictive value of the prostate biopsy using a PSA cut-off of \geq 3.0 ng/ml was only 24%, meaning that 76% of the prostate biopsies could have been delayed or even avoided. These data show that identifying men who are at increased risk of having a biopsy-detectable prostate cancer on the basis of a serum PSA value alone is not efficient.

The most important unwanted side effect of PSA-based screening is overdiagnosis and overtreatment, meaning the detection and treatment of prostate cancers that without screening, would never have been diagnosed during a lifetime.

In 1993, Sakr *et al.* (43) found histologically confirmed prostate cancer in 27% and 34% of men aged 30–39 years and 40–49 years, respectively. In an overview of autopsy studies, the prevalence rates of prostate cancer have been found to range from 31% for men aged 31–40, 44–46% for men aged 51–60, to over 80% for men aged 71–80 (44).

The number of new cases of prostate cancer in 2008 was almost 900,000; three times higher than the number of new cases that occurred in 1985 (45). Suggestions for possible causes include a longer life expectancy, new diagnostic modalities and treatment options, along with PSA testing and systematic prostate biopsies. In the US, the annual age-adjusted prostate cancer incidence rates almost doubled in the period 1980-2000. In the United Kingdom where PSA testing is less common, incidence rates are also increasing but at much lower levels. As a result the ratio of incidence to mortality is currently 6:1 in the developed regions of the world, with the highest score in North America of 8.7:1 (8). Due to the PSA-based screening activities, many men are now diagnosed with low volume and grade (Gleason score 6) disease (46).

The NNT of 48 at nine years is unacceptably high and needs to be reduced. Indeed, longer followup has already shown that this number will decrease. The Goteborg screening trial, with a 14-year follow-up, reported an NNT of 12. Of note, the NNT to prevent one case of metastatic disease is much lower than that to prevent a death. Nevertheless, the detection of potentially indolent prostate cancer and subsequent active treatment remains a problem.

When comparing men treated for prostate cancer to men who are free of prostate cancer, it is noteworthy that all traditional measurements for localized prostate cancer result in specific physical side effects. The main adverse outcomes after surgery are worsening of continence and erectile function. Radiation therapy mainly leads to a decline in potency and bowel problems (47). Despite the fact that it is known that with screening, large numbers of cancers are being detected that would never surfaced clinically, most prostate cancers are treated actively, unnecessarily subjecting patients to the side effects of active treatment (48). This may be due in part to uncertainties over the accuracy of staging at the time of diagnosis.

5.6 Effects on Quality of Life

5.6.1 Quality of life (QoL)

The potential harms of screening, such as unnecessary biopsies through a false-positive PSA test, overdiagnosis and overtreatment, and side effects due to this treatment, might have a negative effect on mental and physical health.

Men who underwent a PSA test can experience uncertainty related to the PSA test, even if the PSA test is normal or elevated, leading to further assessment (49). Carlsson *et al.* showed that 34% of the men who were waiting for the outcome of their PSA tests, and 55% of the screened men who needed further investigation (eg, DRE and prostate biopsy) reported anxiety. For both, the first round of screening was compared to subsequent rounds, and showed a significant difference in anxiety levels. Men who had a high level of anxiety at the first screening had a more than 30-fold increased risk of reporting a high level of anxiety in further rounds compared to men who reported no anxiety (50). Mental and self-rated overall health worsened significantly immediately after the diagnosis of PCa. This effect disappeared, however, after six months (51).

Longitudinal cohort studies showed that prostate cancer therapy may have long-lasting consequences for health-related quality of life (HRQoL) (47, 52-58). In case of prostatectomy, side effects have an immediate onset and mainly affect urinary and sexual functioning, whereas external radiotherapy may result in a continuous decline of bowel and sexual functioning, and brachytherapy was found to mainly result in decreased urinary and sexual function.

Active surveillance, which consists of initially withholding radical treatment after diagnosis and closely monitoring the disease instead, might provide an alternative for managing low-risk PCa (59). It may preserve health-related quality of life, however, whether that is the case depends to a large extent on the patient's preferences (60).

In spite of side effects, prostate cancer patients typically report favourable HRQoL (47, 52, 61, 57). This may be caused by insensitivity of generic HRQoL measures or adaptation to changed health, also called "response shift" (62). It has been argued that prostate cancer screening is a system without negative feedback, since patients are happy with the reassurance of a negative screen result, and grateful for early detection in case of a positive result. In spite of treatment-related side effects, patients may be grateful for being treated "in time" (63). A qualitative study confirmed this latter statement (62). Thus, individual experience provides almost no negative feedback that early detection and aggressive treatment may not work (63).

The ERSPC will report on the effects of mass screening on the quality of life in 2012. These effects will be expressed in quality adjusted life years (QALY) (64). Population based screening may lengthen life on average, 29 days, by annual screening in men aged 55-74, living on average 558 extra days knowing they have cancer.

5.7 Whom to Screen and to Rescreen in Mass Screening?

Screening aims to avoid deaths from cancer by preventing the development of advanced disease. Therefore, effective treatment of early-stage disease that has the potential to become life threatening is essential to attain the aims of screening. Screening may lead to an earlier diagnosis but screening tests will not always benefit the person being screened. Unnecessary testing, overdetection often resulting in overtreatment, increased costs, side effects and complications are potential adverse effects of PSA-based screening for prostate cancer. It is thus of crucial importance to screen those men that actually can benefit from early detection, and to define the target population.

Since population-based screening is not accepted as a standard healthcare policy, various organizations developed guidelines which have resulted in a diversity of recommendations about individual PSA testing in asymptomatic men. These guidelines differ with respect to the age to start PSA testing, the PSA cut-off for prostate biopsy and follow-up screening (Table 3).

USPSTF (208)	< 75 yrs: Insufficient evidence on benefits and harms of screening
ACPM (209)	Insufficient evidence to recommend routine screening Annual conversations about risks and benefits of screening
EAU (210)	Insufficient evidence to recommend widespread population-based PSA screening
ACS (211)	Informed discussion of risks and benefits Begin in 40s for high-risk (African American, family history) or 50s for average risk-risk
AUA (212)	PSA screening for well-informed men who wish to pursue early diagnosis Begin with baseline measurement at age 40
NCCN (213)	Begin risk/benefit discussion and offer baseline DRE/PSA at age 40

TABLE 3 Guidelines and Conclusions on PCa screening from Various Health Organizations

New developments in screening and early detection of prostate cancer

5.7.1 **PSA**

The results of the randomized trials did not include patient individual risk stratifications. Van Leeuwen *et al.* used population-based PSA and incidence data of men in Northern Ireland where screening was not routinely performed and compared these with the screening results of the ERSPC study (65). They found that the difference in prostate cancer-specific mortality increased with increasing PSA level at study entry. For example, the number needed to screen and treat to save one death from prostate cancer for men with PSA levels < 2.0 ng/ml were 24.642 and 724, respectively. This implies that for men with a low serum PSA the benefits of aggressive testing may be limited since it is associated with a large increase in cumulative incidence and potential overtreatment.

This observation is in line with studies that show a strong correlation between the lower baseline PSA values and the detection of prostate cancers with potential indolent characteristics (66). Defining a screening interval based on the initial PSA level (67-69) will undoubtedly have a positive effect on the NNS and NNT.

5.7.2 **Age**

Starting PSA screening in a younger age group is questionable, because of the low incidence of PCa. This is confirmed in a retrospective study of 12,078 men in the age range of 40-96 years, divided in two groups of <50 and ≥ 50 years. The prevalence of PCa was 4.4% for men <50 years and 14.4% for aged \geq 50 (70). In the ERSPC study, the number of men ages 50-54 at baseline with PCa was low with no obvious effect on mortality (2). However, other studies suggested that the outcome of a single PSA test before the age of 50 or younger is a strong predictor of PCa and advanced PCa diagnosed up to 25 years later (71,72). Schröder et al. suggested that a PSA of 1.5 ng/ml or greater in men older than 50 years represents an indicator for greater than average future risk of PCa (73). The American Urological Association (AUA) recommends testing at the age of 40 years, because a baseline PSA level above the median value of 0.6-0.7 ng/ml for men in their 40s is at higher risk for PCa in the future (74). Rationales for screening at this age are: the PSA level is more specific and not influenced by a prostatic enlargement, and the risk of dying from PCa among men older than 50 years may be decreased if detecting lethal cancer earlier. In the PLCO trial analyzing a young and healthy subcohort of men with no or minimal comorbidity, screening resulted in a significant decrease in the risk of dying from prostate cancer (HR 0.56; 95% CI: 0.33 to 0.95; p=0.03) in contrast with men with at least one significant comorbidity in which there was no prostate cancer specific mortality reduction observed (HR, 1.43; 95% CI, 0.96 to 2.11; p=0.08).

According to the USPSTF 2008 recommendations, PSA testing is not recommended in men aged >75 years, because of different reasons, i.e. these men have a limited life expectancy, an increased comorbidity and a low risk of dying from PCa because the percentage of cancers which are found by screening are for a large part indolent. In 2010, a PSA-based strategy for screening was suggested for this age group based on an observational study (75). In the ERSPC data, no statistically relevant specific mortality reduction can be observed for men aged 70 or more (2), as the real benefit is in men aged 65-69. Longer follow-up in ERSPC and PLCO might change these results. However, men aged \geq 75 years may have high-grade disease and therefore might have a substantial risk of dying from PCa (76). A drawback of age-based screening criteria is that these criteria ignore substantial variation in

life expectancy and comorbidity in this age group (77). The long natural history of PCa detected with screening was confirmed by Ulmert *et al.* In this study a total of 5,722 men aged \leq 50 were included with two blood samples approximately six years apart. In this study, with very low screening intensity, the median time from blood draw to PCa diagnosis was 16 years (78).

In general, guidelines for PSA screening recommend testing in the age group of 50-75 years old, but there are other guidelines recommending screening beginning at the age of 40.

5.8 Rescreening interval

To date, probably the most commonly recommended screening interval is annual. In the US, annual screening is recommended for men aged >50 years, and for men aged >45 years who are African American or who have a positive family history (79,80).

One of the main criteria used in evaluating and comparing the effectiveness of a screening algorithm is the change in the rate of disease diagnosed at an advanced stage. This is reflected in the incidence and tumour stage distribution of interval cancers among those screened in the years following a negative screening test. In 2007, the 10-year cumulative incidence rates for prostate cancer, interval cancers and aggressive interval cancers were compared between two ERSPC centers: one with a program applying a two-year screening interval (Gothenburg, Sweden), and one with a four-year screening interval (Rotterdam, The Netherlands) (81). The detection rate of prostate cancer was higher in the two-year versus the four-year group, but the rate of both interval and aggressive interval cancers were not significantly different. However, this analysis was not conclusive since the differences in prostate cancer incidence can vary between populations. Analyzing similar data with a median follow-up of 12 years and using the interval proportionate incidence method showed different results. The proportional prostate cancer incidence was 3.64 in Gothenburg and 3.08 in Rotterdam (RR 1.18; 95%CI 1.04-1.33; p=0.009). The proportional advanced cancer incidence was 0.40 in Gothenburg and 0.69 in Rotterdam (RR 0.57; 95%CI 0.33-0.99; p=0.048). The authors concluded that a two-year screening interval reduced the incidence of advanced prostate cancer, but increased the overall risk of being diagnosed with prostate cancer compared to a four-year interval (82).

The above mentioned study did not address individual characteristics. Several studies have suggested adaptations in screening interval on the basis of PSA level. The risk of prostate cancer mortality in 15,758 men followed within the Dutch ERSPC screening cohort in Rotterdam with a PSA level of less than 3.0 ng/mL was 0.14 per 1,000 life-years. This is 3.5-fold lower than the population-based risk of 0.49 per 1,000 life-years. The median time from diagnosis of prostate cancer in men with initial PSA levels of less than 1.0 ng/ml was over eight years. These favourable outcomes in men with initial PSA values of less than 1 ng/ml, accounting for 45% of men between the ages of 55 and 74 years support prolongation of their screening interval up to eight years (69,82). Based on the data from the PLCO trial, it was suggested that a screening interval of five years might be appropriate if the initial serum PSA value is <1.0 ng/ml (188).

5.9 Early Detection

5.9.1 Diagnostic instruments

The diagnosis of prostate cancer is made by the histologic conformation of cancer in prostatic biopsies. The majority of cancers are adenocarcionoma of the prostate. Grading of differentiation is generally performed by the Gleason scoring system. It has been recognized that even among experts, diagnostic variability is present, predominantly on the issue of grading, and less so on the diagnosis of cancer versus atypia or PIN (83). Central review of (study) biopsies is regarded to be the best quality control mechanism to minimize diagnostic variability due to inter-observer variation amongst pathologists (84).

Traditionally, the indication to perform prostate biopsies is due to an increased PSA value, and/or an abnormal DRE result. Nowadays, this combination is not regarded as sufficiently specific for use in population-based studies. The role of PSA, its derivatives, and their change over time have been analyzed in various studies. Their discussion is essential for the development of individual riskassessment strategies.

For the analysis of new markers like PSA-isoforms, hK2, PCA3, etc., predominantly retrospective studies have been reported, in which selection bias plays an important role.

The detection rate of cancers is not only dependent on the indication for biopsy, but also to the biopsy procedure itself. As the results of biopsies and their prognostic relevance have become increasingly important for the choice of therapy, aspects on the methodology of taking biopsies are reviewed here.

5.9.1.1 PSA, isoforms, PCA3, kallikreins

PSA is a prostate-specific secretory product not specifically related to the presence of cancer. PSA plays a role as a marker for prostatic diseases and monitoring, and its development and standardization as a diagnostic marker is reviewed extensively elsewhere (85). Here, the diagnostic value for PCa, and as a prognostic marker in a screening setting is evaluated. Nevertheless, careful consideration should be given to the standardization issue, as well as to the biological variability, when recommendations are given for the use of nomograms and risk assessment tools. Large international efforts resulted in considerable improvement of analytical performance of PSA measurements. The interassay variation for total PSA measurements is now 3-5% as compared to 10-15% in the beginning of the 1990s. Furthermore, the lower detection limit of 0.3-0.5 ng/ml around 1990 is now in the range of 0.0–0.02 ng/ml. Finally, the between- method variation has shown a considerable improvement: from 25-30% in the early 1990s to 10-15% today. Many observations on the role of PSA are based on the ERSPC that has continued to use the original Hybritech calibration over time. A comparative study in 106 sera of unscreened and asymptomatic men selected from the Rotterdam database of the ERSPC showed a regression equation of PSA-WHO = PSA-Hyb x 0.796 + 0.007. Determination of cut-off values based on the WHO standards in the ERSPC would have resulted in a 30% decrease in the number of biopsies, with an identical decrease in cancers detected, while the characteristics of the detected cancers would remain similar (86).

Authors	Methods	Results							
Thompson <i>et al.</i> , 2005, PCPT (Thompson, Ankerst <i>et al.</i> 2005)	Among 5,587 men a PSA determination and a sextant prostate biopsy was performed to assess the sensitivity and specificity of PCa detection for all PSA ranges in relation to Gleason grade.	DCA	PCa, any grade			PCa,	PCa, Gleason grade \ge 8		
		ng/ml	Sen (%)	Spec (%)	LR	Sen (%)	Spec (%)	LR	
		1.1	83.4	38.9	1.4	94.7	35.9	1.5	N= 1,225 (21.9%) were diagnosed with
		2.1	52.6	72.5	1.9	86.0	65.9	2.5	
		2.6	40.5	81.1	2.1	78.9	75.1	3.2	
		3.1	32.2	86.7	2.4	68.4	81.0	3.6	prostate cancer
		4.1	20.5	93.8	3.3	50.9	89.1	4.7	Lancer
		6.1	4.6	98.5	3.1	26.3	97.5	10.5	
		10.1	0.9	99.7	3.0	5.3	99.5	10.6	
Schröder <i>et al.,</i> 2008, ERSPC (Schröder, Carter <i>et al.</i> 2008)	Among 9,779 men the cancer detection rate for different PSA ranges in the ERSPC, section Rotterdam was assessed. Distribution of PSA and prostate cancers in men aged 55-74 yrs biopsied (n=2,267 men) for PSA \geq 4.0, DRE and TBUS are	PSA, ng/ml	Total biopsies (%)	Cance (n)	er Ca	Fotal ancer (%)	PPV	Biopsy (n) per cancer	
		0.0-0.9	36.4	4		0.8	2.2	45.8	
		1.0-1.9	31.2	45		9.5	8.8	11.4	
		2.0-2.9	12.3	30		6.3	13.6	7.4	
		3.0-3.9	7.2	44		9.3	25.3	3.9	
		4.0-9.9	10.9	241	!	51.0	24.5	4.1	
	demonstrated.	≥ 10.0	2.1	109	2	23.0	56.5	1.8	

TABLE 4. The Continuum of Prostate Cancer (PCa) Risk for Different PSA Ranges

PCPT: Prostate Cancer Prevention Trial, ERSPC: European Randomized Study of Screening for Prostate Cancer, PCa: prostate cancer, PSA: prostate-specific antigen, DRE: digital rectal examination, TRUS: transrectal ultrasound, Sen: sensitivity, Spec: specificity, LR: likelihood ratio, PPV: positive predictive value

In population studies, the positive predictive value of PSA is related to the cut-off level for prostate biopsies. It has been reported to be around 20% for a PSA cut-off of 4.0 ng/ml or more (Table 4), to 10 % for a PSA of more than 1.0 ng/ml. Thompson *et al.* demonstrated this in a study in which men with a PSA \leq 3.0 ng/ml and a normal DRE were randomized to finasteride (5 - α -reductase inhibitor) and placebo (Thompson, Pauler *et al.* 2004). After seven years, in all men with a PSA <4.0 ng/ml and a normal DRE, biopsies were performed, and in 15% of these men PCa was detected. In 15% of these, the Gleason score was \geq 7 (8). According to these study results, a physician who would like an 80% confidence in not missing a PCa, should apply a PSA cut-off value of 1.1 ng/ml as indication for biopsy, which would result in 60% unnecessary (negative) biopsies (88). In Table 4 the continuum of PCa risk for different PSA ranges is presented from the PCPT and the ERSPC (87,89). As shown, increasing the PSA threshold results in a decrease in sensitivity and increase in specificity. Consequently, lowering PSA cut-off levels leads to a higher detection rate of PCa, but also leads to an increase of negative (unnecessary) biopsies and overdiagnosis of cancers which might otherwise not present clinically (potentially overdiagnosed cancers) (90).

Currently, the suggested PSA cut-off for biopsy ranges from 2.6 to 4.0 ng/ml (91-93). Future data that include the comparison of the different studies with long follow-up might show the difference in mortality and morbidity outcomes using these different PSA thresholds.

The specificity for PSA to detect prostate cancer can be improved by utilizing PSA isoforms such as free PSA (94,95), PSA complexed to ACT (alpha-1-antichymotrypsin)(96,97), [-2] pro-PSA (98-100), or nicked/inert PSA (101,102) by a maximum of 30%, losing up to 10% of its sensitivity. A panel of markers can reduce the number of unnecessary biopsies (103). A Finnish study (104) demonstrated in 17,680 participants with a follow-up of 5.8 years that a low %fPSA (less than 15 %) was a strong predictor of later diagnosis of prostate cancer. Men with a %fPSA in the lowest quartile (<14.2%) showed a 6.9-fold increased risk compared with those with a level in the highest quartile (>23.7%).

New markers like serum hK2 (105) seem to be a predictor of pathologic stage for clinically localized prostate cancer, especially in the PSA-range below 10 ng/ml (106), or as a tool to improve discrimination of poorly differentiated and non-organ-confined prostate cancer (107)

PCA3 is a prostate cancer-specific molecular marker in urine that has been evaluated in a multicentre clinical study to enhance the specificity of PSA for positive biopsy after a previous negative result (108). In the third and fourth round of a screening setting, PCA3 contributed little to enhance the specificity, and was not found useful as a first-line test for screening (109).

Conclusions

The PSA assay is a robust biomarker for prostate cancer, and its sensitivity and specificity to detect PCa are dependent on the cut-off value for prostatic biopsy. The specificity can be improved using PSA-isoforms, kallikreins, and molecular urinary tests. The prognostic value of these tests has not been proven.

5.9.1.2 Digital rectal examination

Although DRE is widely used for the diagnosis of PCa, the value of DRE remains controversial in screening and early detection programs for PCa (110). The acceptability of the DRE test as a screening procedure seems to be less than PSA since the participation in a screening program with combined DRE and PSA was twice as low as with PSA alone (93). Table 5 provides an overview of the positive predictive value for DRE in the lower PSA ranges. According to this table, DRE has a low sensitivity and predictive value in men with low PSA levels (111-115). The positive predictive value of DRE is limited to 4–19% at serum PSA levels below 3.0 ng/ml. This proportion equals to the percentage of 15% of cancers that were diagnosed in the study of Thompson *et al.*, involving biopsies for all men with a PSA <4.0 ng/ml without using DRE (87). Therefore, the studies presented in Table 5 might have found a similar PCa detection rate without the use of DRE at PSA levels of 3.0 ng/ml and lower. Accordingly, it might be concluded that men with low PSA values have a 15% PCa detection rate, with or without the use of DRE, and that consequently, the additional value of the DRE is restricted in lower PSA ranges.

In contrast, several researchers still suggest that with the use of DRE, men will be screened more selectively. It is shown that men with a positive DRE are more likely to have high-grade PCa than men with non-palpable tumours (116,117). For this reason, the risk of omitting DRE, and therefore the omission of biopsies at PSA values of: <2.6, <3.0 or <4.0 ng/ml, might be that potentially aggressive tumours at these low PSA levels remain undetected at screening. Catalona *et al.* have confirmed this risk by showing that a substantial proportion of PCa detected by DRE at PSA levels lower than 4.0 ng/ml have features associated with clinically aggressive tumours and that the omission of DRE from screening protocols might comprise treatment outcomes. Specifically, omitting DRE at PSA levels less than 3.0 ng/ml would have detected 14% fewer PCa overall and 7% fewer PCa with a Gleason score of 7 or higher (118). In contrast, it is shown that screening without DRE at low PSA levels (PSA <3.0 ng/ml) did not lead to the detection of significantly more (poorly differentiated) PCa four years later compared to screening with the use of DRE in the ERSPC trial (119).

In contemporary practice and current guidelines, biopsies are advised when a DRE is abnormal, despite the level of PSA. In a large multicentre study, the PPV of an abnormal DRE for obtaining a positive biopsy was 10%, 41%, and 69% for men aged 50 or more with a PSA of <4 ng/ml, 4-10 ng/ ml, or >10 ng/ml, respectively (16). It therefore appears to remain an absolute indication for biopsy. However, when used in a multiparametric setting of a nomogram, the relative contribution of other parameters, such as PSA and prostatic volume, is far greater to predict a positive biopsy.

Conclusions

DRE does not contribute substantially to cancer detection in low PSA ranges (0-2.5 ng/ml) in a population-based screening setting, but increases specificity significantly in the higher ranges.

TABLE 5. Positive Predictive Value (PPV) of DRE for Prostate Cancer Detection in low PSA Ranges

Authors	Methods	Results				
	Methods of prostate cancer early detection, to assess the positive predictive value of DRE for different PSA values. N = 31,953	The positive predictive value of DRE in the lower PSA areas:				
Crawford <i>et al.</i> , 1996 (Crawford, DeAntoni <i>et al.</i> 1996)		PSA	PPV			
		0.0-4.0	15%			
		4.1-9.9	34%			
	To assess the usefulness of DRE as a stand-alone screening test in low PSA ranges, ERSPC-Rotterdam. N= 10,523	The positive predictive value of DRE in the lower PSA areas:				
		PSA	PPV			
Schröder <i>et al.</i> ,1998, ERSPC (Schröder, van der Maas <i>et al.</i> 1998)		0.0-0.9	4%			
		1.0-1.9	10%			
		2.0-2.9	11%			
		3.0-3.9	33%			
		4.0-9.9	45%			
		The positive predictive value of DRE in the lower PSA areas:				
	Investigate the usefulness of DRE for prostate cancer diagnosis in subjects with PSA levels of 4.0 ng/ml or less. N=90	PSA	PPV			
Yamamoto <i>et al.</i> , 2001		0.0-0.9	4%			
(Yamamoto, Ito <i>et al.</i> 2001)		1.0-1.9	0%			
		2.0-2.9	19%			
		3.0-4.0	44%			
	Men with abnormal DRE findings and a PSA level <4.0 ng/ml who underwent prostate biopsy to assess the positive predictive value of DRE for a PSA <4.0 ng/ml. N= 986	The positive predictive value of DRE for PSA <4.0 ng/ml:				
		PSA	PPV			
Bozeman <i>et al.</i> , 2005 (Bozeman, Carver <i>et al</i> . 2005)		0.0-0.9	2%			
		1.0-1.9	6%			
		2.0-2.9	13%			
		3.0-3.9	21%			
	Diagnostic evaluation of DRE as initial screening test in lower PSA ranges. N = 34,115	The positive predictive value of DRE in the lower PSA ranges:				
Andriole <i>et al.</i> , 2005, PLCO		PSA	PPV			
(Andriole, Levin <i>et al.</i> 2005)		0.0-4.0	17%			
		4.1-7.0	47%			

ERSPC: European Randomized Study of Screening for Prostate Cancer, PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, PCa: prostate cancer, PSA: prostate-specific antigen, DRE: digital rectal examination, Gr: group, PPV: positive predictive value, CDR: cancer detection rate

5.9.1.3 **PSA density and PSA changes over time**

Since benign prostatic hyperplasia may also lead to elevations in serum PSA levels, consideration of prostate volume may also be used to improve the specificity of PSA-based screening. In the early 1990s, investigators in the US and Europe suggested dividing PSA by the prostate volume, or the concept known as PSA density (PSAD). (120,121) Multi-institutional studies have shown that a higher PSAD is significantly associated with the presence of prostate cancer and worse tumour features. (122) A variation on PSAD is PSAD-TZ, in which PSA is instead divided by the volume of the transition zone. (123) Disadvantages of these measurements include the requirement for imaging to estimate volume, as well as limitations in the accuracy of these estimates. PSAD may also be used for men with newly diagnosed prostate cancer to predict prognosis and aid in management decisions, including the selection of active surveillance versus definitive therapy.(124,125)

As described in the European Association of Urology (EAU) Guidelines (126,127), there are two main ways to calculate PSA kinetics: PSA velocity (PSAV, absolute change) and PSA doubling time (PSADT, exponential change). For men with prostate cancer after definitive therapy, PSA kinetics has a well-established role in follow-up and prognostication. (128-129)

Many studies have also evaluated the role of PSA kinetics in prostate cancer screening and detection (see also Chapter by Taneja *et al.* [Chapter 4]). In 1992, data from the Baltimore Longitudinal Study of Aging showed that PSAV could distinguish between prostate cancer, benign prostatic hyperplasia and healthy controls. (130) Subsequent studies in both screening and non-screening populations showed that PSAV was useful to predict prostate cancer risk. (131-133) However, other data have suggested that total PSA remains the best predictor of prostate cancer risk, with little additional contribution from PSA kinetics. (134,135) In the Rotterdam section of the ERSPC, for example, Raaijmakers *et al.* showed that PSAV was significantly higher among men with a positive than a negative prostate biopsy, but it did not offer incremental value on multivariable analysis. (136)

More recent studies have demonstrated a more robust relationship between pre-diagnostic PSA kinetics and prostate cancer aggressiveness. (137-140) Further studies are necessary to prospectively evaluate whether PSA kinetics may be used to increase the specificity of screening for life-threatening prostate cancer, or whether it is useful as part of multivariable risk calculators.

At present, the use of PSAV in clinical practice is controversial. The EAU only recommend PSA kinetics in the post-treatment setting, and not in screening. (127) By contrast, both the AUA and National Comprehensive Cancer Network currently include PSAV among their criteria to determine the need for prostate biopsy. (74) PSAD increases specificity for cancer detection, while PSA changes over time are controversial for the selection of men for prostate biopsy.

5.9.1.4 Biopsy numbers and schemes

The diagnosis of prostate cancer is made from the histology of prostatic biopsies. Systematic sextant biopsy was proposed and popularized by Hodge *et al.* (141) and has been the standard protocol for many years. Later studies applying extended biopsy protocols showed that the sextant biopsy misses 10–30% of biopsy-detectable cancers (142,143). Prostate volume can affect the cancer detection rate, as a sextant biopsy might undersample larger prostates (144,145).

So over the last ten years the number and location of diagnostic biopsies has changed, and the traditional systematic sextant biopsy, even when lateralized, does not appear to be common practice anymore. The number of prostatic biopsies needed to detect tumours of various sizes with 90-95 % certainty has been calculated from data of radical prostatectomy series (146). For example, in a 40-gram prostate, eight biopsies are necessary to detect a tumour of 1.5ml with 90% certainty. The data of the European Prostate Cancer Detection Study validate this analysis, as it was concluded that 8 to 18 biopsy cores should be taken, based on prostate volume and age, to ensure a 90% certainty of cancer detection (146).

This conclusion might differ from the situation during the initial round of a screening study. The ERSPC study showed that applying a volume-independent lateralized sextant biopsy scheme in a prostate cancer screening programme with repeated screenings did not result in an undersampling of large prostates with respect to the number and aggressiveness of tumours found during the eight years of follow-up. This study is in line with three studies, including PCPT, that have focused on the relation of tumour grade and prostate volume (147-149). In a review of seven studies (150), it was confirmed that a volume-adjusted and increased-core regimen significantly increased the positive biopsy rate, without significant increase in morbidity of the procedure (151). However, because increased detection also results in an increasing number of indolent tumours found, there are still arguments to consider sextant biopsies acceptable in order to limit overdiagnosis of indolent tumours. Indolent tumours have been associated with a tumour volume of less than 0.5 ml (152). However, this size was recently estimated to be 1.3 ml, based on a longitudinal study within ERSPC (153). These data would suggest that in the setting of repeated screening, a modified biopsy scheme might be justifiable (146). When performed, the biopsy itself also carries a high burden of error; areas of the prostate that can be reached with the biopsy needle are sampled in a "blinded" manner, resulting in detection of insignificant cancers. On the other hand, areas that are out of reach, such as the anterior prostate and apex are either undersampled or never sampled, resulting in non-detection of significant cancers. As a result of this diagnostic strategy, many men are falsely reassured that they are free of clinically significant cancer when they are not. By using multiparametric MRI (mpMRI) to assess the risk status of men with a previous negative biopsy, biopsies can be targeted to visible MRI lesions (154)

There might also be other reasons to repeat a biopsy based on the results of the initial histology. If the biopsy result shows atypical small acinar proliferation (ASAP) a repeat biopsy is warranted (155).

Conclusions

The total number of cancers and aggressive cancers is higher in small prostates. The optimal number of biopsy cores remains subject to debate. If the biopsy result shows atypical small acinar proliferation (ASAP), a repeat biopsy is warranted.

5.10 How to Inform a man who Wishes to be Screened

5.10.1 Information required

Opportunistic screening of the individual (case finding, wild screening) started around the 1990s with the introduction and marketing of PSA assays. The public awareness on prostate cancer and early diagnosis by PSA increased individual PSA testing to a level such that 30-50% of the male population between 50 and 80 years were reported to know their serum PSA value. (215) This resulted not only in contamination of the later phases of RCTs, but also in a significant increase of overall prostate cancer incidence (as described above).

Currently, many men are being screened without actually knowing their current status (156). These men did not have the possibility to make an informed decision about having a PSA test. An informed choice or decision has two core characteristics: first, it is based on relevant, good quality information, and second, the resulting choice reflects the decision-maker's values (157). Physicians play an important role in counselling men about the benefits and harms of screening by PSA testing (158-160). Table 6 lists the pros and cons of PSA screening. The information that should be provided to aid in screening decisions has been described in the various information brochures developed around the world (161). In addition, Table 7 lists the items that are generally regarded as the minimum information needed before initiating a PCa screening.

TABLE 6. Summary of the Most Important Reasons for and Against Early Detection During Individual Assessment

Arguments for Testing	Arguments Against
 If the result of the PSA test is favourable, it may calm down my worries; 	 If my PSA value is elevated and further study does not show prostate cancer, I will have undergone medical testing for nothing and this will have caused unnecessary anxiety;
 The PSA test can help to find prostate cancer at an early stage before it leads to complaints; 	 The PSA test can miss prostate cancer. After a normal result, I may feel relieved for no good reason or may still remain worried;
 If, as a result of a positive PSA test, I undergo successful treatment, I may have a better chance of cure and may live longer; 	 An elevated PSA test may detect a slow, growing tumour which would otherwise never have given me any trouble;
 If the treatment is successful in an early stage, I may be spared the late symptoms of prostate cancer such as spread of the tumour to other parts of my body (metastases). 	 I may be confronted with the possible complications of the treatment of prostate cancer.
 Screening has been shown to lower prostate cancer mortality by 20–27% in men aged 55–69 years. 	

TABLE 7. Information Needed Before Initiating Screening

Information
Regional incidence of PCa
Regional incidence of indolent PCa
Regional mortality of PCa
Natural course of PCa
Familiar PCa
Life expectancy in relation to comorbidity
Results of RCT on screening
Instruments for screening: PSA DRE
Diagnosis of PCa by biopsy
Side effects of biopsy
Diagnosis and prognosis
Treatments and side effects
Active surveillance
QoL after various treatments

5.10.2 Ethnicity and family

It is well known that African American ethnicity is associated with an increased risk of prostate cancer, (162), and it is therefore not surprising that it was shown to be statistically significant in many of the models analyzed (ORs from 1.03 to 1.89). This is not due to PSA-driven ascertainment bias, as PSA testing is less frequent in the African-American population. (163) Given that African American men are often underrepresented in prospective studies examining risk, it is also evident that some of the observed ORs failed to reach statistical significance due to sample-size considerations. This may be the case with the PCPT, an important study, as it included empiric biopsies of men without a clinical indication, where only 3.8% of enrollees were African-Americans. (164)

A family history of prostate cancer has long been identified as a risk factor for the development and diagnosis of the disease (162), and for the most part, has been found to contribute significantly to the predictive models in which it has been analyzed. (164-169). Hereditary prostate cancer is defined as a phenomenon in which the disease is identified before the age of 55, and occurs in three subsequent generations, or in at least three cases (170). Other disease patterns are described as familial. In hereditary cancer, there is little evidence of a robust genetic modifier, though incidentally prognostic SNPs are reported (171). Two meta-analyses have calculated the relative risk of prostate cancer based upon the number and type of affected males in the family (172,173), varying from 2.2-2.5 for a first-degree relative, to 1.88 for a second-degree relative. These risks were even higher for men younger than 65 years, or more family members with a positive history of PCa (174). However, excess risk is minimal or absent if the family member is diagnosed at an age greater than 70 years. (175). Two cohort studies have further emphasized this finding (176,177). Remarkably there is no evidence that a positive family history is associated with more aggressive disease.

5.10.3 Individual risk assessment and nomograms

There are many biological factors that influence the risk of PCa, such as a positive family history, race (African Americans are at higher risk as compared with Caucasians) and age (178). Clinical determinants include an abnormal DRE, an elevated PSA level or a relatively small prostate volume (73,162,178). Higher PSA levels, abnormal DRE, older age and African American race were reported to be predictive for high-grade disease (Gleason score \geq 7) (164).

Because of the complexity of the integration of various factors to provide advice to the individual patient, numerous nomograms have been constructed to aid in risk assessment.

A limited number of nomograms are based on data obtained from the general population, which is a prerequisite for adequate risk assessment of asymptomatic men. These are the ERSPC PCa risk calculator (179), and the PCPT risk calculator (180). The ERSPC risk calculator is based on the data of 20,000 participants from the Rotterdam area, and has been validated successfully on a screening population in Sweden and Finland. (186) In these validation studies, the ERSPC risk calculator showed 33% fewer biopsies with applying both the PSA cut-off of \geq 3ng/ml and a chosen probability cut-off of 12.5%. The PPV of the lateralized sextant biopsy increases from 29% to approximately 40%. This improvement in PPV was achieved with a marginal loss in the detection of aggressive PCa (181). The PCPT risk calculator is based on the control group of the PCPT study, in which all participants underwent an end of

study biopsy. The cohort includes, unlike the European cohorts, information on African Americans in the USA. Nevertheless, for Caucasian Americans, the ERSPC risk calculator outperformed the PCPT calculator, as the ERSPC instrument includes prostate volume in its calculation of probability (216). Direct head-to-head comparisons of the two risk calculators have been published recently and show that the overall the ERSPC risk calculator has better discriminatory capability. (182-184). It should be realized that several other important factors are not included in current models, such as baseline quality of life, comorbidity, life expectancy, and treatment preference (185).

Nomograms can be applied as a decision aid at every level of the process from diagnosis, through therapy and follow-up. The ERSPC risk calculator provides risk assessment to aid in the decision for prostate biopsy with or without prior information on negative screening biopsies, and on the presence of indolent disease for men diagnosed with prostate cancer.

Conclusions

Information on the consequences of screening should be given to every man considering screening for prostate cancer. Race is an independent risk factor for the diagnosis of prostate cancer. A positive family history predisposes to an increased risk of up to two-fold for the detection of prostate cancer.

5.10.4 Risk assessment strategies for individual screening

The benefit for men that consider screening is to remain asymptomatic during life with regards to prostate cancer, and preferably to remain without a diagnosis of prostate cancer. Thus, men with a low probability of cancer may choose not to undergo biopsy, while men being diagnosed with cancer may elect to avoid invasive therapy in case of a high probability on indolent disease. On the other hand, men with clinically significant cancers require early identification and adequate treatment in order to avoid morbidity and mortality from progressive disease.

Avoiding unnecessary biopsies and overdiagnosis can be performed by using the risk assessment tools as described. These instruments have been validated for men between the ages 50-74 years. The compliance with biopsy recommendations provided by the ERSPC prostate cancer risk calculator was evaluated by Van Vugt (186). In 291 men undergoing PSA screening who agreed to the use of this risk assessment instrument, 84% were compliant with the advice to biopsy or to refrain from it. Remarkably, the most important reason for non-compliance in 31 men that were advised not to undergo biopsy, was the reluctance of the physicians due to consideration of the PSA level as a single parameter. This suggested that the traditional biopsy threshold of PSA over 3 ng/ml overruled the advice given by the nomogram.

Men with low initial PSA values are less likely to benefit from early detection with regard to cancerspecific mortality (see the above results of RCTs). This observation allows making specific individualized risk stratifications after measuring the PSA baseline. As a result, men at high risk can be informed about their more favourable harm-benefit trade off with respect to the overall NNS and NNT presented by the randomized controlled trials. Men may present for screening at any age and with any previous history of screening. Therefore, relevant risk factors need to be addressed, such as previous PSA and negative biopsies, in order to analyze their current risk. Based on their individual and objective assessments, a balanced discussion should ensue allowing a decision on how to proceed. For example, in an unscreened population, men aged 60 with PSA concentrations below the median (≤ 1 ng/ml) were unlikely to have clinically relevant PCa (0.5% risk of metastasis by the age 85 and 0.2% risk of death from PCa). The risk of dying from PCa for men with PSA lower than 1.0 ng/ml after nine years of follow-up was 0.1% (187). This implies that on an individual basis, men can be advised to delay rescreening based on the result of their PSA and/or their negative biopsy (69, 188). Such individualized screening strategies have not been validated yet.

When a diagnosis of PCa has been made, there are various multivariate prediction tools to calculate the probability on the presence of indolent PCa as defined by the Epstein criteria (189). These nomograms predict small, low-grade, low-stage pathology on prostatectomy, but none have actually been shown to predict indolent behaviour in a surveillance cohort. The calculated probability of having potentially indolent disease would be useful for treatment decisions (190-192).

In summary, nomograms can assist in clinical decision-making during the entire process, from the risk of having a biopsy-detectable PCa, to survival after the development of metastatic disease (185,193). The importance of comorbidity for PCa treatment decisions, or even for screening, was recently high-lighted by Albertsen (194), illustrating the influence of the Charlson score (195) on the overall and tumour-specific survival. For example, for men aged 66-75 years diagnosed with nonpalpable PCa with a Gleason sum of 7 or less, a Charlson score of 2 or more increases overall mortality by approximately three-fold over a period of twenty years (10-year mortality rate per 100; from 28.8 to 83.1) compared to a Charlson score of 0. At the same time, the cancer-specific mortality rate remained stable at 4.8 to 5.3%. Using this comorbidity information for individual predictions is preferable to overall statistics of life expectancy on a population level that provide a robust but very general impression.

Conclusions

- Information on prostate cancer screening and treatment needs to be balanced and address the regional situation. (Expert opinion)
- Predictive factors for PCa diagnosis can be combined in risk-assessment nomograms.
- The ERSPC risk calculator may represent the best currently available individual risk-assessment tool for the men in the general population. (Level 2 evidence)
- · Family history is a relevant risk factor for individual risk assessment.
- Observations on the level of PSA and its increase over time during the fourth to sixth decade may be useful in an individual risk-assessment strategy. (Level 3 evidence)
- Risk factors for overall survival, such as comorbidity, need to be taken into account for individual screening and treatment counselling. (Expert opinion)
- Risk-assessment instruments, combined with information on prostate cancer, provide acceptable tools to avoid prostate biopsies in low-risk men. (Level 2 evidence)

5.11 Improvements

5.11.1 Improving screening protocols

There is no unanimous opinion about when and how to perform PSA screening in the general population. There is strong evidence that population-based screening can reduce PCa mortality. However, screening also induces overdiagnosis and overtreatment. These adverse effects of PSA screening need to be lowered to acceptable levels, and the uncertainties of screening with respect to quality of life and cost-effectiveness need to be determined. It is possible that the widespread nature of individual screening may influence the decision of health authorities to install national programs for population-based screening, which may eventually replace the latter.

The consequence of intensive screening algorithms starting at a young age, with relatively short screening intervals and low PSA thresholds for prostate biopsy (< 3ng/ml), require further exploration before any evidence-based recommendations can be made.

PCa research should not only focus on early detection of PCa, but also on a reduction in overdiagnosis and overtreatment. So far, risk reduction strategies through chemoprevention or lifestyle interventions appear controversial, and are not supported by authorities.

5.11.2 Improving imaging and targeted biopsies

The use of MRI in prostate cancer management remains controversial, but its use is growing fast. As a result, current clinical practice guidelines fail to keep up with developments that are both technological and clinical. Multiparametric MRI (mp-MRI) is widely available, but its application requires a degree of discipline in its conduct, reporting and evaluation. (196) Transrectal ultrasonography (TRUS) imaging has reasonable accuracy for lesions located in the PZ, but the observed heterogeneity of the transition zone (TZ) during TRUS prevents consistent detection of TZ cancers (217). The role and place of modern ultrasound techniques, such as real-time elastography and contrast-enhanced colour Doppler ultrasound is still under evaluation.

The strategy of targeting biopsies to an mp-MRI-suspicious area has the potential to improve biopsy results by improving detection of clinically significant cancers, reduce detection of clinically insignificant cancer, and allow for a more representative sampling of cancer (length and grade on biopsy) which permits improved risk stratification. It could do all this and use fewer number of biopsy cores required to obtain this information. For instance, in men with previous negative biopsies, a number of centres have independently obtained detection rates ranging from 30% to 59% (mostly anterior cancers), by performing targeted biopsies to an MRI-suspicious lesion. (197) Indeed, as an additional benefit, cancer staging and upgrading were also improved by 44% using targeted biopsies. (198)

In addition to the role of mp-MRI as a target-generation test prior to a first or a subsequent biopsy, mp-MRI may have an even more important role in deferring prostate biopsy in men who have a low probability of harboring clinically significant disease. A normal mp-MRI, due to its very high negative predictive value for clinically significant disease, can be used as a triage test, much in the way that a normal mammogram will be used to reassure a woman that she is at low risk of breast cancer. Recent work by Haffner and colleagues from Lille University-France and Cleveland Clinic Foundation-USA illustrates just what benefits might result (198). Just under half of subjects (42%) might be able to avoid a biopsy by virtue of a normal mp-MRI. This translates to a 13% reduction in the proportion of men that are diagnosed as having clinically insignificant prostate cancer.

Targeting biopsies guidance to an MRI-suspicious area can be carried out in several ways. Targeting biopsies to an MRI-suspicious area was proven to be very effective in improving detection of anterior located cancers, beyond the area sampled by posterior biopsies, which represent 20% of the largest cancers in unselected patients suspected to have prostate cancer (200). This was true when tissue biopsy was performed under TRUS guidance with MRI "cognitive" co-registration. (198)

5.11.3 Improving nomograms

The confidence interval on the predictions given by nomogram calculations might be improved by incorporating novel parameters, or through the introduction of improved risk-assessment tools. Candidate markers include the kallikreins (201), proPSA (85), molecular markers like the urinary PCA3 test (202), and TMPRSS2-ERG fusion gene, or histologic markers on biopsies (203). Validation of candidate markers is restricted by the availability of adequate biomaterials, and the retrospective interpretation induces a verification bias that can only be solved by small prospective trials.

Imaging is expected to play a larger role in the initial assessment of risk, with continuous technological improvements in the various modalities. Multimodality MRI may have utility in lesion detection, making targeted prostatic biopsies feasible (204). The identification of lesions of relevant size (index lesions) might reduce the number of unnecessary biopsy procedures, the number of biopsies per procedure, and eventually reduce overdiagnosis (205). Repeated screening would then detect growing lesions that were initially undetected. The development of focal therapy as a possible future option is supported by this technology. Cost-efficient alternatives based on ultrasonography are also being assessed (206). Positron emission tomography with radiotracers are under development which may further improve the accuracy of imaging. (207)

5.12 Conclusions and Recommendations

Based on the results of population-based studies using fixed screening algorithms, a prostate cancer-specific mortality reduction with PSA screening has been proven. For individual screening, a number of strategies can be followed in order to reduce the potential for overdiagnosis, although it is unproven whether these will be associated with overall disease-related mortality reduction in the population. In order to validate this, future mass screening protocols should incorporate personalized screening protocols.

The committee comes to the following conclusions regarding individual and mass screening for prostate cancer, indicating the level of scientific proof. In addition a number of recommendations are given for the development of scientific actions to be taken in order to develop a safe and efficient screening protocol.

Conclusions

- 1. The decrease in prostate cancer-specific mortality observed in various populations around the world is a combined result of screening and improved treatment modalities. (Expert opinion)
- 2. Population-based screening of men aged 50-74 years reduced prostate cancer mortality by at least 21% in an intent-to-treat situation, and by 29% when corrected for non-compliance. (Level 1 evidence)
- 3. Population-based screening may lengthen life, on average by 29 days, by annual screening in men aged 55-74 years, living on average 558 extra days, knowing they have cancer.
- 4. PSA-based population-based screening induces overdiagnosis of indolent tumours in 23-50% of cases. (Level 1 evidence)
- 5. Current biopsy schemes likely detect all tumours sized 1.5 ml or larger, and therefore, most tumours that become clinically significant. Systematic sextant prostate biopsies are sufficient for population-based studies, but volume-adjusted biopsy schemes are obligatory to make adequate treatment choices. (Expert opinion)
- 6. PSA changes over less than 10 years require further evaluation in screening.
- 7. The best age to start screening is unknown, and might be dependent on risk factors such as family history or genetic factors. The level of PSA in the fourth decade of life is predictive for the detection of PCa during the next 25 years. (Expert opinion)
- 8. The optimal interval for repeated screening in population-based screening protocols might be optimized based on individual parameters. (Expert opinion)

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Conclusions *Cont'd*

- 9. Individual risk assessment leads to a reduction of false-positive biopsy indications (increased specificity), at the cost of a minimal decrease in the overall sensitivity for PCa, and no decrease in the sensitivity for relevant cancers. (Level 3 evidence)
- 10. The ERSPC risk calculator is a currently available individual predictive risk-assessment tool for use in the general population. (Level 2 evidence)
- 11. Risk-assessment instruments, combined with information on prostate cancer, provide mechanisms to avoid prostate biopsies in men with a low risk for prostate cancer. (Level 2 evidence)

Recommendations

- 1. Continuation of current RCTs is needed, as data on longer follow-up will provide greater insight on risk classifications for metastatic disease, cancer-specific mortality, as well as on interval cancers and screening intervals.
- 2. Prospective studies, including new parameters like imaging and novel markers, are needed to reduce overdiagnosis and subsequent overtreatment.
- New screening protocols need to increase specificity (reduce the number of unnecessary biopsies) by incorporating clinically validated candidate markers such as PSA-isoforms, kallekreins, prostate volume, urine and serum molecular markers, preferably in a multimodal risk-assessment tool.
- 4. Information on prostate cancer screening and treatment need to be balanced and address the regional situation.



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New Developments in the Anatomical and Metabolic Imagery of the Prostate and Metastatic Sites

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6.1 Transrectal Ultrasonography

6.1.1 Introduction

The development of ultrasound technology originated with (Sound Navigation and Ranging [SONAR]), which made great strides in submarine navigation during World War II. Dussik is regarded as the first physician to have employed ultrasound in medical diagnosis. In 1942, he attempted to locate brain tumours and the cerebral ventricles by measuring the transmission of an ultrasound beam through the skull (1). Nine years later, Wild and Reid invented A-mode transrectal ultrasono-graphy (TRUS), which was intially described as a technique to evaluate rectal pathology (2). TRUS was first used in 1963 by Takahashi and Ouchi to evaluate the prostate (3), and Watanabe *et al.* described the first clinically applicable images of the prostate obtained with TRUS in 1967 (4). They used chairmounted radial scanners with a 3.5 MHz transducer that was considered state of the art at the time. However, the images obtained with these early transducers provided information only about prostate size and shape. Over the years, the ultrasound technology has become more refined, enabling the visualization of the internal architecture of the prostate. By the mid-1980s, the 7-MHz ultrasound probe had been introduced. It produces a high-resolution image with a focal range of 1 to 4 cm from the transducer. Handheld scanners have revolutionized prostate biopsy techniques, and today, TRUS with high-frequency transducers is a standard diagnostic tool for evaluation of the prostate.

6.1.2 **Sonographic appearance of the prostate**

Advances in technology now allow visualization of the inner structure of the prostate, corresponding to McNeal's concept of zonal anatomy (5,6). McNeal was the first to describe prostatic zonal anatomy, dividing the gland into the peripheral zone (PZ), the central zone (CZ), and the transition zone (TZ), which have differing structural and functional characteristics. The anatomic distinction between the CZ and PZ is generally not appreciated by TRUS. In a healthy man, these two zones are seen as a homogenous light- to medium-grey area in the posterior section of the prostate. Their normal echo pattern is used as a reference for defining other structures as hypoechoic or hyperechoic. The normal TZ in a young man comprises only a small percentage of the gland and exhibits heterogeneous hypoechogenicity relative to the other two zones.

The TZ surrounds the urethra and extends proximal- ly from the ejaculatory ducts. It is the site of origin of benign prostatic hyperplasia (BPH). Benign prostatic hyperplasia nodules are most often hypoechoic, but can also be isoechoic or hyperechoic. Heterogeneity and hypoechogenicity are likely due to variations in the stroma and glands that comprise the BPH. In a man with increasing BPH, the TZ expands and compresses the CZ and PZ. The boundary between the TZ and the PZ is the "surgical capsule" of the prostate, a hypoechoic convex line and a sonographic landmark of zonal demarcation. Strongly reflecting objects are often seen in this region, which is consistent with the appearance of the corpora amylacea. Calcified deposits in this area interrupt the ultrasound waves, causing posterior shadowing that obscures the visualization of the TZ. Approximately 20% of prostate cancer cases arise from this zone.

The PZ, occupying the posterolateral aspect of the prostate from the base to the apex, accounts for most of the volume (nearly 75%) of the normal prostate. The majority (70–80%) of prostate cancers arise from this zone.

The CZ is composed of tissue immediately surrounding the ejaculatory ducts, and it expands inferiorly. Approximately 5–10% of prostate cancer cases arise from this zone.

The seminal vesicles are visualized at the base of the bladder and are hypoechoic. The periprostatic fatty tissues are hyperechoic, while the neurovascular structures in the posterolateral prostate are generally hypoechoic.

6.1.3 Volume measurement

Volume measurement of the prostate is useful and important in treatment planning for both BPH and cancer, monitoring the response to therapies and improving the specificity of prostate-specific antigen (PSA) levels for the presence of cancer. To estimate the size of the prostate using TRUS, either the step-section planimetric method (4) or one of several formulas is used. The step-section planimetric method is generally accepted as the most accurate (7). However, owing to its simplicity and ease of use, the elliptical volume calculation using three dimensions of the prostate is the most commonly used method. The formula is: (transverse diameter) x (cephalo-caudal diameter) x (anterior-posterior diameter) x ($\pi/6$). Though the prostate is not a perfect sphere, ellipse, or prolate spheroid, this formula correlates well with prostate specimen weight, with a correlation coefficient greater than 0.90 (8).

6.1.4 Appearance of prostate cancer

In the early 1980s, the debate arose as to whether prostate cancer is hyperechoic or hypoechoic. It is now accepted that most prostate cancers delineate as hypoechoic (see **Figure 1**). However, the specificity is low (40–63%) (9-12), and the probability that hypoechoic areas are cancerous is less than 60% (see **Figure 2**) (7,9,13,14). Moreover, 8–30% of palpable tumours are not visualized with TRUS (15). Hypoechoic lesions also include inflammation, atrophy, hyperplasia, and even normal prostate tissue (11). Greater than 80% of TZ cancers are isoechoic, as are 30–50% of PZ tumours (9), and 1–2% of tumours are hyperechoic (see **Figure 3**) (6,16). The positive predictive value (PPV) of a hypoechoic lesion increases with the size of the lesion, the presence of a palpable nodule, and elevated PSA levels (10,17,18). The number of "invisible" cancers is probably much higher today with stage migration during the PSA era. To improve lesion detection, the evaluation of secondary signs such as bulging and contour abnormalities has been advocated (13,19).

Of the 1,158 patients who underwent prostate biopsy, 391 were diagnosed with prostate cancer, and 63.1% with adenocarcinoma in the hypoechoic areas as detected on a site-by-site basis (**Table 1**). The sensitivity of TRUS was 58.8% on a site-by-site basis (**Table 2**).

FIGURE 1



TRUS showing a hypoechoic lesion in the left PZ (white arrow).



pT3a prostate cancer, with Gleason score of 3+3=6, corresponding to the lesion seen on TRUS, was confirmed on examination of step sections of the radical prostatectomy specimen.

FIGURE 2

A 72-year-old man with prostate cancer. Upon histopathologic examination of the prostatectomized specimen, adenocarcinoma, with Gleason score of 7, was seen in the left PZ of the apex (not shown).



Preoperative TRUS showed a hypoechoic area in the right PZ of the mid gland (white arrow).



The nodule corresponding to the lesion on the ultrasound (white arrow) was confirmed as BPH.

FIGURE 3

A 65-year-old man with pT3a prostate cancer.



Preoperative TRUS showed a hyperechoic area in the right lobe.



Step-section analysis of the prostatectomized specimen showed adenocarcinoma, with a Gleason score of 3+3=6, in the corresponding area.

TABLE 1 Comparison of Different Biopsy Regimens and Targeted Biopsies on a Site-by-Site Basis

Biopsy Regimens	No. of Cores	Cancer	(%)
All	8,194	1,210	14.8
Sextant	6,948	999	14.4
Lateral	968	164	16.9
Transitional zone	86	8	9.3
Hypoechoic area	1,126	711	63.1
Hypervascular area	813	704	86.6

Of the 1,158 men who underwent transrectal prostate biopsy for detection of prostate cancer in our institution between April 1998 and December 2004, 391 were diagnosed with prostate cancer. On histologic examination of 8,194 specimens, adenocarcinoma was detected in 1,210. Lateral biopsies were performed by adding a biopsy from each side of the gland. A total of eight specimens have been obtained using our standard systematic biopsy method since September 2002. Targeted biopsies of hypoechoic lesions or abnormal Doppler signals were added, except when the puncture line of the systematic biopsy passed through the lesion.

TABLE 2 Results of Grey-Scale TRUS Findings and Histopathologic Examination on a Site-by-Site Basis

Grey-Scale TRUS	Cancer		Total
	(+) n (%)	(-) n (%)	N (%)
Abnormal findings (+)	711 (63.1)	415 (36.9)	1,126 (100)
Abnormal findings (-)	499 (7.1)	6,569 (92.9)	7,068 (100)
Total	1,210 (14.8)	6,984 (85.2)	8,194 (100)

Sensitivity, 58.8%; specificity, 94.1%; positive predictive value (PPV), 63.1%; negative predictive value (NPV), 92.9%.

6.2 Prostate Biopsy in the Detection of Prostate Cancer

Systematic biopsy of the prostate is the gold standard method for diagnosing prostate cancer. The more biopsies are obtained, the higher the positivity rate for a matched group. Patient tolerance is, however, a limiting factor so that, in practice, the number of biopsies has to be limited. A compromise is therefore necessary. To decide at what level to compromise, accurate data on positivity is needed.

Published comparisons of different biopsy regimens assume that the number of biopsies obtained is the only important factor. However, evidence from matched populations who have the same number of biopsies shows that positivity rates still vary greatly. This is almost certainly due to differences in the technique of obtaining the biopsies and preparing them for histologic analysis.

In some patients who have had a set of biopsies that are negative for cancer but who are still thought to be at high risk for cancer, it is common practice to advise re-biopsy. This group includes those with a persistent high serum PSA, a rising PSA, a suspicious or atypical core on the first biopsy (atypical small acinar proliferation [ASAP]) or prostatic intraepithelial neoplasia (PIN) on the first biopsy. These groups are often recommended to consider re-biopsy. The indications for re-biopsy should be clarified during patient counselling to convey an understanding of the diminished likelihood of detecting a significant cancer in this setting. Diagnosis of any cancer on repeat biopsy after PIN is estimated at 25% (compared with 18% for prior negative biopsy) and after ASAP is 40%. However, 80% of these cancers detected are ultimately found to be indolent tumours (Gleason 6, organ confined). It also bears noting that patients with low-volume cancers are often recommended for active surveillance management strategies, which entail a scheduled program of follow-up that would seem reasonable, as well for the benign finding of PIN or ASAP. Therefore, the decision to re-biopsy in these groups can be tempered with reason.

6.2.1 Method of biopsy

Biopsy of the prostate guided by the finger during a digital rectal examination (DRE) was, at one time, the accepted method. The needle may be directed to separate quadrants of the prostate or to a palpable abnormal area. This method is still appropriate for patients suspected, on DRE, of having clinically large advanced prostate cancer. It is quick, easy, and inexpensive, and may be performed in the outpatient clinic. For the majority of patients, however, biopsy is performed under real-time guidance by TRUS.

Currently, most biopsies are obtained using a core biopsy needle with an automated spring gun. A needle size of 18 gauge is sufficient for histologic examination. Needles as large as 14 gauge are available and sometimes used, though they are rarely needed to obtain tissue sufficient for diagnostic purposes. Concerns regarding pain and risk of bleeding from larger-gauge needles have prompted the use of finer-biopsy needles, with no discernable drawbacks. What is important is to use a needle that is capable of providing maximal length of core. The largest commercially available needle gives a core length of 20 mm.

Needle placement during biopsy procedures is facilitated by use of a needle guide that is typically a thin, hollow tube attached either to the side of the transrectal transducer (for end-fire probes) or passes obliquely through the probe (for side-fire probes). These needle guides may be disposable or capable of sterilization, allowing them to be re-used. The predicted path of the needle is often displayed graphically as an overlay on the ultrasound image as a line of the predicted path the needle will take through the tissue when it is advanced and fired into the gland. As the guide is long, the needle usually follows the predicted path. Errors in targeting accuracy may occur if the needle guide is fitted into the probe improperly, if the needle guide is incorrectly matched to the imaging algorithm, or when biopsies are taken from targets far from the tip of the needle guide, such as the extreme anterior prostate and TZ. Needle deflection often occurs predictably along the direction of the needle bevel as the needle passes through the gland. If needle accuracy consistently occurs in one direction, then changing the direction of the bevel of the needle may correct this error.

The prostate may be biopsied with image guidance in the axial or the parasagittal plane. Biopsies obtained with the imaging aligned in the axial plane may enable more predictable placement along the medial to lateral coordinate. Biopsies using parasagittal imaging may facilitate needle placement along the cranio-caudal dimension. In most cases, preference for one form of imaging over the other is a matter of surgeon choice, and the positivity rate for either technique appears to be similar. However, in some cases, one approach may be required, as in the case of biopsies obtained from the anterior apical prostate, which can be easily obtained in the axial plane with the needle directed from lateral to medial to sample the region above the urethra without piercing it.

Over the last few years, several systems, if not all, have provided probes with the capability of simultaneous biplanar imaging to allow coordinated imaging and targeting. Potential advantages would include the ability to optimize biopsy needle placement in the established regions of the prostate most often targeted for systematic biopsy. The utility of this approach, however, has not been definitively evaluated.

In preparation for biopsy, patients complete an informed consent, following counselling, regarding the associated risks. The main adverse events discussed are the risks of bleeding from the rectum, bladder, or prostate and infection. Previously, cumulative rates of these events were lower than 5–7% (20). Antibiotics (typically fluoroquinolones) given prior to the procedure are used to minimize the risk for infection. Prospective studies have demonstrated decreased risk for clinical infections when following such regimens. However, recent evidence now suggests the emergence of an increasing problem with organisms resistant to antibiotics, significantly increasing the risk for infection following biopsy, with rates now approaching 5–8% in some series (21). Risk factors appear to include recent travel history and prior antibiotic use (22). Strategies to minimize these risks are a new focus of needed research.

Preparation with a pre-procedure enema is of value in cleansing the rectum. Local anesthetic injection in various patterns around the prostate is administered by many clinicians. Rectal lidocaine jelly and oral analgesics may also be used. Details of these are, however, outside the scope of this article.

6.2.2 Biopsy patterns

During the early years of prostate biopsy, it was customary to obtain four biopsies (quadrant biopsies)—two each of the right and left lobes, one directed toward the base, one toward the apex. This was often performed under digital rectal guidance, and in other cases, by ultrasound guidance. With ultrasound guidance, a transrectal or transperineal route was available with the great advantage of visualizing the prostate gland during biopsy to allow development of approaches for systematic sampling based on anatomic features. The transperineal route had the advantage of being more sterile, but guidance was less accurate and a general anesthetic was often necessary. The transperineal route is used exclusively in patients who have had an abdominal perineal (AP) resection when the rectal route is not available. In these cases, guidance is also by transperineal ultrasound imaging.

TRUS guidance with biopsy via the transrectal route has been adopted as the standard for most prostate biopsies, and it is currently the most utilized means for sampling the prostate. Main advantages of this approach are patient tolerance and the ability to perform the procedure in the outpatient setting.

Biopsy patterns have continued to evolve in an effort to improve upon the diagnostic detection of prostate cancer. These endeavours in increasing the number of biopsies, though well intentioned, were carried out early in the experience of prostate cancer screening following the introduction of PSA testing. In this setting, the intention was to diagnose prostate cancer very early, when cancers are suspected and yet likely to be of very small volume—therefore limiting the size of the tumour that can be targeted and accurately identified. Not surprisingly, prostate volume also plays a role, as it is more difficult to identify small tumours in increasingly larger glands.

Original systematic patterns of biopsy were somewhat arbitrary, logically dividing the prostate into the right and left lobes and then apical and basal segments. With experience and incorporation of mapping studies from whole mount tissue evaluation, sampling techniques have been adapted to address regions of the prostate in which tumours are more likely to be discovered. These include laterally directed locations within the PZ, and now, the anterior apical prostate.

Standard biopsy sampling using the conceptualized segmentation of the prostate into the base, mid, and apical regions from left and right has been the basis for the termed *sextant* patterns of prostate biopsy. Additional sampling has essentially built upon this base pattern of six biopsies to include routine sampling of eight, 12, 14, and 16 or more biopsies. The performance of these biopsy templates would be assumed to improve with the addition of more biopsy cores, though essential questions remain regarding the requirements for detection with biopsy. This issue has also evolved over time, from "what is the best biopsy strategy to diagnose *any* prostate cancer" to "what is the best biopsy strategy to detect and quantify *clinically significant* prostate cancer." These approaches remain a challenge to address in finding the correct balance between the invasiveness of biopsy, the need for detection, and the potential benefits from imaging.

Guided biopsies to sample abnormalities identified on imaging have been performed based on sonographic evidence of abnormalities and magnetic resonance imaging (MRI). The imaging features of cancers based on these imaging modalities are covered elsewhere. Biopsy of sonographic lesions using grey-scale imaging parameters may be directed at a hypoechoic nodule with the intent of improving the likelihood of detecting cancer on biopsy. The incremental yield in using this technique is marginal, improving detection by 3–4% over standard template biopsy alone, although these lesions may have a greater likelihood of corresponding to a higher-grade tumour than those detected on systematic biopsy alone (23).

6.2.2.1 MRI-guided biopsy

Magnetic resonance imaging guided biopsy has been used for sampling areas of suspicion, albeit with mixed success. What is clear from all related approaches is the primary dependence upon the imaging technology itself and the ability to discern tumours within the gland. These features are clearly understood to be the rate-limiting step—if the tumour is not detectable with imaging, then it cannot be targeted. Equally true is the issue with over-reading of imaging and the potential for false

positives from prostate artifacts that may resemble the imaging features of cancer. The interpretation of MRI for prostate cancer remains a challenge and is highly dependent upon experience. In a setting where the clinician is specifically asking for regions to target during prostate biopsy after MRI, the reader is earnestly attempting to identify suspicious regions of interest that fall along a spectrum of suspicion based upon features of size, shape, and the presence of co-localizing abnormalities on several types of scans. Therefore, it is appropriate to assign such values along a Likert scale, ranging from low to high degrees of suspicion. Finally, the accuracy and ease with which regions of interest can be sampled is a matter of concern.

Original attempts at developing these MR-directed biopsy modalities were fraught with difficulties due to the restraints imposed on the use of ferromagnetic instruments within the scanner. Several groups developed MR-compatible devices for this purpose. These devices can be broadly categorized into those that allow live image guided biopsy inside the scanner and those providing image tracking for needle biopsy outside of the scanner (24-28).

The important difference is in image confirmation of the needle actually sampling the targeted tissue—an advantage of the in-scanner technique. The drawback from this is the limited working space within the magnet bore, affecting access to the patient and the ability perform multiple biopsies during the required image sequences (29). Out-of-scanner biopsies are certainly faster; however, prostate movement during needle insertion can have profound effects on targeting accuracy. Still, biopsy yields with this approach have been reasonable, though patients in these series tend to have clinical features associated with greater tumour burden (30).

6.2.2.2 MRI—ultrasound fusion biopsy

A hybrid approach to MR-targeted biopsy is the use of MRI-ultrasound fusion imaging for targeting regions seen on MRI but sampled in a separate procedure that utilizes ultrasound guided visualization to place the biopsy needle into the area seen on the MRI. Early experience with this approach was performed using freehand visual co-registration in which the operator would localize the region of interest spatially using anatomic landmarks common to both MRI and ultrasound images (31). Yields of positive biopsies were modest, though questions remain regarding the targeting accuracy and sensitivity of MRI in these earlier studies.

To overcome these issues, use of instrument tracking technologies have produced several systems that allow annotated three dimensional (3D) MR images of the prostate to be imported into the ultrasound unit and co-registered or "fused" to the live ultrasound image in order to provide an overlay of the MR representation of the prostate onto the live image. 3-dimensional elastic registration system of prostate biopsy location by real-time 3-dimensional transrectal ultrasound guidance with magnetic resonance/transrectal ultrasound image fusion (32).

Biopsies are then directed into the regions of interest in real time and may also be taken from standard sextant locations to provide adequate sampling of the gland. This approach has advantages, allowing for careful MR image evaluation and annotation prior to biopsy, unlike the online approach for image interpretation during MR guided biopsy procedures. Furthermore, this approach can be performed easily in the outpatient setting in a limited timeframe and allow for both diagnostic and characteristic biopsy to be performed simultaneously. Experience with MRI-ultrasound fusion biopsy has been promising. Large series using this approach have demonstrated an improved biopsy yield over template guided biopsy alone, including better characterization of index tumours within the gland. These improvements have come simultaneously with better MRI techniques and the advent of diffusion weighted imaging. Further studies are needed to validate these findings and develop these technologies for use in specialized centres. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging (33).

6.2.3 How to measure the sensitivity of biopsies

6.2.3.1 Autopsy evidence

A measure of the sensitivity of different biopsy regimens would be extremely valuable. We do not, how- ever, have a gold standard, as it is not possible to know how many cancers are missed. A study of autopsy specimens in the US has shown that a very high percentage of men have small histologically detectable foci of prostate cancer (see **Table 3**). In this study (34), the prostate of men who died of trauma were examined histologically for evidence of prostate cancer. This showed that 47% of men between 50 and 59 years of age have foci of the prostate cancer. Between ages 60 and 69, the figure is 65%. Most men biopsied for suspected prostate cancer are aged between 50 and 70 years of age. We might, therefore, expect our positivity rate to be at least 56%.

Ν	Cores	Pick-Up Rate	Author
202	12	41.5	O'Connell <i>et al.</i> (45)
119	13	40%	Eskew <i>et al.</i> (49)
483	10 + D	42%	Presti <i>et al.</i> (51)
264	12	42.2%	Gore <i>et al.</i> (52)
303	10	38.9%	Ravery <i>et al.</i> (56)
244	12	27%	Naughton <i>et al.</i> (57)
273	10 + D	44%	Chang <i>et al.</i> (58)
187	12	38.5%	Lui <i>et al.</i> (59)
736	6	42%	Terris <i>et al.</i> (60)
D – directed or targeted biopsies (12, 15, 19, 51, 52, 56, 60)			

TABLE 3 Percentage of Autopsied Specimens With Small Histologically Detectable Foci of Prostate Cancer

Most studies normally biopsy a selected population who have elevated PSA levels and/or abnormal DRE, rather than the unselected population in the autopsy study. While the assumption that these indicate an increased probability of prostate cancer (This has been challenged [35]), one would expect the positivity rates to be higher than those in the autopsy study. Whether this is true or not, the autopsy study would indicate that we miss many cancer foci. It may be argued that many of the

cancer foci detected in the autopsy study were 'clinically insignificant' cancers. However, although an arbitrary distinction may be made in size, (a common figure being larger or smaller than 0.5 cc.), the definition of clinically insignificant cancers is unclear (36).

6.2.3.2 **Positivity rates on repeat biopsies**

A number of patients with negative biopsy studies, who have a rising PSA level, will be offered repeat biopsies. Any positive results in the patients probably (though not necessarily) indicate false negatives (sampling error) in the original studies.

Patients whose biopsies show PIN but no cancer also often have repeat biopsies. In this group, as there is only a short interval between the two procedures, any cancer detected on re-biopsy indicates false negatives on the original biopsy. Most papers quote positivity rates on re-biopsy following an initial sextant biopsy. In these positivity rates on re-biopsy are high—typically from 25 to 65% (37-39).

This suggests a high miss rate on the original biopsies. More recent studies with 8 or more biopsies show a far lower positivity rate on re-biopsy—typically less than 10% of the patients re-biopsied (40,41). This represents approximately 1–2% of the original cohort of patients. This correlates with the higher positivity rate in the initial biopsies in this group, i.e. most of the cancers were detected on the first set of biopsies.

6.2.3.3 Studies using the same patients

Another method of analyzing the subject is to study biopsy results of patients who have had extensive biopsies, all of which have been studied histologically and recorded separately. From this data, the positivity rates for the standard pattern of six, eight, and 10 biopsies may be calculated. One such series showed a significant increase in positivity from 6 to 8 biopsies of 5%, but a less marked increase of less than 2% from 8 to 10 (42,43). Few centres however label their biopsy specimens separately, so few such studies are available.

6.2.4 **Comparison of published series**

Another method of comparing regimens is to study relative positivity rates in different series with similar populations. True matching of population is however difficult due to the multiple potential sources of bias: race is important, as black men may have significantly higher incidence of 'clinically significant' (though probably not overall) prostate cancer than Caucasians and Hispanics.

Age may be a bias. Certainly, the level at which serum PSA levels become significant appears to be related to age.

Indication for biopsy may also introduce a bias. Most series use an elevated serum PSA and/or an abnormal DRE. A few studies, however, have only patients with both an elevated serum PSA and an abnormal DRE. Also, the threshold of PSA level differs in different series.

From the published literature, despite differences in methodology and patient selection in studies, a distinct pattern emerges. Six biopsies give an unacceptably low positivity rate. Ten or more biopsies, or eight in a gland under 40 g, or 10 in a gland over 40 g is now common practice. The figure of eight to 10 provides a means for balancing a small increase in positivity against patient tolerance (11,43-55).

When large series, all with eight, 10 or more biopsies, are studied, positivity rates of between 39 and 43% are seen (**Table 3**) (42,45,49,51,52,56-60), with a few exceptions that are significantly lower. Present evidence denotes that this figure may be regarded as the gold standard.

Ultrasound-guided samples only from either hypoechoic lesions or palpable abnormalities is far superior to the previously used, digitally directed, blind biopsy. However, these targeted biopsies tend to miss many malignancies due to limitations in detecting cancer based on sonographic findings. Shigeno *et al.* report that 14.4% of cores obtained from sextant biopsies were positive, while 16.9% of cores were positive from lateral biopsies (**Figure 4**).

In 10 of 391 men with prostate cancer, tumours were detected only in the lateral biopsy specimens (61).



6.2.5 **Technique of the biopsy**

Within matched series with the same number of biopsies, a large variation in positivity rates exists (62). The reason for this has not been fully validated, but it is certainly related to the total core length. Poor biopsy technique may produce some cores that are only part prostatic tissue and others that contain no prostatic tissue.

Pathologists have found a positive correlation between positivity rates with total core length (63). While the total core length is related to the number of cores obtained, it is also related to the biopsy system used, the technique of biopsy, and the preparation of the histology sample.

It is also probable that positivity rates may be related to accurate placement of the biopsies. A relatively even spacing throughout the gland may, intuitively, increase the likelihood of detecting a cancerous nodule, while poor placement with perhaps two biopsies at or near the same site, with a significant gap to the next, may reduce the likelihood. Although this hypothesis is likely, it is impossible to test.

Most cancers arise in the PZ. In many patients studied, the PZ is considerably thinned because of benign prostatic hypertrophy in the TZ. If the biopsy needle is advanced into the gland before firing, a thin PZ may be entirely missed. The operator must know the sampling area the biopsy gun employs. Some models advance 0.5 cm and sample the subsequent 1.5 cm when fired, whereas other models sample from the point of the needle tip prior to firing. It is important therefore to back the needle away from the prostate surface for the former biopsy gun and to fire the needle of the latter when its tip is just touching the gland. Whether this is achieved may be assessed on the pathology core by seeing the pseudocapsule. This has the added advantage of sometimes detecting extraprostatic spread. With the laterally placed (lateral horn) biopsies, placing the biopsy only slightly too medially may also miss a thin PZ, while a slightly too lateral placement will miss the prostate gland completely.

Many operators with experience in imaging the prostate practice what is referred to as "informal targeting." This is not overt targeting of a visible nodule with an extra biopsy, but a small alteration in the positions of the individual biopsies so that, while they remain within the overall pattern of systematic biopsies, they are subtly moved, within, for instance, the right apex to include any suspicious looking area of that sector of the gland. Again, this may well have an effect on positivity rates. This hypothesis would be difficult, though not impossible, to test.

6.2.5.1 Simple mathematical model

Another way of looking at biopsies is to assume that the prostate gland is a cube, and that cancer may occur equally in different parts of the gland. Further assume that biopsies are taken at even intervals throughout the gland. If such a model gland is 20 cc in size, we can divide the cube up into 10 separate cubes of 1 cc each. A 20-mm biopsy needle will transverse 2 cubes. Then, 10 biopsies evenly spaced across the gland will detect a 1 cc cancer within that model gland.

If we reduce the size of the cancer to 0.625 cc (a 5-mm cube), then we increase the number of cubes in which the cancer may be situated by 8 times (16 cubes). As the cubes are smaller, each biopsy will sample 4 cubes rather than 2. In this model, we would only detect 25% of cancers.

The same would be true if we leave the cancer size the same, but increase the size of the gland to 80 cc.

If we assume that a "clinically significant" tumour is one of less than 0.5 cc, then by the same calculation, in a 20-cc gland 16 biopsies are needed for cancer detection, and in a 40-g prostate 32 biopsies are needed.

This is, of course, a grossly simplified model. Cancers do not occur randomly within the gland. Biopsy patterns are designed to concentrate the lateral PZ where cancers are most likely to occur. Also cancers are not cubed, or even often not ovoid, but rather stellate, which increases the likelihood of detection on biopsy. Nevertheless, this very simple model demonstrates that we are less likely to miss larger tumours than small tumours. This may explain the discrepancy between the autopsy study and biopsy studies. In our simplified model, to be sure of detecting a 0.25-cc tumour in a 20-cc gland we would need 40 biopsies. To detect a 0.25-cc tumour in an 80-g prostate, we would need 120 biopsies! We know, however, that the vast majority of cancer foci found in the autopsy study would not have developed into cancers that would have affected the patient during his lifetime. We have no real way of knowing which one would have progressed. One possible discriminator, however, is the size of the tumour—a significant size indicates that, as the tumour has already grown to that size, it is likely to progress further. A tumour that is likely to progress to a level that it is symptomatic or fatal is loosely termed a "clinically significant" tumour. It is these tumours, often defined as larger than 0.5 cc, that are important to detect. Assuming that size is one of the important parameters, we are less likely to miss these than smaller, perhaps "clinically significant," tumours.

The converse of this argument is that many of the tumours that we detected are "clinically significant" tumours. This may be suggested by a small length of tumour biopsy core. Unfortunately, however, this is not necessary accurate, as small foci could be found when the biopsy crosses a tenticle-like extension of a larger tumour.

There is evidence, however, that if sufficient (at least 8-10) biopsies are taken, tumour volume (measured on radical prostatectomy specimens) correlates well with the length of the tumour in the biopsy cores and the number of cores involved. Thus, evidence indicates that the increased positivity rate obtained when increasing from 6 to 8 or more cores does detect more clinically significant (>0.5 cc) tumours, and that the percentage of tumours detected that are clinically insignificant is not increased.

In summary, there is neither a good measure of the sensitivity of biopsy detection of prostate cancer, nor is it clearly known what is being sought.

6.2.5.2 Histopathological preparation

Having obtained a set of biopsies, it is important that they be carefully prepared for histologic analysis. The pathologist can only interpret that which he or she is finally presented with. A common practice is to place all the biopsies from one side of the prostate into one container of formalin, and place these together into one wax block to be cut, stained, and examined. It is difficult, using this technique, to embed the cores so that the maximum length of all the cores is cut. The practice of putting the cores into separate containers, and embedding them separately makes it easier to cut the cores level so that the maximum length is available for histologic examination, but is prohibitively expensive at many facilities, making a meticulous technique by the pathology technicians essential (64,65).

6.2.6 Adding targeted biopsies

Abnormal areas of the prostate may be detected by grey-scale ultrasound, Doppler ultrasound, contrasted ultrasound or elastography. Targeted biopsies of these areas may be added to the systematic biopsies. Such a technique typically increases the relative positivity by only a small percentage. The degree of increase in positivity is predictably smaller if more systematic biopsies are obtained (11,66-69). Abnormal areas may also be detected by standard T2W, MRI and by MR spectroscopy (70-73). MRI guided biopsy is not easy, though possible (26). However, these abnormal areas, or at

least the prostatic segment in which they are detected, may subsequently be biopsied by ultrasound guidance. Although they may not be visible on the ultrasound images, their position may be assessed from the MRI images. These techniques are discussed elsewhere.

6.2.6.1 When to re-biopsy

Another important question is how and when to re-biopsy patients. Indications for re-biopsy are:

 Suspicious or atypical small acinar hyperplasia (ASAP) but non-diagnostic cores
 High-grade PIN
 Rising PSA levels

Suspicious or atypical cores and the presence of ASAP are a definite indication for re-biopsy. The area of the atypical core or cores is biopsied at several sites. Whether the rest of the gland should also be re-biopsied is unclear. Positivity rates in this group of patients are high (38).

Prostatic intraepithelial neoplasia is a histologic change in the prostatic glandular epithelium. It is neither prostate cancer, nor is it pre-cancerous. The high grade variant of PIN is associated with prostate cancer in a large proportion, though not all cases. The cancers are not necessarily close to the foci of high-grade PIN. It is therefore customary to re-biopsy patients whose initial biopsies show high-grade PIN but no cancer. Most papers quote a positivity rate of 30–40% (74,75). This indicates false negatives (geographic misses) on the first set of biopsies. This data is based on sextant biopsies. More recent data suggest that with extended biopsy regimes that achieve a higher positivity rate on the first set of biopsies, positivity rates for re-biopsy are correspondingly low, at about 2% (41,76). It is therefore suggested that if PSA level remains stable, then re-biopsy for high-grade PIN alone is not necessary.

A rising PSA level is an indication for re-biopsy. As re-biopsy is undertaken at varying time intervals after the first biopsy, sometimes quite long, it is difficult to tell how re-biopsy results relate to the first biopsy results. It is relevant, however, to discuss whether the pattern on repeat biopsies should be different to the first biopsies. Positivity rates in this group are high (37,38). If, however, the first set of re-biopies are negative, then subsequent sets of re-biopsies have a low positivity rate. This probably reflects the increased positivity rates of increasing numbers of biopsies. Two sets of sextant biopsies probably (though not necessarily) equate to a set of 12 biopsies.

6.2.6.2 Pattern of repeat biopsies

There is no consensus about biopsy patterns in re-biopsied patients. Some simply repeat the standard pattern. Some position the re-biopsies approximately between the first set—i.e. the apical biopsies a little lower, the base a little higher, and so on. Others include the anterior gland, particularly in large glands in which standard biopsies do not reach the anterior gland. Some do this by placing appropriate biopsies more anteriorly by advancing the needle further before firing. Others add anterior biopsies to the standard set. Additional anterior biopsies aimed at the most anteriormedial aspect of the gland where TZ tumours tend to arise would be expected to provide the highest yield. There is no evidence as to which if any biopsy pattern is superior.

6.2.7 **Discussion**

There is no way of accurately assessing the sensitivity of prostate biopsy. Furthermore, we are not certain what to measure with regard to so-called clinically significant and insignificant tumours. There is also the whole vexed question of whether we should be biopsying patients because of elevated PSA levels, at least at the lower end of the range, at all. What does emerge, however, is that if we decide to biopsy patients, it is incumbent upon us to use the best methods available.

It appears that at least 8 or 10 biopsies are necessary to achieve a reasonable sensitivity. A good biopsy and histology preparation technique are also necessary. Such a regime should yield a positivity rate for a PSA-elevated population of above 39%, at least in non-oriental populations. There is a need to set some sort of benchmark standard. It is not clear how this can be achieved. Positivity rates are one possible solution. A record of the total length of biopsy cores at histology and the presence of pseudocapsule at the end of the cores is another. Positivity rates at re-biopsy should also be recorded.

6.2.8 Local Staging

Extracapsular extension can be characterized by an irregularity or interruption of the capsule, an irregular capsular bulge, or an obvious extension of a hypoechoic lesion in the surrounding fatty tissue. However, TRUS is limited in its ability to locally stage advanced cancer. The sensitivity and specificity of TRUS for detecting extracapsular extension is 48–86% and 50–90%, respectively (77-80). Significant interobserver variability in the interpretation of extracapsular extension or seminal vesicle involvement is also a variable with TRUS analysis (90). The inability of TRUS to detect microscopic extracapsular extension has been confirmed (77, 82).

When tumours are hypoechoic, increased length of contact between the lesion and the capsule correlate with the presence of extracapsular extension (83). The loss of the triangle formed in the sagittal plane by the prostatic apex, urethra, and rectal wall is also a predictor of extracapsular extension (84). Recent advances in Doppler TRUS, attempts at reconstructing a 3D image of the prostate (85), and introduction of artificial neural network analysis (86) might improve the accuracy at staging.

6.2.9 **Doppler ultrasonography**

The use of Doppler ultrasound with targeted biopsy is expected to improve cancer diagnosis because of the increased detection of neovascularity found in pathologic specimens of prostate cancer. Blood flow assessed by Doppler ultrasound may reflect the state of angiogenesis in prostate cancer (**Figures 5** and **6**) (87). Colour and power Doppler ultrasonography have been shown to be an important adjunct to conventional grey-scale TRUS, improving the accuracy of cancer detection (19,61, 88-90). Cancer has been detected in 86.6% of hypervascular areas (**Table 1**). Doppler TRUS has shown a sensitivity of 58.2%, similar to that of grey-scale TRUS, and a PPV of 86.6%, much higher than that of grey-scale TRUS (**Table 4**).

TABLE 4 Results of Doppler Ultrasonography and Histopathology on a Site-by-Site Basis

Doppler Ultrasonography	CANCER		TOTAL (+) n
	(%)	(-) n (%)	N (%)
Abnormal signals (+)	704 (86.6)	109 (13.4)	813 (100)
Abnormal signals (-)	506 (6.9)	6,875 (93.1)	7,381 (100)
Total	1,210 (14.8)	6,984 (85.2)	8,194 (100)

Sensitivity, 58.2%; specificity, 98.4%; PPV, 86.6%; NPV, 93.1%.

FIGURE 5

A 68-year-old man with pT2a prostate cancer. The pre-operative PSA level was 23.4 ng/ml.

- A An intense increase in Doppler signals was delineated in the right PZ and the defined rectangle (20 mm²) for the measurement of pixel intensity (PI) is shown.
- **B** A tumour with a Gleason score of 7, consistent with the lesion on ultrasonography, was confirmed on examination of whole-mount sections of the radical prostatectomy specimen.
- C Cytoplasmic staining for vascular endothelial growth factor (VEGF) in the tumour was intense.
- D The microvessel density was 110/mm².













6.3 Contrasted Ultrasound Studies in the Detection and Study of Prostate Cancer

6.3.1 Background

All cancers develop their own blood supply (neovascularity), which differs in pattern from the vascular bed of the tissue in which they develop (13,91-93). If this vascular pattern can be imaged, then a potential exists for using such imaging to detect tumours.

The recognition of tumours by their vascularity is well founded. Before the advance of computerized tomography (CT) and MRI, renal tumours were detected by angiography by virtue of detecting their abnormal vascular pattern. The pattern of tumour neovascularity also has a potential for the study of other tumours. Histologic studies indicate that tumour microvascular density correlates with agressiveness. Also, the changes in vascularity may potentially be used to monitor tumour progression. This could be used in patients on an active surveillance regimen, or those who have been treated with high-intensity focused ultrasound (HIFU), or those on anti-tumour agents, particularly those designed to block neovascularity (anti-neoangiogenesis agents).

In the case of prostate cancers, the use of the Doppler technique has been studied for some time (66,88,89,94-103). Doppler, either 'standard' velocity domain or 'power' domain, may only detect vessels down to a fairly large size, typically arterioles. Tumour neovascularity is composed largely of vessels smaller than this. Nevertheless, studies using the Doppler technique had limited success

in detecting prostate cancers by comparing the vascularity, as vessel density, on both sides of the prostate in each scan plane. Some information about staging and tumour aggressiveness was also obtained. In general, tumour vessel density was found to correlate with high Gleason stages, more aggressive tumours, and poor prognosis (13,104-111); hypervascular areas may then be target biopsied. The vessels shown in studies using uncontrasted Doppler are probably largely the tumour feeding vessels rather than the intratumoural vessels.

The reason that smaller vessels are not visualized is that blood flow through them is of small volume and low velocity. It is this low volume, low power flow that can be shown by ultrasound contrast agents.

Ultrasound contrast agents are stabilized microbubbles of a size similar to red blood cells (RBCs). Contrast-specific imaging is a different way of visualizing vessels after the intravenous (IV) administration of the contrast agent. These bubbles are about 1,000 times more reflective than RBCs (112). This enables Doppler systems to detect flow in small vessels down to 10 cm/sec or perhaps less. This work prompted further studies in the prostate using colour Doppler with ultrasound IV contrast.

The technique is well validated in liver tumours and, to a lesser extent, in other sites (66,94-116). Its use in the prostate has lagged behind these other areas due to technical difficulties with the procedure, at the high frequencies normally used in the prostate. These difficulties have now been overcome and software is now available on a number of commercially available systems. Work in progress, however, would suggest that contrast studies using a contrast-specific technique has a significantly more potential than the older Doppler techniques.

Microbubbles are extremely reflective and return powerful ultrasound echoes. Within fine blood vessels, however, they are present in small numbers and move rather slowly. The ultrasound and the Doppler signals from them are therefore relatively low and are lost in the echoes from the surrounding tissues. A different imaging technique is therefore necessary.

In addition to reflecting the ultrasound beam, the bubbles vibrate. Their vibration is non-linear. They expand more than they contract. The result is that the returned echoes are not only at the frequency of insonation, but at frequencies above and below this frequency. The surrounding tissue, on the other hand, returns frequencies that are mainly at the fundamental frequency. Although other frequencies are produced (tissue harmonics), these are weak compared with the non-linear frequencies from the contrast bubbles.

A broad hand-held transducer is capable of detecting a wide range of frequencies. If the fundamental frequency is removed from the returned signal, the additional frequencies produced by the contrast bubbles produce the predominant images. The weak non-linear frequencies from the surrounding tissue produce a low-intensity image that, while sufficient for localization, does not interfere with the vascular map image.

The fundamental frequency may be removed in several ways: by filtration; by introducing a second pulse at 180 degrees to the first, thus canceling out the fundamental frequency (pulse inversion); or by more complex methods utilizing pulse coding.

In addition to causing vibration of the bubbles, the ultrasound beam, at the power normally used, causes such violent expansion of the bubbles that they rupture. This has the effect of severely shortening the life of the contrast. This can be a severe disadvantage, as it limits the time of imaging to one, or at most two passes. When the bubbles burst, however, they produce very high energies of ultrasound signal at a wide range of frequencies. This may be utilized to produce an image. There are thus two different methods of producing contrast images.

The first is a technique in which the power of the ultrasound beam (normally expressed as the mechanical index, or MI) is kept low (low-MI technique). This preserves the intravascular contrast agent, allowing continuous scanning for many minutes.

The second technique is to utilize a high-power pulse to burst a large proportion of the bubbles in the slice being studied. The resultant high-energy returned signal is then imaged (high-MI technique). This may be repeated for other slices, after a period to allow new contrast to enter. Eventually a large proportion of the contrast is destroyed and no further images are possible. This may be counteracted by giving multiple smaller IV injections of the contrast agent, or by continuous infusion.

The low-MI technique is the easier technique to use. Present-generation contrast agents have more robust bubbles than the previous agents and lend themselves to low-MI imaging. The intermittent high-MI technique is however better at detecting low concentrations of microbubbles. As the vessels in the prostate and also in prostate cancers are largely very small, the high-MI technique may be superior in detecting them.

Another method of imaging very fine vessels is a persistence technique in which consecutive frames are added together. With this technique, as little as a single bubble passing slowly down a vessel may be enough to produce an image of that vessel. By its nature, the technique produces blurring and artifacts with the slightest movement. With careful technique, it is however useable in the prostate.

6.3.2 **Technique**

The prostate is first imaged by a conventional ultrasound technique. The chosen contrast imaging technique is then selected, and contrast is injected or perfused through an IV cannula. The pattern of uptake and washout may be studied, but this does not appear to be very useful in the prostate—shortly after contrast is seen to enter the vascular tree of the prostate, a steady state is achieved. Multiple images are recorded from approximately 2-mm spaced slices, usually in the axial plane, throughout the prostate.

Real-time technique analysis at the time of scan enables targeted biopsies of abnormal areas to be performed at the same examination.

6.3.3 **Results and Discussion**

Early results using Doppler methods were encouraging, despite limitations of the techniques used.

Studies with enhanced conventional Doppler techniques showed that the technique could detect prostate cancer (95,98,117-119).

Experience has shown that there is a recognizable pattern in the normal prostate. The CZ and TZ have easily seen blood vessels that radiate from the midline outwards. The outer gland or PZ appears relatively hypovascular (see **Figure 7**). The PZ probably has the same vessel density but has very fine vessels that run parallel to the surgical capsule and pseudocapsule. High-resolution scans are necessary to demonstrate this pattern. One of these is persistence mode in which movement of individual bubbles may be tracked to outline the path of a vessel (see **Figure 8**).

Benign prostatic hypertrophy nodules have a variable vascular pattern. They tend to displace normal vessels that curve around them. The nodules themselves are mostly hypervascular but some are hypovascular (see **Figures 9** and **10**). This variability makes it difficult to differentiate them from inner gland cancers.

Cancers are detected by their hypervascularity (see **Figure 11**), and it is this pattern that is described in most of the literature. A small number of hypovascular tumours have been seen (see **Figure 12**). The fact that not all tumours are detected by their vascular density makes it likely that many are isovascular with the rest of the PZ. Some tumours are seen as subtle alterations of the normal vascular pattern in the PZ (see **Figures 11b** and **12a**). Appreciation of this sign requires a system that shows very fine vessels in great detail. At present, such detail is sometimes achieved, but not in all patients.

It is too early to present any hard data that has been validated. Latest studies do suggest that there is potential for combining vascular targeted biopsies with various systematic biopsy regimens to increase positivity or to maintain positivity while reducing the number of biopsies.

FIGURE 7

A and **B** Normal glands in which the PZ (arrowed) appears relatively hypovascular.



FIGURE 8

A and **B** Normal glands in high-resolution 'persistence' mode. The fine vessels of the PZ are seen running parallel to the capsule.



Contrast imaging of the fine vasculature of the prostate is a viable proposition with commercially available contrast agents and ultrasound equipment. Most sophisticated ultrasound machines are capable of contrast-specific imaging, though extra software must be purchased. Not all machines offer the capability of contrast-specific imaging via a transrectal prostate transducer, though more systems will probably have this capability in the near future.

The technique has low sensitivity in the detection of prostate tumours and cannot replace the standard tumour detection method of multiple ultrasound guided systematic biopsies. It is possible, however, that adding targeted biopsies of areas of suspected tumour vascularity and possibly areas of under perfusion may significantly increase relative positivity.

The downside is that it adds 10–15 minutes to the standard technique, as well as the added cost of the contrast agent.

The technique is relatively new. It relies on a complex interaction of transducer, software, and the characteristics of the contrast agents used. Research and development is ongoing to further optimize these factors and future improvements may make the technique more sensitive.

Imaging of tumour vascularity is a potentially useful tool in the study and detection of tumours. In those patients who opt for active surveillance of their tumours, change in vascularity may give important information about progression of the tumour and when it is appropriate to intervene.

FIGURE 9 Hypervascular BPH nodules.



FIGURE 10

Hypovascular BPH nodules.



FIGURE 11

Prostate cancer.

- **A** A hypervascular cancer.
- **B** A slightly hypervascular cancer with altered vascular architecture.
- **C** A hypervascular cancer involving the inner gland.
- D A hypervascular cancer (arrowed). Compare the bilateral BPH nodules hypovascular on the right, hypervascular on the left.



Contrast ultrasound may have a place in mapping tumour for HIFU treatment and for monitoring the benefit of treatment.

FIGURE 12

A In the PZ.B In the TZ.

Hypovascular cancers.

New drugs are being developed to prevent or delay the progress of prostate cancer. Contrast ultrasound, with its ability to study the neovascularity of tumour will have a place in the monitoring of such treatment.

Finally, study of tumour neovascularity may have a place in assessing the aggressiveness of prostate cancer (120-124).

These are possible fields for further research, if contrast ultrasound proves to be sufficiently sensitive in mapping the tumour vessels.

6.3.4 Conclusion

Transrectal ultrasonography is a versatile tool that is frequently used in urologic practice. Its application covers many areas such as the assessment of prostatic size and volume, diagnosis of different prostatic diseases, detection and staging of prostate cancer, monitoring of the response to therapy, and guidance of prostate biopsy.

Concerning the detection of prostate cancer, however, targeted biopsies at lesions detected on ultrasound or DRE are becoming less common with the stage migration seen in the current PSA era. Based on the lack of satisfactory sensitivity and specificity for detecting malignancy by TRUS, systematic biopsies are indispensable, and it seems that the current concern is tending toward increasing the number of cores. However, when TRUS indicates the presence of a lesion, a targeted biopsy should be performed, as the specificity of an ultrasonographic abnormality is sufficiently high to justify the additional biopsy. Recent developments such as Doppler imaging, contrast-enhancement or 3-D imaging may provide higher specificity and positive predictive value for TRUS. Efforts need to be made to find any abnormalities in TRUS images in order to increase the sensitivity for cancer detection and decrease the number of unnecessary biopsies.

6.4 **Prostatic Sonoelastography**

Elastography is a technique of mapping tissues by their elastic properties (soft or hard). As most cancers are harder than the surrounding tissue, elastography is a potential method of detecting cancers. Prostatic elastographs has been shown to be technically effective in many phantom studies, *in vivo* studies on resected specimens and animal studies. It has also been shown to be technically possible in a small number of *in vivo* human studies. It has low sensitivity compared with cancer detection by multiple systematic biopsies and also a low specificity. The technique, in its present form at least, cannot replace multiple systematic biopsies. It may have a role in increasing relative positivity rates by detecting abnormal areas outside normally biopsied areas. It may have a similar role in patients who have had a negative set of biopsies but have a rising serum PSA level. Finally, it may have a role in staging prostate cancer by accurately mapping tumour size.

In its present form, however, prostatic elastographs have poor reproducibility principally due to the lack of an accurate way of compressing the tissue uniformly to the same degree every time. Better methods are needed before the technique can become a useful clinical tool.

6.4.1 Background

Elastography is a technique that measures the elasticity (stiffness hardness) of tissue by detecting the movement of individual elements in the tissue when it is vibrated by an external force, when it is compressed or, more usually, when it relaxes or vibrates following compression.

The physical principles of the technique have been known for many years and its potential application for medical use were first described in 1990 (125-127). Tissue elastography may be presented in a number of ways: numerically, as an x-y graph or as a 2-D image, the elastogram in which relative elasticity is represented by a grey-scale, or a colour image map.

Potential clinical applications are mostly directed toward cancer detection. This is based on the principle that most cancers are harder and less elastic than the surrounding normal tissue. It is this property that is the main reason that cancers are clinically palpable.

Early work in elastography was directed toward developing the technique. First experiments were done on gel phantoms, then on *in vitro* tissue, muscle, or liver, in which an area had been hardened by heat (cooked) (128). Early work on the prostate studied excised (radical prostatectomy) specimens (129). These early experiments produced elastography techniques that could clearly differentiate tissues of differing elasticity.

In vivo work has been undertaken in the breast, liver, and prostate. Much of the work in the prostate has been performed on dogs (130), but increasingly studies are being performed on humans.

6.4.2 **Technique**

The technique of elastography requires three steps:

- 1. The tissue studied must be stimulated vibrated or compressed, preferably in an even and reproducible way.
- 2. The movement of individual elements within the tissue during vibration compression or relaxation must be detected and quantified.
- **3.** The results must be displayed in a way that can be easily interpreted.

For the technique to be clinically useful, another step needs to be added:

4. An algorithm that decides how to use the information from the elastogram.

The four points will be discussed in turn.

6.4.2.1 **Excitation of the tissue**

There are a number of ways in which the tissue may be excited, not all applicable to the *in vivo* prostate:

- Internal excitation by utilizing the 'natural' movement from cardiac pulsation, pulsation of blood vessels, or muscle contraction. This method is not applicable to the prostate, as the pulsation of the intraprostatic vessels is too weak.
- 2. External excitation by mechanical compression.

This may be achieved in several ways. The easiest is simple mechanical compression. The probable better alternative is with alternate compressions and relaxation (vibration) by applying a modulated high-power pressure wave or sound wave.

The simple compression method, in the prostate, is achieved by compressing the prostate with the transrectal transducer with a flicking motion. It has the benefit of being simple, but lacks good reproducibility (69,131).

Compression via a water-filled balloon around the end of the transrectal transducer is another method that has been used (132).

External mechanical vibration has been used. The prostate lies deep within the pelvic cavity, which makes this form of stimulation difficult. Success has nevertheless been achieved by applying the vibrational source via the pubic bone (69), though in this case MR elastography is used as the method of detection.

Stimulation by a source from the ultrasound transducer itself would seem intuitively to be a good solution and this has also been utilized, termed acoustic radiation forse impulse (ARFI) (133).

These methods all rely on simple stimulation and resultant vibration of the tissue. More complex methods are also possible. One such method that causes vibration at a small circumscribed point within the tissue is described later in this article (134).

6.4.2.2 Measurement of tissue motion

Measurement of elasticity may be achieved by a number of different methods (135). These include the following:

- 1. Parametric measurement in which the change in position of elements within the ultrasound image is measured by a variety of methods. [69,136,137].
- **3.** Cross correlation and phase detection techniques that measure displacement of tissue [135].
- **4.** MRI techniques may also be used for elastograph measurements [133,136].
- **2.** Doppler tissue velocity measurements [131,138].

The best method of detecting and quantifying the resultant tissue movement during compression or relaxation is by a frame-by-frame analysis of the ultrasound image, with the transducer held still. Computer analysis of the movement of individual speckles within the image detects and quantifies tissue movement.

While this method produces the best results, it is, at present, not a real-time technique. While this does not discount its use, a real-time technique has distinct advantages for clinical use.

Doppler techniques may also be used to detect tissue motion. Such techniques are commonly used to measure cardiac wall motion. They produce real-time images of tissue movement, and are readily available. They do not, however, allow for any, other than very crude, quantifications of movement. They rely on setting the machine parameters so that normal tissues are displayed in colour, while less elastic tissues are displayed as a different colour or hue, or as areas of no colour.

Both techniques detect movement. This reflects elasticity, as less elastic tissues move more slowly than more elastic ones. There are more sophisticated, potentially more successful methods of achieving images based on the elastic properties of tissue. One such method is briefly described (134).

Tissues may be compressed by insonating it with high-power sound waves in the lower ultrasound frequency range. If the sound is made intermittent or the amplitude is modulated, then the tissue will be alternately compressed and allowed to relax. The resultant alternate compression and relaxation of the tissue cause it to emit sound waves that may be detected and quantified. Harder, less elastic tissue will produce higher energies of sound.

This technique, when applied to a point source in tissue will quantify the elasticity of that point.

The simplest method is to direct a narrow amplitude modulated beam across the tissue to be studied. If this is moved in a line across the tissue, then a 2D graph of the average elastograph across this line may be constructed. With this technique, however, each point along the graph represents an average of the elasticity of a number of points at every depth within the tissue. It would be advantageous to confine the measurement to a point, or small volume (voxule) within the tissue. This may be achieved by using two unmodulated continuous wave beams of slightly different frequencies at different angles such that they converge at the desired point within the tissues. This achieves tissue vibration at the point of intersection.

The vibrating tissue emits a sound wave, the amplitude of which is related to its stiffness. This sound may be detected by a microphone. By mapping the sound intensities from many points, a 2D elastograph image may be produced.

This technique has obvious advantages. However, it requires a totally different equipment from ultrasound images, and would therefore need to be performed as a separate imaging technique.

6.4.2.3 **Displaying the motion (elasticity)**

The tissue motion that reflects elasticity may be displayed as a numerical value for a particular volume of tissue or as a matrix of numerical values corresponding to voxules of tissue. Alternatively, an x-y graph can be displayed for a given line across the tissue. Or a two dimensional image may be produced of a slice of tissue, with a grey scale or colour map corresponding to different numerical values of elasticity.

The absolute valve of the numbers produced is hardly relevant, as it is the comparison of abnormal with normal tissue that is important.

It is the 2D image that is most appealing to most radiologists and clinicians, as it may be directly related to the fundamental grey-scale ultrasound image, as well as other cross sectional imaging techniques such as MRI. Numerical values are, however, valuable for scientific study of the technique.

6.4.2.4 **Tissue harmonic imaging**

While tissue harmonic imaging (THI) is a different technique to sonoelastography there are some similarities, so it is worth mentioning here.

Tissue harmonic imaging is a technique that utilizes the non-linear echoes returned from insonated tissues rather than the fundamental reflected frequency. It relies on the fact that the transmitted ultrasound beam causes vibration of the tissues. These are at far higher frequencies that those used for elastography imaging, and so rely on different tissue parameters. The technique, however, does reflect partly the elastic properties of the tissue. Tissue harmonic imaging in the prostate produces broadly similar images to fundamental ultrasound imaging. There are, however, differences in the images. Some prostatic nodules are more hypoechoic on THI than on fundamental imaging; others are the same. This may reflect their elastic properties. At present, work in progress shows little correlation with biopsy results, and current numbers are too small to be definite.

6.4.2.5 Algorithm for acting on results

The principal reason for initial imaging of the prostate is to detect abnormal as suspicious areas for biopsy. Biopsy is necessary for definitive diagnosis and also for histologic (Gleason) staging. Thus suspicious areas detected on elastography imaging are biopsied. With present results, biopsying only these areas lacks sensitivity. Some method of systematic biopsy therefore still needs to be performed. Most suspicious areas will be included in the systematic biopsies. Any that are not should be biopsied. The size of the tumour should be recorded. Size of the tumour is very important in deciding on treatment and for prognosis. At present, however, elastography estimation of tumour size has not been fully validated. It is important to compare results with radical prostatectomy specimens and also with MRI studies, the present pre-operative gold standard.

6.4.3 **Clinical results**

It has been clearly shown that elastography techniques can detect cancers in excised prostates (129).

Measurements have shown a large difference in elastic properties between normal prostate tissues and prostate cancer and importantly also between cancer and BPH. (A) (133,138) (**Table 5**).

Normal glandular prostate	64 ± 17	
BPH	36 ± 9	
Prostate cancer	100 ± 20	
Parinted with normination from Krowelson TA at al		

TABLE 5 Elasticity of Prostate Tissue in Kilopascals (kPa)

It has also been shown, using a variety of different methods of tissue excitation and detection of vibration, that some prostate cancers may be detected *in vivo* in humans. Cancers may be distinguished from normal prostate tissue and from BPH (129,131,136,139) (**Figures 13-16**).

It is difficult from most of the literature to find the sensitivity and specificity of prostate elastography. By inference, and from our personal experience, it would appear to be significantly lower than multiple (131-135) systematic biopsies.

Most papers state the possible benefits as adding extra positivity to systematic biopsies. Most, however, quote figures for sextant (130) biopsies, not 8 to 12, which is the current norm in most centres. Furthermore, most positivity figures for sextant plus elastography targeted biopsies are not significantly better than published figures for 8 to 12 systematic biopsies.

Another possible benefit of elastography imaging is in staging prostate cancers, by mapping the tumour more accurately than grey-scale ultrasound (136). This may be useful in local staging and in assessing the volume of the tumour. This aspect has not, however, been compared with MRI, which is the correct gold standard for staging.

6.4.4 **Discussion**

Elastography is an emerging technology. It has been developed to a level that makes it useable in clinical practice. In the case of the more prognostic, simpler methods, their main drawback is lack of reproducibility. Some of the more sophisticated methods produce more reproducible results. The relative complexity of some methods, however, makes them difficult to use in clinical practice. Future improvements in the technology may overcome its present limitations.

Using available technology, elastography has far too low a sensitivity to replace systematic ultrasound guided prostate biopsy. Given the heterogeneous growth pattern and histology of prostate cancer, this is likely to remain so. The possible place of elastography therefore seems to be as an adjunt to systematic biopsy, adding extra biopsies of abnormal areas, with the aim of increasing the relative positivity rates of the technique, or possibly reducing the number of biopsies necessary while maintaining adequate positivity (sensitivity).
Protons in a magnetic field spin (or "precess") at almost the exact same frequency of 42.6 MHz per Tesla. Slight differences in precessional frequency are the basis of MR spectroscopy, as shown in this spectrum (map of signal intensity versus frequency) showing the separate peaks of fat and water protons.



FIGURE 14

Normal prostate elastogram. The fibromuscular stroma (green arrows) is stiff and so is shown as a void.



FIGURE 15

Prostate cancer.

- A The grey-scale image shows some nonhomogeneity of the outer gland but no definite tumour nodules.
- **B** The elastogram shows a large irregular void corresponding to the tumour confirmed by biopsy and prostatectomy.





Another prostate cancer. In this case, a small nodule was seen on the grey-scale image but the elastogram more accurately mapped the extent of the tumour.



Both have been shown to be effective, but increased positivity in published series has been low, typically about 2%. Whether this figure justifies the use of the technique is debatable, but for most people, the figure needs to be substantially higher to justify introducing elastography into routine TRUS and prostate biopsy lists. Improvements in technology may well achieve this in time.

Mapping of tumour size and local staging are also possibilities, but elastography must be shown to have significant benefits over MRI for it to find a place in the detection of prostate cancer.

6.5 Ultrasound Radiofrequency Tissue Characterization with Histoscanning

6.5.1 Background

Prostate HistoScanning (PHS) is an imaging technique that uses radiofrequency (RF) signals from backscattered ultrasound waves to detect abnormal, so-called differentiated tissue. The RF signals, or the raw data, are analyzed with mathematical algorithms to determine whether they were reflected by normal (benign) or abnormal (cancerous) tissue. This technique was first applied to ovarian tumours and further developed in the prostate (2,3). The goal of PHS is to indicate suspicious areas in the prostate by a red colour code (see **Figure 17**) on a background of a grey-scale reproduction 3D model of the prostate.

Axial plane of HistoScanning™ with suspicious tissue in red.



6.5.2 **Technique**

The patients are best examined after a small enema and with an empty bladder. A computer (the PHS unit) is connected to the ultrasound machine (B&K Pro Focus). After a conventional examination of the prostate by TRUS, a handhold rotating motor is magnetically attached to the 8818 B&K ultrasound probe to obtain a 180° 3D reconstruction of the sagittal projections of the prostate at continuous speed (see **Figure 18**). Tissue-specific data are thus acquired by the PHS unit (the acquisition phase). Depending upon the size of the prostate and the visual quality of the reconstructed images, up to four acquisitions, each taking approximately 1 minute, are collected during the same session. The probe is then removed and the patient is allowed to redress. The next step is data analysis: after drawing the outlines of the prostate, or part of the prostate to be examined, the computer starts the tissue analysis. After 5 to 10 minutes, the examinator is able to scrutinize the prostate in search of suspicious areas in the axial, sagittal, coronal plane, or directly in the 3D reconstructed model. The volumes of suspicious lesions, marked with a red colour code, can be measured very rapidly with the connection tool. A graphical reconstruction of the prostate divided in six to nine parts can also be saved for further use (biopsy or follow-up).

FIGURE 18

Setup for HistoScanning™



6.5.3 Diagnostic accuracy

In a study setting, where optimally collected data are compared to whole mount pathology after radical prostatectomy in patients with known prostate cancer, the diagnostic accuracy was excellent and comparable to MRI (2). In a clinical setting, ongoing since 2008, the positive prediction rate for biopsy-proven prostate cancer is actually >75 % and the negative prediction rate is >95 %. With further technical improvements, such as replacement of the external rotating motor by a transrectal probe with an internally rotating crystal, the precision should even increase. That is because this more easily avoids excessive compression of the PZ of the prostate, which leads to reduced tissue elasticity and potential for false positive signals.

6.5.4 **Prostate biopsy**

Although it is common in our practice to biopsy solely suspicious lesions of ≥ 0.5 cc, we cannot always be sure that the biopsy is representative of the suspicious tissue. That is because it is not yet possible to guide the biopsy in a real-time PHS image. The biopsy, if deemed useful, is performed immediately after the PHS session or at a later date if the patient needed to be more informed and/ or prepared (antibiotics, interrupt medication for anticoagulation). With the PHS images, especially the sagittal projections, on one screen the biopsy is guided on the maximally corresponding sagittal scan on the conventional ultrasound monitor. These so-called geographical biopsies (see **Figure 19**) are usually pretty accurate for bigger lesions (>1 cc) but may miss the target for smaller lesions.

PHS image and graphical reproduction of the gland

- A Suspicious lesion 0.38 cc in the left PZ of the prostate in a patient with elevated PSA level (22 ng/ml) and two previous negative conventional biopsy sessions (8–10). Geographical biopsy of the lesion revealed Gleason 6 prostate cancer in 2 of 3 cores.
- **B** Graphical reproduction in sextant prostate model of the abovedescribed lesion.



There are three possibilities for overcoming this drawback:

- 1. Collecting more biopsies, which is basically not the purpose of PHS biopsies.
- **2.** Following up of small lesions with negative biopsies and considering re-biopsy when the volume is increased.
- **3.** Performing real-time biopsies in the PHS mode, which will probably be available in the future.

6.5.5 **Conclusion and possible future applications of prostate histoscanning**

If actual promising results can be reproduced by other examinators and major technical improvements can be achieved, PHS might become the number one imaging modality for detection of early prostate cancer, with certain advantages (140,141):

- Early diagnosis of clinically significant prostate cancer (≥ 0.5 cc)
- 2. Fewer or no more biopsies for clinically insignificant prostate cancer
- **3.** Fewer and more representative prostate biopsy procedures with a smaller number of biopsies per session
- 4. Easy follow-up in the active surveillance setting
- 5. Guidance of focal therapy?

6.6 Computerized Tomography

Computerized tomography is based on the X-ray principle with the computer displaying cross sectional images of the body. Since the 1980s, the upgrade to helical or spiral CT allows for fast and detailed image acquisition with minimal movement artifacts and high-quality 3D image reconstruction of virtually any organ in the body.

6.6.1 Benign prostatic hyperplasia

The diagnosis of symptomatic BPH is based upon symptom analysis (lower urinary tract symptoms [LUTS], International Prostate Symptom Score [IPSS]) and urodynamic findings such as uroflow, residual urine, and urethral pressure profile. Imaging is not part of the routine workup for BPH.

To rule out possible coexistent prostate cancer, PSA testing, DRE, TRUS, and ultrasonically guided biopsies are usually sufficient.

Patients with LUTS may have complicated BPH or suffer from another pathologic condition in the urinary tract. Imaging of the urinary tract is usually mandatory in such patients. Intravenous urography has long been the gold standard, but today it seems that a CT urography adds more information with just an acceptable elevation of the radiation dose plus the advantage of no need for contrast injection (139). Measurement of the volume of the prostate or of its ftransition zone is sometimes helpful for optimizing the choice of a surgical or non invasive treatment. Routine CT scan is hardly able to differentiate between the transition zone and the other anatomical zones and overestimates the prostate volume with approximately 50 % compared to transrectal ultrasound (142).

6.6.2 **Prostatitis**

The suspected diagnosis of acute or chronic bacterial prostatitis is confirmed by cytobacteriological tests. Computierzied tomography scan may be useful to rule out underlying pathology both inside or outside the urinary tract. It is also indicated when prostatic abscesses are suspected (143).

Although TRUS is at least as good to demonstrate the abscess, CT also permits to see the entire urinary tract and the adjacent structures.

In the chronic pelvic pain syndrome, historically related to prostatitis, CT scan can also be helpful to find related or other diseases.

6.6.3 **Prostate cancer**

6.6.3.1 **Primary diagnosis**

For years, CT scan did not appear to be of any use for early diagnosis of prostate cancer, as it could not show a different X-ray absorption coefficient between benign and malignant prostatic tissue (144).

Besides this lack of soft tissue contrast resolution, it also has a low accuracy in the prediction of extracapsular extension (ECE; 29%) and seminal vesicle invasion (SVI; 69%), according to Hricak *et al.* (145).

It was recently demonstrated that contrast-enhanced helical CT is able to distinguish prostate cancer from benign tissue in some instances (80). This might be useful in patients with elevated PSA levels who have undergone abdominoperineal resection.

In normal circumstances, however, TRUS remains the gold standard for initial imaging and guidance of biopsies.

6.6.3.2 **Biopsy**

Over the 1980s and 90s, the blind finger guided biopsies of the prostate were replaced almost entirely by the technique of TRUS guided punctures. The use of CT for guidance of prostate biopsy is limited to patients after proctectomy (146).

6.6.3.3 Staging

For primary tumour staging purposes, provided DRE and TRUS are inconclusive, MRI using an endorectal coil (ERC) in conjunction with a pelvic phased array is the best available technique today. Yu and Hricak report a 50% sensitivity and 95% specificity for the detection of ECE of prostate cancer (80). This is consistent with other studies showing sensitivity of between 51 and 89%, specificity of between 67 and 87%, and overall accuracy of between 54 and 88% (147,148) (**Figures 20** and **21**).

Although it is still overused in clinical practice (149), the role of CT scan for locoregional staging of prostate cancer is actually limited to patients who would be candidates for pelvic lymphadenectomy (150). Functional CT imaging, an established tool for measuring the microvasculature of prostate cancer (151), could assist in optimal treatment selection. The tumor microvasculature is a key element that influences the tumour's aggressiveness and response to therapy. In their investigation, Henderson *et al.* (152) showed that measurement of the blood flow in the prostate by functional CT was reliable, but that other parameters of microvasculature such as capillary permeability and blood volume could only be precisely measured in regions of elevated blood flow. Dynamic contrast-enhanced magnetic resonance imaging has proven to be a better technique for measurement of the microvessel density (153).

6.6.3.4 External radiation therapy planning

Computerized tomography has long been, and in many centres, still is the primary imaging modality for external radiotherapy (RT) planning (154).

Today it is challenged by MRI, said to be associated with less inter-observer variation in marking the contour of the prostate (155) and in defining its apex to accomplish potency-sparing RT (156).

On the other hand, with new techniques, developed to reduce movement artifacts, CT pre-planned external RT can be performed with markedly less local toxicity (155,157,158).

6.6.3.5 Brachytherapy

Transrectal ultrasound is the state-of-the-art imaging tool for planning and guiding of brachytherapy in prostate cancer (159). A large prostate size, interference of the pubic arch, urinary obstruction, or defects from transurethral resection of the prostate may preclude its use. In these instances, 3D stereotactic posterior ischiorectal space CT offers an alternative for brachytherapy guidance (160). In patients with possible or known invasion of the seminal vesicles, 3D CT scan might also be superior for direction of radioactive implants into these structures (161).

FIGURE 20

CT scan of prostate cancer demonstrating local invasion of right seminal vesicle.



FIGURE 21

CT scan of prostate cancer demonstrating local invasion of bladder.



6.6.3.6 Local recurrence

Computerized tomography does not seem to be a suitable method for diagnosis of locally recurrent prostate cancer after radical prostatectomy. Only 2 of 18 patients with biochemical relapse and local recurrence were correctly identified by CT in a study by Johnstone *et al.* (162). Kramer *et al.* reported only a 36% detection rate of residual cancer by CT in patients who all had recurrences larger than 2 cm (163).

Provided DRE and TRUS are negative, MRI is the best performing technique to demonstrate early local recurrence of prostate cancer after treatment with curative intent, especially after radical prostatectomy (164).

6.6.4 **Conclusion**

Since its introduction in the radiologic clinics in 1974, CT quickly became and still is the state-ofthe-art technique for the evaluation of the chest, abdomen, and pelvis. In prostatic disease, however, its usefulness is limited to prostate cancer in specific conditions.

Computerized tomography can replace TRUS in proctectomized patients and it is especially appreciated for preoperative planning of external RT. In the future, much is expected from techniques of imaging fusion with either ProstaScint® or positron emission tomography (PET) with CT scanning.

6.7 Magnetic Resonance Imaging

6.7.1 Introduction

The role of MRI in the management of prostate cancer has grown considerably in recent years. Initially, MRI was used predominantly for radiographic staging but proved insufficiently accurate. Over time and with increasing experience and technological advances, its role has evolved toward more broad applications in diagnosing and identifying the main foci of cancer and as an aid in the clinical management of prostate cancer through characterizing aggressive tumour features, the detection of recurrences, and response to therapy.

Accurate staging remains an essential component of successful management of prostate cancer. Magnetic resonance imaging has improved in determining whether a tumour has extended beyond the prostatic capsule, which may profoundly influence decisions regarding management options and prognosis.

Traditionally, parameters analyzed by nomograms for assessing the probability of organ-confined disease have included rectal examination, PSA level, Gleason score, and the percentage of positive biopsies. However, the continuing development of MRI in prostate cancer has led to the inclusion of this method in newer predictive nomograms, used for deciding on appropriate, patient-specific treat-

ment options. For example, authors from Memorial Sloan-Kettering Cancer Center have demonstrated an incremental value in adding endorectal MRI to the Kattan nomogram in the prediction of SVI (165,166).

Convincing evidence has emerged showing that dedicated training in prostate MR interpretation improves diagnostic accuracy. Akin *et al.* showed the benefit of an interactive dedicated training curriculum in MR of the prostate for body imaging fellows. This study revealed a significant improvement in localizing and staging tumours following a standardized training program (167).

These findings support earlier work suggesting dedicated gastrourinary (GU) radiologists perform better in reporting prostate MRI when compared with general body imaging radiologists. Further studies indicate experienced readers have a greater accuracy than non-experienced readers in staging (168).

Twenty-seven patients undergoing radical prostatectomy were evaluated by Futterer *et al.* with highresolution endorectal T2-weighted fast spin-echo images (169). Minimal capsular penetration was detectable by some readers, though more striking was the data regarding tumour localization, with an established accuracy of 79% for the experienced reader and 64% for inexperienced radiologists. Thus, experience indeed plays a role in the evaluation, interpretation, and utility of MRI for prostate cancer and in the management of the disease. Important elements that facilitate this process appear to include standardization of imaging parameters, criteria for image evaluation, and reporting standards that utilize defined nomenclature.

6.7.2 Image acquisition in MRI of prostate cancer

A typical MRI prostate protocol at a tertiary centre would include the following sequences:

T1 axial: to evaluate anatomic detail, hemorrhage, and lymphadenopathy

T2 axial, coronal, sagittal: to allow volume calculation, tumour localization, and staging with respect to the prostatic capsule

To further improve tumour margin definition, tumour volume, and tumour aggressiveness, a number of other techniques can be considered as part of a validated multiparametric approach. These include diffusion-weighted imaging (DWI), dynamic contrast-enhanced magnetic resonance imaging (DCE MRI), and magnetic resonance spectroscopy (MRS) (see following sections).

Procedures performed on the prostate gland may lead to imaging abnormalities that can interfere with accuracy. It is recommended that MRI be performed at least 4–6 weeks after prostate biopsy to avoid artifacts from post-biopsy hemorrhage. During prostate imaging, a preliminary MRI should be done to determine whether hemorrhage is present and to what degree. Serious consideration should be paid to deferring the exam for several weeks if severe hemorrhage is present, as this will interfere notably with all of the imaging parameters and interpretation.

6.7.3 Endorectal coil imaging

As MRI is used in the assessment of prostate cancer, ERCs have demonstrated their superiority to body coils for evaluation of the tumour. This is because ERCs produce a higher signal-to-noise ratio (SNR) than body coils, thus allowing for better spatial, spectroscopic, and temporal resolution. In order, these benefit the T2-weighted image, the MRI spectroscopic images, and the DCE MRI images. Endorectal coils not only produce more signal to noise, but also displace air from the rectum that can otherwise lead to susceptibility artifacts.

Several authors have hypothesized that the signal is sufficient from external-phased array coils at 3T to obtain comparable signal to noise with ERC MRI at 1.5T (170). The SNR of 3T should be 2 times better than a comparable 1.5T system. Subsequently, endorectal 3T coils demonstrate excellent spatial resolution and could reveal pathologic details not seen on endorectal 1.5T or 3T external phased array coil. Thus, controversy surrounds whether it is better to use an ERC at 3T to exploit any potential gain in resolution or dispense with it and therefore obtain images comparable in quality to 1.5T ERC images but with less invasiveness.

Limitations exist in using ERCs, the most significant of which appears to be patient discomfort and concern or reluctance to undergo the investigation. Many centres in Europe forego the use of ERCs. Although ERC use is considered mandatory for adequate imaging at magnet strengths of 1.5T, the increasing use of 3T MRI has enabled obtaining non-ERC images of acceptable quality. At highly experienced centres; however, routine use of ERCs has not proven to pose a concern and is well tolerated by patients, including those in active surveillance programs who are willing to undergo repeat testing with ERCs (171).

One drawback is the susceptibility to artifacts from ERCs, particularly when air may be introduced or trapped by the balloon, or when air is used to inflate the balloon. Thus, other compounds such as barium and perflubron have been advocated to fill the balloon, although these agents may increase the cost and complexity of the procedure (172).

Other limitations of ERC use include the time and training needed for accurate placement of the coil, and the expense associated with disposable versions of ERCs. Finally, the shape and volume of the prostate may also be altered with ERC use, which may have an impact on treatment planning (173).

6.7.4 MRI appearance of prostate cancer

T2-weighted MR images are essential in the evaluation of prostate cancer. On these images, prostate cancer is seen most commonly as a low-signal intensity area within the high-signal intensity normal PZ. Benign prostatic hyperplasia nodules may obscure cancer in the TZ. However, features such as homogeneously low-signal intensity, ill-defined margins, and lack of a capsule help identify cancers in the TZ. Careful attention to these features is essential for lesion localization in the TZ and will improve diagnostic accuracy significantly, particularly when tumour volumes are taken into consideration (174).

Post-biopsy inflammation, prostatitis, infarct, atrophy, and post-treatment changes secondary to radiation or hormonal ablation therapy can be seen as low-signal intensity areas on T2WIs and may mimic cancer (175).

In addition to T2-weighted images, DCE T1-weighted imaging is sometimes used in prostate cancer localization and staging. Dynamic enhancement in prostate carcinoma differs from that in normal prostate tissue. These differences can be quantified and used to discriminate prostate carcinoma from normal tissue in both the PZ and the TZ and provide improvement of cancer detection and staging performance in comparison with imaging protocols that rely on T2-weighted MR imaging alone (176). However, further studies are necessary to improve the temporal and spatial resolution of the DCE-MR sequences and to standardize the analysis of the signal-intensity-time curves.

6.7.5 Diffusion-weighted MRI of the prostate (DW MRI)

Diffusion-weight MRI (DW MRI) provides information on the diffusion of water in tissue and thus, indirectly, provides information on the cellularity of a given tissue. As the cellular density increases, the mean water molecule movement becomes "restricted" and this is reflected on DW images as increased signal relative to background.

Diffusion-sensitizing gradients are used to create DW-MRI images and the strength of these gradients can be manipulated by varying 'b-values' on MRI scanners. Although no international recommendations exist on the optimal b values for prostate imaging, most institutions range from 0 to 1500. To avoid contributions related to tissue perfusion, b values greater than 100 are recommended for the lower value, and to retain adequate SNRs, the upper b value should be less than 800. On higher b value images, the tumour appears to be higher in signal intensity than the surrounding normal tissue, reflecting restricted diffusion. This signal intensity progressively increases when reviewing sequential images from low to high b values.

The Apparent Diffusion Coefficient (ADC) map is generated from fitting the line generated by the two images obtained at low and high b value. It is imperative to review the ADC maps alongside the b value images. This is because restricted diffusion appears low on ADC maps, allowing a confirmatory qualitative parameter. In addition, the ADC value is not only a quantitative parameter, but also correlates with tumour aggressiveness (lower ADC, more aggressive tumour) (177).

Unfortunately, the ADC value is dependent upon the method of image acquisition and therefore can be difficult to compare when images have been acquired on different protocols. Although no absolute value of ADC indicates cancer, low values have consistently been shown to correlate with the presence of tumour, and the quantitative values also serve as an excellent tool for follow-up of tumours.

In addition to diagnosis, localization, and follow-up, DW MRI has also been shown to have a potential prognostic role in prostate cancer. Several studies have shown a correlation with ADC values and Gleason score, with higher-grade tumours exhibiting lower ADC values. In addition, baseline ADC values have been shown to be the only independently predictive factor for biochemical relapse in one study (178). A recent study involving 51 patients with prostate cancer who had DWI on 3T MRI found that lower mean ADC values were significantly associated with a higher tumour Gleason score (179).

Several limitations and pitfalls exist with DW-MRI interpretation. As the technique is an indicator for restriction of water diffusion, other causes of water restriction cannot be easily distinguished from a tumour. For example, a highly cellular nodule of BPH in the central gland can be very difficult to distinguish from tumour foci in the central gland.

Post-biopsy change and hemorrhage may also reduce ADC values and decrease diagnostic accuracy. Depite this, in areas of hemorrhage, DW MRI has a slightly greater sensitivity for tumour detection than T2-weighted image (180).

DWI at 3T benefits from higher-quality imaging and higher spatial resolution. Unfortunately, greater susceptibility artifacts, chemical shift, and distortion occur at 3T. Important steps to maintain a high-quality image acquisition include limiting rectal peristalsis (for example with glucagon use) and the use of parallel imaging to reduce the number of phase-encoding steps (181,182).

6.7.6 **Dynamic contrast-enhanced MRI of the prostate (DCE MRI)**

The principle of dynamic DCE is to act as an imaging biomarker for neoangiogenesis—a key component of active tumour formation.

FIGURE 22

Time-intensity curves of malignant (left) and benign (right) prostatic tissue.

A A tumour focus generates a 'malignant'-looking curve, with rapid early enhancement (steep upstroke) and relatively rapid washout (absence of plateau).



FIGURE 22, CONT'D

B Normal prostatic tissue shows a more gradual uptake to the plateau phase, distinct from the malignant graph.



Recent developments allow fast multi-slice contrast-enhanced MR at an acceptable spatial resolution, and these modifications of the technique provide a significant advantage for tissue evaluation, allowing for analysis of the entire prostate gland.

Gadolinium is currently used for DCE-MRI prostate cancer evaluation. After peripheral intravenous bolus injection with an injector, typically at 2–4 cc/sec, the contrast agent reaches the arterial system as a bolus. During the first pass, the difference in concentration between the intravascular and extravascular compartment is maximal, and leakage into the extravascular compartment occurs rapidly and contributes to the increase in signal intensity on T1-weighted images. Thereafter, the enhancement gradually decreases (183). This process of enhancement and de-enhancement/washout can be graphically displayed by a time-signal intensity curve, (184) with several distinct features: the start of enhancement, time to peak, slope, plateau, and washout. (see Figure 22).

Tissue enhancement following contrast media administration is multifactorial and dependent upon physical factors: sequence, parameter contrast medium dose, machine gain setting, and scaling factors; and physiological factors: tissue microvessels density, capillary permeability, and interstitial leakage space.

Several studies have shown that tumour neovascularity correlates with an increased risk for distant metastasis, tumour recurrence after surgery, and poorer overall survival (185-188). Several studies have found DCE to improve tumour localization, although the techniques of image acquisition have varied. When correlating preoperatively acquired images with prostatectomy specimen, Kim *et al.* showed an improvement in sensitivity in localization of 96% with DCE compared with 65% using T2-weighted MRI alone (189). Other authors have shown smaller increases (190). However, the impact on staging is debated. Compared with more experienced readers, those with less experience demonstrated a significant improvement in staging performance using DCE in addition to T2 (191).

DCE-MRI studies have three main goals: (192,193)

- Confirm the suspicion of a malignancy based on T2 and DW MRI.
- Identify lesions not perceived on the T2 weighted and DW MRI.
- Assess lesion "risk." The presence of active enhancement within the lesion elevates the risk that the lesion contains cancer to at least "moderate."

To achieve DCE-MRI images of diagnostic value, high temporal resolution is needed to assess kinetic parameters relating to microvascular characteristics of the tissue. Therefore, compromises must be made between spatial and temporal resolution (194). A typical "malignant" time intensity curve after bolus injection of a gadolinium chelate is described by Padhani *et al.* (184). Despite clear advantages for identifying the tumour, the improvement in staging accuracy, particularly in defining extracap-sular extension, using contrast-enhanced T1-weighted MRI compared with T2 MRI sequences alone is still under debate (80).

6.7.7 MRI studies using a multiparametric approach

The multiparametric approach to prostate MRI has been proven to improve accuracy in multiple studies using both 1.5T and 3.0T MRI units. While the individual sensitivity and specificity of each pulse sequence on MRI are typically low, when combined, both the sensitivity and the specificity often improve (see **Figure 23**).

FIGURE 23

Multiparametric MRI with T2, DCE, and DWI.



MRI of the prostate of a 52-year-old man with Gleason 3+4 prostate cancer. The arrows indicate the site of tumour at the right postero-lateral mid-gland. This is seen on the T2-weighted image (left) as an area of low signal, as an area of hyperenhancement on the DCE image (center), and as an area of restricted diffusion on the ADC map (right).

In a study of 57 patients with intermediately elevated PSA levels (range, 4–11 ng/ml), an improved per-region lesion detection was seen using DCE combined with DWI (53%), compared with 36% for T2 alone, 43% for DCE alone, and 38% for DWI alone. Specificity was comparable in all three groups (95–97%) (195).

In a study of 16 men with biochemical recurrence following high-dose brachytherapy, multiparametric imaging similarly proved to be the most sensitive method for detecting recurrent tumour (77%), compared with T2 alone, DCE alone, and DWI alone (27%, 50%, and 68%, respectively).

Delongchamps also studied multiparametric MRI in 58 patients and found that T2 combined with DWI and DCE performed significantly better than T2 combined with DWI, or T2 alone in the detection of PZ tumours (P<0.001) (196).

In a separate study, Delongchamps showed the benefit to diagnostic performance of adding DWI and DCE to T2 in PZ tumours, but this study failed to show an improved performance in TZ tumours (197).

Although a multiparametric approach consistently improves lesion detection, DWI and DCE do not necessarily identify the same voxels as being suspicious for tumour. This, in turn, has significant implications for treatment planning/dose painting and was highlighted in a study by Groenendaal *et al.* where consistency between parametric maps of DWI and DCE in 21 patients with proven prostate cancer varied greatly and average area under the curve (AUC) values were 0.60 (198).

The relative value of each of the parametric components was also studied by Langer *et al.* Using logistic regression analysis in 25 patients, ADC was shown to be the single best performing parameter and that combining ADC with T2 and Ktrans (derived from DCE-MRI) was the optimal multiparametric model (199).

6.7.8 Role of MRI in prostate cancer diagnosis and staging

Increasing evidence indicates that MRI guided biopsies may improve cancer detection compared with systematic TRUS guided biopsies. Anterior tumours have a lower detection rate on conventional biopsy, and MRI is particularly useful in indicating high-risk areas outside the posterior PZ, typically sampled in conventional TRUS guided biopsies.

In addition, real-time MRI-ultrasound fusion biopsy is gaining popularity. This involves co-registration of the MR data set with landmarks identified on ultrasound examination. Once the images are co-registered, MRI-positive lesions can then be sampled under real-time ultrasound. A major advantage of MRI-ultrasound fusion over MRI guided biopsy is the speed and number of biopsies that can be performed.

In a recent study of 101 men, Pinto *et al.* demonstrated that MR-ultrasound fusion biopsies were able to detect more cancers per core than standard 12-core TRUS biopsy for all levels of suspicion on MRI, but particularly for the moderate and high-likelihood regions (33).

Magnetic resonance imaging is considered to be very useful in prostate cancer detection, particularly in the PZ. Compared with DRE and other imaging methods, MRI has a higher accuracy in the assessment of local disease stage. However, the staging accuracy of MRI varies widely (range, 50–92%) (194). Magnetic resonance imaging also plays an important role in the evaluation of prostate cancer to demonstrate extracapsular extension and SVI. Magnetic resonance imaging findings of ECE include irregular bulging of the prostatic capsule; contour deformity with step-off or angulated margin; overt disruption of the capsule with direct tumour extension; obliteration of recto-prostatic angle; and asymmetry of neurovascular bundles. When these findings are present, the surgeon may elect to obtain wider margins from that area, sparing areas that the MRI indicates are not involved. This can lead to improved quality of life.

Seminal vesicle invasion is diagnosed when low-signal intensity is seen within and around the seminal vesicles. Seminal vesicle invasion can also be identified on DCE MRI, as it is typically enhanced. The normal high signal within the fluid-filled seminal vesicles makes identification of the SVI easier; however, many older patients have atrophic seminal vesicles and thus identification of SVI in those patients is difficult (200,201).

There is also potential clinical utility in staging outside of the prostate. Extracapsular extension should alert for the risk of disease within the pelvis, including lymph node and bone marrow metastases. Magnetic resonance imaging is helpful for diagnosing the invasion of cancer into adjacent organs, such as the pelvic wall, urinary bladder, and rectum.

It is now well known that size alone is not always reliable in assessing malignancy in pelvic lymph nodes. Malignant nodes with normal short axis diametres can be seen on MRI due to the presence of micrometastases. Therefore, other imaging features should be searched for, including the loss of a fatty hilum, irregular contour, and increased signal heterogeneity, indicating replacement of normal nodal architecture with tumour. However, MRI continues to be limited in the prediction of lymph node metastases and systematic lymph node sampling at surgery continues to be necessary in patients with higher risk for cancer based on nomograms.

Ultrasmall superparamagnetic iron oxide (USPIO) particles (ferumoxtran-10) have demonstrated improved sensitivity and specificity in the detection of lymph node metastases from prostate cancer including those nodes <5 mm in size. Unfortunately, despite promising results, the agent is not commercially available. A new USPIO, ferumoxytol, has been approved for human use as an iron replacement therapy and may be useful in this setting, but recommendations supporting ferumoxytol use await the results of definitive trials (202,203).

Bone metastases should be searched for within the pelvic bones. Low-signal foci on T1 on T2 should raise suspicion, but it can be difficult to distinguish small metastases from benign bone lesions. Growing evidence suggests that DW MRI may also be of use in identifying metastases from prostate cancer, as demonstrated in several studies. Some centres now routinely adopt a large field-of-view DWI sequence to look for occult metastases in the pelvis.

Delayed imaging after DCE MRI commonly demonstrates enhanced metastases in high-risk patients and is performed quickly through the axial skeleton. However, benign and degenerative bone lesions may also be enhances, and correlation with bone scan and/or CT may be necessary (204,205).

6.7.9 Role of MRI in the treatment planning

Magnetic resonance imaging can provide important information about the size, location, and extent of the prostate cancer. This information may be useful for the surgeon to perform optimal resection, minimizing the risks of urinary and erectile dysfunction (ED) and positive surgical margins. Magnetic resonance imaging can also be useful for predicting intra-operative blood loss during radical retropubic prostatectomy (RRP) by showing the extent of periprostatic veins (206). In addition, MRI can help predict urinary incontinence after RRP by allowing assessment of the membranous urethral length (207).

Because MRI provides excellent anatomic images of the prostate, periprostatic tissues, and adjacent organs, it is a very useful tool in radiation treatment planning. Tumour mapping with MRI optimizes dose delivery to the cancer foci and reduces the risk for normal tissue damage.

In recent years, an increase in the prevalence and incidence of prostate cancer has been seen, but with a lower disease-specific mortality. This is most likely explained by an aging population and wide-spread use of PSA testing. The latter has led to the detection of more patients with a 'favourable' risk profile. That is, a disease that is of low volume and low grade, and unlikely to be a cause of mortality. Such patients are now offered active surveillance, whereby they are monitored with clinical assessment, repeat biopsy, and PSA testing, and administred 'active treatment' such as hormonal therapy or RT is only offered when a change is noted on follow-up. Patients eligible for active surveillance may benefit from MRI. Magnetic resonance imaging may show that the lesion is larger than predicted based on the conventional biopsy or that it has features suggesting increased aggressiveness. This can prompt re-biopsy, leading to more tumour upgrading and reconsideration of active surveillance as a treatment option. For those patients whose MRI confirms minimal disease, MRI can be used in place of repeated biopsy to ensure lack of change. However, the ideal protocol for incorporating MRI into active surveillance management regimens remains to be determined. Prospective multicentre trials are investigating the potential of multiparamentric MRI to improve outcomes in active surveillance.

As focal therapy matures as a treatment option, the role of MRI in this setting is also expanding. First, those patients suitable for focal treatment (small lesion, away from critical structures, low grade) can be identified on MRI, together with targeted biopsy. Second, the actual ablative process may be guided with MRI. Although most current ablation procedures are performed in the operating room, success of MRI placement of brachytherapy seeds and focal laser ablation, as well as recent work on MRI guided biopsy suggest this technique is likely to develop in the near future. Although preliminary work is being done on laser ablation and high-intensity focused ultrasound with real-time MR guidance, the technique remains at a very early stage, and outcome data is necessary to evaluate further.

6.7.10 Role of MRI in detection of tumour recurrence

There is no consensus about the use of MRI in the evaluation of recurrent prostate cancer. Magnetic resonance imaging can provide valuable information in the evaluation of the extent of local tumour recurrence and lymph node status after radical prostatectomy.

Any retained seminal vesicles should be identified on T2 sequences by the characteristic high signal and tubular structure. Recurrent tumour may appear as lobular masses, with intermediate signal on T2. Dynamic contrast-enhanced magnetic resonance imaging demonstrates enhancement of the recurrent tissue, and sensitivity and specificity of detection has been shown to be superior with DCE either alone or with T2 imaging (208).

Magnetic resonance imaging can also provide useful information after RT. However, the prostate demonstrates diffusely low T2 signal intensity and indistinct zonal anatomy due to radiation changes, which may limit evaluation for recurrent tumour (209). It is helpful if the patient had a pre-radiation MRI, as the location of the original tumour is highly predictive for the site of recurrence.

Westphalen *et al.* studied the influence of adding MRI features to the Kattan nomogram in the prediction of biochemical relapse following external beam radiotherapy (EBRT) in 99 men. This study showed an improvement in risk classification of approximately 28% with inclusion of imaging findings (210).

The incremental value of multiparametric MRI (T2, DWI, and DCE) has been recently demonstrated over T2 alone in a cohort of patients who had biochemical recurrence following EBRT (211).

This expanded on earlier work that had shown the value of DCE MRI in detecting tumour recurrence following EBRT (212).

Magnetic resonance imaging has an important role post-ablation therapy in assessing the degree of tissue necrosis as an indicator for success of treatment. Considerable reduction in necrotic tissue volume has been demonstrated at 1 month following treatment compared with 1 week post-treatment, indicating the earlier study is more useful in assessing treatment (212,213).

Diffuse or multifocal low-signal intensity changes occur in the post-ablated prostate within months of the treatment. This limits the usefulness of T2 imaging in detecting tumour recurrence. Fortunately, dynamic contrast-enhanced imaging has demonstrated some success in the detection of tumour recurrence in the ablated prostate, with high sensitivity for lesion detection (214-216). However, care must be taken to avoid false positive findings in areas of hypervascularity due to benign prostatic tissue.

6.8 Magnetic Resonance Spectroscopy

6.8.1 Introduction: MR spectroscopy and MR spectroscopic imaging

Magnetic resonance imaging uses strong magnetic fields to induce coherent spinning of hydrogen protons, and then applies radiofrequency pulses (radiowaves) to generate an anatomic image showing proton signal intensity by location. Each picture element (pixel) contains data from a corresponding small volume of tissue (voxel). In routine MRI, the signal intensity of all hydrogen protons in each voxel is combined, although the signals from hydrogen protons in different molecules have slightly different resonance frequencies (a property known as chemical shift). Magnetic resonance

spectroscopy exploits this chemical shift property to produce a map of signal intensity versus frequency (i.e., a spectrum). At its simplest, MRS can be used to compare the relative concentration of fat and water in the volume of tissue being interrogated, as fat protons precess at a slightly slower frequency than water protons (see **Figure 24**).

This technology can be used to generate useful biomedical information. For example, protons in molecules other than fat and water also have distinct spectral peaks (albeit at much smaller levels, that can only be detected when the signal from protons in fat and water are entirely or largely suppressed). In addition, the information can be spatially encoded so that spectra from individual voxels are obtained, rather than from one large volume of tissue, and such anatomic localization of MR spectra is known as magnetic resonance spectroscopic imaging (MRSI). Magnetic resonance spectroscopic imaging generates spectra for multiple voxels, where each spectrum is a map of metabolites within the voxel. That is, the x- and y-axes of the spectral trace from an individual voxel represent frequency and metabolite concentration, respectively. The y-axis lacks absolute units. By convention, the x-axis is plotted as the downward frequency shift relative to water expressed in parts per million (ppm). This ratio adjusts for magnetic field strength, so the x-axis units are fixed irrespective of the magnetic field strength of the MRI scanner used.

The metabolic peaks relevant to prostatic MRSI are choline, polyamines, creatine, and citrate, occurring at shifts of approximately 3.2, 3.1, 3.0, and 2.6 ppm, respectively (see **Figure 25**).



The peaks for choline, creatine, and polyamines frequently overlap when MRSI is performed *in vivo* at 1.5T but can be distinguished at 3T and *ex vivo*. The areas under these peaks or resonances are proportional to the concentration of the respective metabolites, and changes in these concentrations can be used for tissue characterization and assessment. It is important to note that MRSI is always performed in conjunction with MRI, as MR spectra can only be fully interpreted when the source tissue for the spectra can be anatomically correlated and evaluated for MRI changes.

6.8.2 MRSI data acquisition

Combined MRI and MRSI of the prostate can be performed in less than 1 hour using a standard clinical 1.5T or 3.0T MRI scanner and commercially available ERCs (71,217). An ERC is essential for performing a spectroscopy and significantly improves the accuracy of tumour staging by MRI (219). The total examination time includes coil placement, patient positioning, and both MRI (including T2, DW MRI, DCE MRI) and MRSI data acquisition. Several vendors are offering or are close to releasing product versions of this combined MRI and MRSI examination. No change in patient position or coil placement is required to perform the MRSI, which is essentially an additional MR sequence similar to the T1 or T2 weighted sequences that are routinely acquired. The major difference is that the MRSI sequence requires more time—15 to 20 minutes to perform. The failure rate for MRSI (due to patient motion during the relatively long acquisition time) is approximately 5–20%.

FIGURE 25

Magnetic resonance spectrum showing the characteristic metabolic "fingerprint" of healthy peripheral zone tissue, with low choline, high citrate, and polyamine "filling" of the "dip" between choline and creatine. The metabolic peaks relevant to prostatic MRSI are choline, polyamines, creatine, and citrate, occurring at shifts of approximately 3.2, 3.1, 3.0, and 2.6 ppm, respectively.



Three-dimensional MRSI data are acquired using a water and lipid suppressed double-spin echo point-resolved spectroscopy (PRESS) sequence (180). Water and lipid suppression is achieved using either band selective inversion with gradient dephasing (BASING) pulses placed within the PRESS volume selection (220) or using spectral-spatial pulses capable of both volume selection and frequency selection (220,221). Both of these approaches to water and lipid suppression allow for residual water to be left in the spectra to serve as a phase and frequency reference. Residual water also allows for assessment of technical success of the acquisition when there are no metabolite peaks present in prostate spectra due to successful therapy (71). That is, if there are no metabolic peaks visible, the detection of residual water confirms that this reflects atrophy in the prostate rather than MRSI technical failure. Axial T2-weighted images are typically used to graphically select the PRESS volume with the goal of maximizing coverage of the prostate, while minimizing the inclusion of periprostatic fat and rectal air. The sharpness of the PRESS volume selection is enhanced through the use of high bandwidth spectral-spatial 180° pulses that also reduce chemical shift misregistration errors (220,222). Even with the use of these optimized pulses, spectroscopic voxels at the edge of the PRESS volume can still be contaminated by residual signal arising in adjacent tissues. To further reduce contamination from tissues surrounding the prostate, outer volume very selective saturation (VSS) pulses with very sharp transition bands are placed at the edges of the originally selected volume to better conform the

rectangular PRESS volume to the shape of the prostate (223). This often involves placing saturation bands across the corners of the PRESS volume to eliminate periprostatic lipids that normally occupy these regions.

Some of the technical challenges in obtaining high-quality MR spectra of the prostate can be appreciated by considering the resolution required in the x- and y-axes. Citrate protons spin with a frequency that is just 2.6 Hz per Tesla less than water protons, which spin with a frequency of 42.6 MHz per Tesla. The concentration of metabolites detected at MRSI is 1–10 mM, which is about 10,000 to 100,000 times less than the molar concentration of water protons. For these and other reasons, the voxels required for MRSI are relatively large. For example, the standard endorectal MRSI protocol has a voxel size of 0.34 cc. A spherical tumour must be at least 0.66 cc in size in order to completely fill a 0.34 cc voxel. Otherwise, incomplete filling of a voxel by tumour may result in a partial voluming artifact. One of the prerequisites for good spectroscopy is a homogeneous magnetic field within the PRESS volume; otherwise the spectral peaks cannot be properly resolved. Optimizing field homogeneity over the sample volume is known as "shimming the field." The "sharpness" of the MR spectral peaks (*i.e.*, linewidth) is a reflection of field homogeneity, and it provides a measure of study technical quality.

At 3T, MRSI provides increased spectral resolution, allowing adjacent peaks to be distinguished and, therefore, providing more metabolic data/tumour characteristics. Also, 3T provides increased SNR, which, in turn, can translate into increased spatial resolution. This, in turn, leads to more reliable and accurate tumour detection (169).

6.8.3 MRSI data display

MRSI produces spectra from contiguous voxels that are of approximately 0.3 cc in volume and cover most or the entire prostate. As MRSI and MRI are acquired within the same exam, the data sets are already in alignment and can be directly overlaid (see **Figure 26A**). In this way, areas of anatomic abnormality (decreased signal intensity on T2-weighted images) can be correlated with the corresponding area of metabolic abnormality (increased choline and decreased citrate and polyamines). Several different approaches have been used to display the combination of anatomic and metabolic information derived from simultaneous MRI and MRSI (224-228). These include superimposing a grid on the MR image and plotting the corresponding arrays of spectra, and generating colour-coded images of the spatial distribution of metabolites to overlay on the corresponding MR images. These formats provide an excellent summary of the spatial distribution of different metabolites, enabling rapid identification of regions of suspected abnormal anatomy and metabolism. Additionally, as 3D volumetric MRI and MRSI data are collected, the data can be viewed in any plane (axial, coronal, or sagittal), and the position of spectroscopic voxels can be retrospectively changed to better examine a region of abnormality on MRI after the data is acquired.

6.8.4 MRSI data interpretation

A number of general observations should be remembered when examining MR spectra. First, there is no absolute scale for the y-axis, which is a "unitless" dimension. The absence of an absolute scale requires use of internal denominators or ratios for objective quantification. In prostate MRSI, the

ratio of choline and creatine to citrate and the ratio of choline to creatine are frequently reported (see below). The interpretation of prostate MR spectra requires knowledge of the zonal location of the corresponding voxel, as the different zones of the prostate have differing metabolic profiles. High levels of citrate and intermediate levels of choline have been observed throughout a normal PZ. The CZ and TZ contain less citrate (see **Figures 26A** and **26B**) (217).

The choline peak can be elevated in tissues surrounding the urethra and seminal vesicles due to the presence of high levels of glycerophosphocholine in the fluid within in these structures, and may result in "overcalling" of tumour in these locations (see **Figures 27A–27E**). With increasing age, the glandular and stromal content of the TZ changes due to the development of BPH, which can be predominately glandular, stromal, or most often, a mixture of glandular and stromal proliferation. Predominately glandular BPH demonstrates very high citrate levels similar to healthy peripheral zone tissue, while predominately stromal benign prostatic hyperplasia demonstrates dramatically reduced citrate (217).

Therefore, the first step in the analysis of the spectral data is to identify whether the corresponding voxels are in the peripheral zone or the transition zone. Since most prostate cancers arise in the peripheral zone, most MRI/MRSI research has focused on peripheral zone cancer. The interpretation of transition zone voxels is complicated by metabolic overlap between prostate cancer and predominately stromal benign prostatic hyperplasia that is almost always present in the prostate of older men (229). The metabolic criteria that we have been developed to identify prostate cancer in PZ have evolved from an understanding of prostate cancer metabolism and empirical observations in more than 4,000 clinical MRI/MRSI examinations and from *ex-vivo* high-resolution magic angle spinning (HR-MAS) spectroscopy of biopsy and surgical tissues that underwent subsequent full pathologic analysis (71,230).



FIGURE 26A

Axial T2-weighted image of the prostate. A grid has been overlaid on the image, corresponding to the spectral array shown in Fig. 26B.

FIGURE 26B

Spectral array corresponding to the grid shown in Fig. 26A. Such an overlay and array illustrates one method of displaying and correlating MRI and MRSI data.



FIGURE 27A

Axial T2-weighted MR image of the mid prostate in a healthy 35-year-old volunteer. The spectra from the grid marked in the image are shown in Fig. 27B.





Spectra from the normal prostate demonstrate three distinct metabolic patterns, shown in greater magnification and details in Figs. 27C–E.



FIGURE 27C





FIGURE 27D

Spectrum from normal central gland demonstrates lower citrate levels but similar choline and creatine levels than the PZ.



FIGURE 27E

Spectrum from normal periurethral tissue demonstrates low citrate and mildly elevated choline. The latter presumably reflects choline levels within the muscular layer of the distal prostatic urethra.

Healthy prostate epithelial cells possess the unique ability to synthesize and secrete enormous quantities of citrate. The decrease in citrate with prostate cancer (see **Figure 28A–28C**) is due both to changes in cellular function (231,232) and changes in the organization of the tissue, resulting in a loss of its characteristic ductal morphology (233,234). Malignant prostatic epithelial cells demonstrate a diminished capacity for net citrate production and secretion (235,236). Unfortunately, citrate can also be reduced by prostatitis or post-biopsy hemorrhage or any condition that causes a reduction in prostatic ductal morphology and the associated citrate rich fluids.

As in other human cancers, the elevation of the choline peak in prostate cancer is associated with changes in cell membrane synthesis and degradation that occur with the evolution and progression of cancer (237,238), and changes in epithelial cell density and altered phospholipid metabolism likely contribute to the observed increase in choline content seen in prostate cancer (233,239). Recent high-resolution NMR studies of ex vivo prostatic tissues have identified several new metabolic markers for prostate cancer including polyamines, which appear very elevated in spectra of healthy prostatic PZ tissues and predominantly glandular BPH and dramatically reduced in prostate cancer. Similar to changes in choline-containing compounds, changes in cellular polyamine levels have been associated with cellular differentiation and proliferation (240,241). Moreover, it has recently been demonstrated that the loss of polyamines in regions of cancer can be detected by MRSI as an improvement in the resolution of the choline and creatine peaks (242).

Given that prostate cancer is characterized at MRSI by raised choline content (a normal cell membrane constituent, which is elevated in many tumours) reduced citrate content (a constituent of normal prostatic tissue) or both (243), the ratio of choline and creatine to citrate was examined in early studies as a quantitative measure for tissue characterization, with a higher number indicating a greater likelihood of malignancy. Creatine is included with choline because the spectral peaks of these two compounds often overlap, and may be inseparable. Inclusion of creatine in this ratio is not considered a potential source of error, as creatine appears to remain at a relatively constant level in both healthy and cancerous prostatic tissue.

The ratio of choline and creatine to citrate in normal prostatic tissue has been established as 0.22 +/- 0.13 [John Kurhanewicz, personal communication], while the ratio frequently exceeds 0.5 in malignant voxels (more than two standard deviations above normal). More recently, choline elevation has been recognized to be more specific for cancer than citrate reduction, so we also determine the choline to creatine ratio (suspicious if greater than 2). Based on metabolic changes in choline, polyamines and citrate in regions of prostate cancer a standardized 5-point scale for the interpretation of PZ metabolism in the pre-therapy prostate was developed and validated (see **Figure 29**A and **29B**) (244).

Representative spectra illustrating this scoring system are shown in **Figure 30**. This scoring system has proved to be highly accurate (approximately 88% accuracy) in distinguishing benign and malignant tissue with excellent inter-observer agreement (kappa statistic = 0.80).

6.8.5 **Applications of prostate MRSI**

6.8.5.1 **Tumour diagnosis**

Patients with an elevated PSA level and one or more negative transrectal prostate biopsies are frequently encountered in clinical practice, and form a population in whom MRI/MRSI could potentially be of interest as a diagnostic test (see **Figure 31A** and **31B**). To determine the diagnostic accuracy of endorectal MRI/MRSI in the diagnosis of prostate cancer, 40 patients were retrospectively identified who were referred for endorectal MRI/MRSI prior to biopsy (245). All patients had an elevated serum

PSA level. None of the patients had a histologic diagnosis of prostate cancer at the time of imaging; 36 patients had a previous negative biopsy and 4 patients had never undergone biopsy. Based on MRI alone and then based on the combination of MRI/MRSI, the presence or absence of prostate cancer in each side of the prostate was rated on a 5-point scale (1 = definitely absent, 5 = definitely present) by a single experienced reader. Data were analyzed for each side of the prostate, using the presence or absence of cancer on TRUS guided biopsy performed after MR as the standard of reference. Transrectal ultrasonography guided biopsy demonstrated no cancer in 24 patients, bilateral cancer in 11 patients, and unilateral cancer in 5 patients. The area under the receiver operating characteristic curve for the diagnosis of prostate cancer was 0.70 for MRI and 0.63 for combined MRI/MRSI. These values were not significantly different. These results suggest that (using current technology) MRI/MRSI has high specificity but low sensitivity for the diagnosis of prostate cancer in patients with an elevated serum PSA level. Also, the addition of MRSI does not appear to have a significant impact compared with evaluation by MRI alone. However, a positive MRSI highly supports the diagnosis of prostate cancer with with an increases the "risk" score of an individual lesion.



FIGURE 28A

Axial T2-weighted image of the prostate in a patient with prostate cancer.



FIGURE 28B

Corresponding MRSI grid shows several voxels with elevated choline levels (arrows), corresponding to PZ tissue near the midline. These spectral findings could be considered suspicious for malignancy.



FIGURE 28C

Axial T2-weighted image of the prostate at a level just superior to the image shown in Fig. 17C. The seminal vesicles are seen at this level, strongly suggesting that the spectral findings in Fig. 17B represented "pseudotumor" secondary to downward contamination or "leakage" of choline signal from the very high choline content in the ejaculatory fluid.



FIGURE 29A

Axial T2-weighted image of the prostate in a patient with Gleason 9 prostate cancer in multiple biopsy specimens.



FIGURE 29B

Corresponding MRSI grid shows widespread elevation of choline content in virtually all the PZ voxels, particularly on the left side, consistent with extensive and aggressive tumour.

UCSF interpretative scale for MRSI of prostate cancer. The 5-point scale assigns a score of 1 (probably benign) to 5 (probably malignant) for each voxel. The score is primarily based on the choline and creatine to citrate ratio (Ch+Cr/Cit), with an initial adjustment for the choline to creatine ratio (Ch:Cr) and polyamine level and a final adjustment for the SNR.

• Primary score based on Ch-Cr/Cit ratio:

SOs over normal	0-1	1-2	2-3	3-4	4+
Score	1	2	3	4	5

Initial adjustment:

```
- Ch:Cr > 2:1-2 or 3 to 4
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- Ch:Cr < 2:1 or normal polyamines - 4 to 3, 5 to 4

Final adjustment

- SNR < 8:4 to 3, 5 to 4

6.8.5.2 **Tumour localization**

In a study with two readers using step-section histopathology as the standard of reference in 53 patients (221), MRI alone had a sensitivity of 77-81% and a specificity of 46-61% for the sextant localization of prostate cancer. With the addition of MRSI, sensitivity fell slightly to 68–73%, but specificity increased substantially to 70-80%. These data suggest that MRSI is particularly helpful in preventing "overcalls" of tumour by demonstrating normal metabolism in areas of equivocally reduced T2 signal intensity (see Figure 32A and 32B). It should be emphasized that the results described above refer to the sextant localization of prostate cancer, which is not synonymous with volumetric localization. In another study (200), MRI and MRSI were performed in 37 patients prior to radical prostatectomy. Two independent readers recorded PZ tumour nodule location and volume. Results were analyzed using step-section histopathologic tumour volumetry as the standard of reference. The mean volume of all PZ tumour nodules (n=51) was 0.79 cc (range, 0.02-3.70). Readers detected 20 (65%) and 23 (74%) of the 31 PZ tumour nodules greater than 0.5 cc. For these nodules, tumour volume measurements by MRI alone and combined MRI and MRSI were all positively correlated with histopathologic volume (Pearson's correlation coefficients of 0.49 and 0.55, respectively), but only measurements by combined MRI and MRSI reached statistical sig nificance (p < 0.05). These results for prostate cancer tumour volume measurement may appear disappointing, particularly in the context of other studies indicating high accuracy for sextant localization. Two factors probably account for this discrepancy. First, per-sextant rather than per-nodule analysis does not require size concordance between imaging and pathology, so a very small imaging abnormality counts as a true positive even if the tumour is pathologically much larger, and vice versa. Second, there has been a general downward stage migration of prostate cancer in the era of widespread PSA testing.



FIGURE 31A

Axial T2-weighted MR image through the mid-prostate in a 64-year-old man with a PSA of 7.9 ng/ml and a recent sextant biopsy demonstrating Gleason 7 adenocarcinoma in the left mid-gland of the prostate only. A large focus (white arrow) of reduced signal intensity is visible in the left mid-gland. A less marked focus (black arrow) of reduced T2 signal intensity is seen in the right mid-gland.



FIGURE 31B

MR spectral array at the level of the slice shown in Fig. 26A. In each voxel, the upper number is the choline to creatine ratio, and the lower number is the choline plus creatine to citrate ratio. Several voxels in the lateral aspect of the left mid-gland demonstrate elevation of choline and reduction of citrate content, consistent with malignancy. The right mid-gland appears spectroscopically unremarkable. Concordant MRI/MRSI findings in the left mid-gland are consistent with a relatively large focus of cancer. MRI findings in right mid-gland are probably not due to malignancy, given negative MRSI and biopsy findings.



FIGURE 32A

Axial T2-weighted image of the prostate in a 52-year-old man with a PSA of 5.4 ng/ml and a palpable right-sided nodule on DRE. A focus of low T2 signal intensity (asterisk) is suggestive of tumour, and associated obliteration of the rectoprostatic angle (arrow) is concerning for ECE.



FIGURE 32B

MRSI grid at the same level as Fig. 15A, with highlighted voxels corresponding to the area of suspected cancer (C) and an area of healthy PZ tissue (H). Note the relative elevation of choline and reduction in citrate content in the malignant voxel (choline peaks indicated by grey arrows, citrate peak by white arrows). Subsequent biopsy confirmed right-sided malignancy.

Magnetic resonance spectroscopy has been shown to be of potential benefit in the localization of TZ tumours with increased sensitivity in detection compared with conventional MRI. Unfortunately, the metabolite ratio in the TZ varies greatly, limiting widespread use for these tumours (174).

To add to the controversy, the role of MRSI in a multicentre trial headed by the ACR Imaging Network showed that for sextant localization in PZ prostate cancer, MRS had no incremental benefit compared with MRI alone (246).

6.8.5.3 **Tumour staging**

Multivariate feature analysis has shown the MRI findings that are most predictive for ECE are a focal irregular capsular bulge, asymmetry or invasion of the neurovascular bundles, and obliteration of the rectoprostatic angle (247). The addition of MRSI to MRI has been shown to increase staging accuracy for less experienced readers and to reduce inter-observer variability (248). The role of MRSI is not to directly depict extracapsular tumour, but rather to indicate whether a tumour is metabolically present and aggressive in an area where a questionable finding of ECE is present (see **Figures 33A** and **33B**).

6.8.5.4 Treatment planning

Several groups have reported the use of MRSI to increase the brachytherapy radiation dose in prostatic locations considered suspicious for cancer (249,250). Such studies, which suggest technically successful dose escalation in spectroscopically suspicious locations, imply improved clinical outcome must be viewed with caution, given the limited ability of MRI and MRSI to assess tumour volume. More recently, MRI/MRSI has been shown to improve pre-operative surgical planning with respect to the decision to preserve or resect the neurovascular bundle, although this study did not separate the relative contribution of MRI versus MRSI (251).



FIGURE 33A

Axial T2-weighted MR image through the mid- prostate in a 57-year-old man with a PSA of 8.6 ng/ml and a recent sextant biopsy demonstrating adenocarcinoma in the left gland. An ill-defined focus of reduced signal intensity is visible in the left gland, and is associated with questionable irregularity (arrow) of the prostatic capsule.



FIGURE 33B

MR spectral array at the level of the slice shown in Fig. 16A. In each voxel, the upper number is the choline to creatine ratio, and the lower number is the choline plus creatine to citrate ratio. Multiple voxels in the left gland demonstrate striking elevation of choline and reduction of citrate. The presence of such extensive and aggressive tumour metabolism on MRSI increases reader confidence that the questionable capsular irregularity seen in 16A truly represents extracapsular tumour extension.

6.8.5.5 **Post-treatment follow-up**

In one study (252), endorectal MRSI was performed at 1.5T in 21 patients with biochemical failure after EBRT for prostate cancer. Spectroscopic voxels were considered suspicious for malignancy if choline was elevated and citrate was absent (compared with pretreatment studies, spectroscopic evaluation after therapy is simplified by radiation-induced metabolic atrophy). Receiver-operating characteristic curve analysis was used to analyze cancer detection in each side of the prostate by MRSI at different thresholds based on the number of suspicious voxels in each hemiprostate, respectively.

The presence or absence of cancer on subsequent transrectal biopsy was used as the standard of reference. Biopsy demonstrated locally recurrent prostate cancer in 9 hemiprostates of 6 patients. The area under the receiver operating characteristic curve for MRSI was 0.81. In particular, the presence of three or more suspicious voxels in a hemiprostate showed a sensitivity and specificity of 87% and 72%, respectively, for the diagnosis of local recurrence (see **Figure 34**). Of note, 7 hemiprostates demonstrated complete metabolic atrophy (i.e., no metabolic peaks) on MRSI, and showed only postradiation atrophy on biopsy (see **Figure 35**).

These preliminary data suggest MRSI can accurately detect locally recurrent prostate cancer after EBRT. In particular, complete metabolic atrophy appears to have high NPV and may indicate that local salvage therapy will be unhelpful. Recent work investigating the role of MRSI for the evaluation of local control after EBRT is analogous to the primary indication for MRSI in neuroradiology, i.e., the distinction of post-radiation necrosis from recurrent tumour (253).

Hormone therapy has been shown to cause a time-dependent loss of prostatic metabolites, a feature that may be used in response assessment. Mueller Lisse *et al.* demonstrated a loss of the ratio of choline and creatine to citrate in 25% of patients following 4 months of hormone deprivation therapy (254,255). Further studies are needed to explore these trends.

FIGURE 34

A 60-year-old man with a rising PSA 3 years after EBRT for prostate cancer. Photomontage showing an axial T2- weighted MR image of the prostate. A grid overlaid on the image corresponds to the adjacent MR spectral array, which demonstrates several suspicious voxels (arrows) with elevated choline in the left side of the gland. Transrectal ultrasonography quided biopsy confirmed the presence of locally recurrent prostate cancer in the left gland.



A 69-year-old man with a rising PSA (to 1.0 ng/ml) 2 years after EBRT for prostate cancer. Photomontage showing an axial T2-weighted MR image of the prostate. The adjacent MR spectral array, which demonstrates complete metabolic atrophy, with no detectable metabolic peaks in any of the PZ voxels. Subsequent biopsy showed no evidence of locally recurrent prostate cancer in the gland, and his PSA has stabilized spontaneously.



6.8.6 New metabolic markers

13C MRS with hyperpolarized 13C is a potentially useful method for characterizing prostate cancer and for monitoring disease progression due to far greater spatial and temporal resolution. Hyperpolarizing 13C dramatically increases the signal and thus permits metabolic imaging.

Preclinical studies have yielded very promising results by using 13C MRS with hyperpolarized 13C. For example, lactate production was shown to increase with progressive disease in mouse models (256).

Currently, the technique remains a research tool. Recently, hypolarized 13C imaging has been performed in limited research settings in humans. A low gyromagnetic ratio and low natural abundance of 13C make the background signal low. By injecting hyperpolarized 13C metabolites such as labelled pyruvate, explorations of basic tumour metabolism may be possible. Further studies are needed to evaluate the precise role for this technique in humans, as well as advancement of clinical scanners to become compatible with the use of 13C MRS (257).

6.8.7 Conclusions

Combined endorectal MRI/MRSI provide combined anatomic and metabolic data and arguably represents the single best modality for local evaluation of prostate cancer extent and aggressiveness. The addition of MRSI to MRI (including T2, DW MRI, and DCE MRI) has proven benefit in tumour localization, volume estimation, and staging. Magnetic resonance spectroscopic imaging may be particularly useful in the evaluation of suspected local recurrence after RT. It is important in increasing the confidence of the diagnosis and in particular, in assigning risk category to a particular lesion. It is also important to remember that this is a technology that remains in evolution (e.g., results for MRI/MRSI performed at 3T has great promise) although it may be some time before the true roles and benefits of endorectal MRI/MRSI are fully realized.

6.9 **Positron Emission Tomography** (PET) for Evaluation of the Prostate

Positron emission tomography images *in vivo* biologic processes three-dimensionally. A specific radiopharmaceutical, labelled with a radioactive isotope is injected. In the tissue, the unstable isotope is transformed by a physical process called beta decay. Basically, a proton turns into a neutron and a positron, and the positron is emitted. When this positron, in fact a positively charged electron, fuses with a true electron, their mass is transformed into energy. This process is known as annihilation and the released energy is emitted as a photon. With photon detectors and photomultiplier tubes, the process can be localized and translated into images.

Depending upon the radiopharmaceutical injected, a number of metabolic processes in the body, varying from glucose metabolism, amino acid transport, DNA synthesis, and membrane synthesis, can be studied.

Although PET has been in existence since the 1960s, it did not gain complete clinical acceptance until the 1990s after Di Chiro *et al.* demonstrated the ability of PET to differentiate between recurrent brain tumour and radiation necrosis, prompting the recognition of PET as a valid method of tumour imaging (258). Researchers and clinicians have been able to detect a wide variety of malignancies with PET including lymphoma, melanoma, sarcoma, lung cancer, colon cancer, and squamous cell carcinoma (259-265). As current radiographic techniques such as MRI and CT scans are often unable to accurately stage the extent of prostatic malignancies, (266,267) the utilization of PET for assessing this disease is an attractive alternative.

Some centres, equipped with a cyclotron, have the possibility to prepare positron emitters with short half-lives. This almost instant availability of tracers with the possibility of short acquisition times was the start of a spectacular application of the PET scanners in the last years. It is already routine clinical practice in cardiology, neurology, and some domains of oncology. Positron emission tomography is now the reference for the detection of viable myocardial tissue, for the evaluation of dementia, and for localisation of epileptic foci. It is also used in case of fever of unknown origin in search for an infected or inflammatory process. The technique is also used for tumour imaging and management, and it is already commonly accepted in the oncologic work up for tumours of the brain, lung, colon, breast, ovaries, thyroid, andthe musculoskeletal system, lymphoma, and squamous cell carcinoma of the head and neck (268).

6.9.1 **Positron emitters**

The most commonly used PET tracer is 18-Fluoro-deoxy-Glucose (18-FDG). It allows to study the glucose metabolism *in vivo* and has a half life time of 110 minutes, which is very useful for transport to other places or centres. Other positron emitters than 18-FDG (**Table 6**) have rapid decays and can only be used if they can be prepared on site. 18-FDG is in general very useful for imaging of tumour pathology because most malignant cells have a markedly increased glycolisation activity.

TABLE 6 Positron Emitters

Isotope	Half-life (min)
11-C	20.4
13-N	10.0
15-0	2.1
18-F	110

6.9.2 **PET tracers and related metabolic process**

Today's most commonly used and studied tracers for PET scanning and the metabolic or physiologic process they interfere in are listed in **Table 7**.

TABLE 7 Most Commonly Used and	d Studied Radiotracers for PET
--------------------------------	--------------------------------

Tracer	Metabolic process
18-F-deoxyglucose (18-FDG)	glucose consumption
18-F-thymidine (18-FLT)	nucleic acid consumption
11-C-methionine	amino acid transport
H² (15)0	perfusion
82-Rubidium	perfusion
13-NH3	perfusion
18-F-misonidazole	hypoxia
18-F-DOPA	dopamine receptor binding

6.9.3 **Preparation of 18-FDG PET in oncology patients**

Precise planning is necessary because of the half-life of the tracer. Patients are typically asked to fast for 6 hours prior to the examination to minimize glycemia and insulinemia that may limit the sensitivity of the study. Patients with diabetes may be given more detailed preparatory instructions and may undergo spot glucose testing before the test is performed; those with hyperglycemia are

re-scheduled for the examination once their glucose levels are better controlled. Images are acquired 60 minutes after injection of 12-17 mCi of 18-fluoro-2-deoxyglucose (18-FDG). During the time between injection and tissue acquisition, the patient is asked to avoid muscular activity. Emission images of the abdomen are acquired, followed by a Ga-68 transmission scan of the same area. Images are corrected for signal attenuation and reconstructed using filtered back projection in the transaxial, coronal, and sagittal planes.

6.9.4 Normal biodistribution of 18-FDG 60 minutes after the injection

The normal biodistribution of 18-FDG is characterized by an important cerebral activity and a good visualization of the tonsilla, sublingual salivary glands, and vocal cords. The tracer accumulates moderately in the liver, spleen, and bone marrow, but it varies in the heart and gastrointestinal system. The renal clearance of the radiopharmaceutical permits good visualization of the urinary tract.

6.9.5 **Possible clinical applications of 18-FDG PET in general oncology**

6.9.5.1 **Primary diagnosis**

Because of their rapid growth pattern and therefore increased need for energy and nutrition under hypoxic conditions, malignant tumours preferably consume glucose. This avidity for glucose is well suited for 18-FDG PET, and the intensity of the signal is to a certain extent a marker for the malignant potential.

6.9.5.2 **Staging**

T staging

Because of their lower resolution and the absence of anatomical landmarks, PET images are less useful than conventional imaging techniques for primary tumour (T) staging.

N staging

The malignant state of the locoregional and distant lymph nodes is not always proportional to the nodes' size, but certainly to their metabolic activity. This explains why 18-FDG PET is often more accurate then conventional imaging techniques for N staging of malignant tumours (284).

• *M staging*

Positron emission tomography is a very sensitive imaging tool for detection of organic metastases, but conventional imaging techniques are more suitable for precise localization of the lesions. Combining the advantages of both tests might be the answer. Protocols for PET-CT and PET-MRI fusion imaging are currently under investigation.

6.9.5.3 Recurrent disease

The specificity of the conventional radiologic techniques is significantly reduced after surgery, RT, or chemotherapy because anatomical landmarks may have been disturbed and because of scar tissue formation. Positron emission tomography may be able to show the difference between cancer and scar, but the test should not be done within the first 3 months after surgery or RT, as 18-FDG is also increasingly absorbed by inflammatory cells.

6.9.5.4 Monitoring therapy

Early re-evaluation of the target lesions by PET scan during chemotherapy can differentiate responders from non-responders and help to avoid unnecessary prolonged toxic treatment in the latter.

6.9.5.5 Planning radiotherapy

Incorporation of PET images in the planning of RT provides relevant adaptations of the target zone in 30% of the cases.

6.9.6 Limitations of 18-FDG PET

6.9.6.1 **The resolution**

The spatial resolution is limited to 4–5 mm for two adjacent hot spots; however, single lesions smaller then 4 mm may be visualized.

6.9.6.2 **The tracer**

An important normal accumulation of 18-FDG precludes the diagnosis of hot spots in the brain and urinary tract.

6.9.6.3 Absence of anatomic landmarks

The precise anatomic localization of the hot spots is difficult, as there are no clear 18-FDG accumulating landmarks. This problem might be solved in the future with the possible availability of PET-CT or PET-MRI fused images.

6.9.6.4 **Tumour-associated limitations**

The intensity of the signal depends upon the degree of hypermetabolic activity inside the tumour cells. Tumours with low proliferation rates are thus difficult to recognize. With the radioisotope accumulating both in malignant and inflammatory cells, tumours from surgically or radiotherapeutically treated patients may produce false-positive signals.

6.9.7 **PET in urologic tumours**

The use of PET scan in urologic oncology is still under investigation. As with other tumours, most experience is with 18-FDG. To date, high-grade renal cell and testicular cancer appear to be good indications (269). Primary bladder cancer is not a good indication, but PET is currently under investigation for detection of pelvic recurrence or metastatic lesions.

Prostate cancer is another story—certainly in its early stages.
6.9.8 **PET imaging of the prostate**

Prostate imaging with PET scanning is currently studied with different tracers, not surprisingly mostly, if not all, aimed at prostate cancer. Experiments with the most commonly used tracer, 18-FDG, are still disappointing, and most investigators are now turning their attention and experiments to other tracers.

6.9.9 **18-FDG**

6.9.9.1 **Primary prostate cancer**

The potential of PET for imaging prostate cancer was initially established in animal models of metastatic prostate tumours using the radiotracer N-3-18-fluoropropylputrecine (270,271).

Certainly in its early stages, prostate cancer is a slow growing neoplasm, and thus had lower uptakes of radiotracers such as 18-FDG (see **Figure 36**). Image obscuring due to the adjacent bladder through which the radiopharmaceutical is eliminated and the relatively high uptake of 18-FDG by BPH account for the varying reported amounts of FDG activity in prostate cancer cells and the altogether conflicting results (272-274).

6.9.9.2 Relapse after primary local treatment

Positron emission tomography with 18-FDG cannot reliably distinguish post-operative scar tissue from a local recurrence after radical prostatectomy (275). Haseman *et al.* (274) found only one positive FDG PET in 6 patients with biopsy-proven local recurrence. Because of too many false-positive and false-negative findings, this tracer is not recommended in post-prostatectomy patients (276).

6.9.9.3 Monitoring treatment response

There appears to be a trend of decreased FDG accumulation both in primary and metastatic prostate cancer with positive biologic response to hormone ablative therapy, but the changes are of different orders of magnitude. This suggests the unreliability of the biologic markers (277).

Inaba reported the first use of PET in imaging in humans for metastatic prostate cancer using 15-oxygen, demonstrating increased uptake in areas of hypervascularity (276). Bares *et al.* presented the initial experience with FDG for prostate cancer imaging in 1993 (277). These authors, in a subsequent study found increased uptake and 100% of 7 patients with untreated metastatic disease (278). Metastatic bone lesions are more consistently identified than nodal metastases in most series. Oyama *et al.* found showed increased boney uptake by PET in 9 patients with metastases on bone scintigraphy (272). Similarly, Kao *et al.* reported PET detection of bone lesions in 11 patients with increased uptake on bone scintigraphy due to benign bone lesions (278). Schreve *et al.* evaluated the sensitivity of PET for detecting individual metastatic bone lesions (279). Of 202 lesions in 22 patients, PET identified 131 lesions (sensitivity, 65%) with only 2 false-positive lesions (PPV, 98%). Sung *et al.* found that in patients experiencing a favourable response to androgen deprivation therapy, PET did not reveal metastatic sites apparent on bone scintigraphy (280). In untreated patients, however, PET identified lesions apparent on bone scintigraphy (280). In untreated patients, however, PET identified lesions apparent on bone scintigraphy in 3 patients and detected a metastatic bone lesion in one patient with normal bone scintigraphy (see **Figure 36**).

Although the detection of lymph node metastases is not as reliable as bone metastases, it remains superior to other imaging modalities (see **Figure 37**). Heicappell *et al.* found increased PET uptake in 4 of 6 patients with lymph node metastases as small as 0.9 cm, which were not detected on CT scanning but were discovered pathologically following radical prostatectomy with pelvic lymph node dissection (281) (see **Figure 38**).

There were 2 patients in that series with nodal metastases <0.5 cm in the surgical specimen that were not detected by either CT or PET imaging.

FIGURE 36

Pelvic 18-FDG PET image in a 73-year-old with PSA of 21.2 ng/ml, 83-cc gland, and Gleason's 3+4 in 4 of 12 biopsies. Image shows no increased prostatic uptake with diuretic PET imaging.



FIGURE 37

Bone scintigraphy (**Panel A**) and whole-body 18- FDG PET image (**Panel B**) in the same patient showing bone lesions detected by PET but not by bone scan.



Pelvic 18-FDG PET image in a 57-year-old man with PSA of 43.2 ng/ml and Gleason 4+5 prostate cancer in all 10 biopsy cores. Image shows increased uptake through entire prostate as well as in the right seminal vesicle and left pelvic lymph node, consistent with prostate cancer involvement of these structures.



In a comparable study, Sanz *et al.* found that PET revealed nodal metastases in 3 (27.3%) of 11 patients found to have metastases at radical prostatectomy and pelvic lymph node dissection (282). In contrast, Seltzer *et al.* showed no difference in the detection of nodal metastases in 45 patients by CT and PET imaging, with both demonstrating a detection rate of 50% (283). In the series published by Sung *et al.*, PET identified nodal metastases in 3 patients, 2 of which (66.7%) had no evidence of adenopathy by CT imaging; no patients had adenopathy by CT that did not demonstrate increased uptake by PET (280).

Multiple authors have found that locally advanced and metastatic prostate cancer are best detected by FDG PET imaging in untreated and hormone refractory tumours (267,272,279-285). In addition, Sung *et al.* found variable tumour detection in patients with a partial biochemical response to hormone therapy and lack of FDG uptake in patients with undetectable PSA levels in response to hormone therapy (280).

Based on these data, it may be concluded that FDG PET performs inconsistently in the management of prostate cancer (286).

Application of PET imaging to prostate cancer has been problematic due to the relatively slow-growing nature of this tumour, which is reflected as a concomitantly low rate of glycolysis (271). Furthermore, local assessment of prostate cancer is inconsistent, as FDG is excreted in the urine, accumulates in the bladder and prostatic urethra, (see **Figure 39**) and can effectively mask any uptake in the prostatic parenchyma (271,287). Liu *et al.* utilized hydration, diuretic administration, and pre-procedure bladder emptying to evacuate the non-specific isotope in the urine, which allowed visualization of 8 (61.5%) of 13 locally advanced untreated or hormone refractory prostate tumours (see **Figure 40**) (284). Effert *et al.* used urethral catheterization and bladder irrigation to clear the isotope from the bladder (288).

Normal whole body 18-FDG PET image demonstrating the limited usefulness of PET in urologic tumours due to excretion of the isotope into the urine, masking any lesions.



But, with this technique, these investigators only found increased uptake in 2 of 14 (14.2%) untreated locally advanced, T3 or T4, tumours (see **Figure 41**). This low detection rate may be due in part to their use of muscle as a measure of background intensity; they found that both benign prostate cancer and primary prostate malignancy were not significantly different. Hara and colleagues suggested the use of 11-carbon-choline (11C-choline) PET over FDG PET in the imaging of prostate cancer, as 11C-choline has negligible urinary excretion (289).

There are conflicting reports on the uptake of FDG by BPH. Effert *et al.* did not show increased uptake by clinically organ-confined prostate tumours; however, increased uptake was noted in patients with BPH, which was theorized to be masking any small prostate tumours (288). Laubenbacher *et al.* found no significant difference in the FDG activity of primary prostatic adenocarcinoma compared with that of BPH (271). Lui *et al.* found no increased uptake by BPH or clinically organ-confined prostate cancers, but noted increase uptake in prostate cancer patients with concomitant prostatitis (290).

The tendency of inflammatory processes, such as prostatitis, to demonstrate increased FDG uptake represents another limitation of this imaging technique (see **Figure 39**) (291). Inflammatory lesions resulting in false-positive interpretation of FDG-PET imaging has historically been problematic primarily in the detection of lung malignancies when granulomatous disease is present (290,292). Most experienced nuclear medicine radiologists have learned to detect the sometimes subtle differences between the uptake demonstrated by granulomas and the uptake seen with malignancy. Inflammation from diverticular disease and prostatitis is less commonly recognized as a source of increased uptake in the pelvis that can simulate locally extensive urologic malignancies (285,293).

Most current investigations on the application of PET in prostate cancer are aimed at identifying alternative isotopes that, unlike 18-FDG, do not depend on a high rate of glycolysis or are not excreted in the urine (294-299).

Normal whole body 18-FDG PET image after hydration, furosemide administration, and bladder emptying which has resulted in evacuation of non-specific isotope excreted in the urine.



FIGURE 41

Pelvic 18-FDG PET image in a 65-year-old patient with PSA of 5.7 ng/ml, Gleason 3+3 prostate cancer on prostate biopsy as well as BPH (65.2 cc), and prostatitis. Image reveals slight diffuse prostatic uptake (arrow).



6.9.10 **11-C-Acetate**

The uptake of acetate in tumour cells is related to their lipid synthesis. Acetate is metabolized and incorporated into phosphatidylcholine and into neutral lipids. Its lack of urinary excretion and its good tumour-to-background ratio make this tracer more suitable for prostate cancer imaging than FDG. But acetate is not a cancer-specific tracer; it also accumulates in normal and hyperplastic prostatic tissue (300).

This tracer has been investigated for pre-operative staging of prostate cancer (301) and for the detection of local recurrent disease after radical prostatectomy, (302) resulting in moderate findings. The biologic uptake of 11-carbon-acetate (11-C-acetate) in the normal prostate and especially in BPH seems to be too high and restricts the applicability of this technique (303). In an analysis comparing 18-FDG and 11-C-acetate, sensitivity was increased by approximately 10% using the latter pharmaceutical when evaluating patients for local recurrence and regional metastasis (280). In that study, 20 of 24 patients (83%) had detectable recurrent disease using 11C-acetate PET, with the majority being on hormonal therapy at the time of imaging.

Like all C-labelled radiotracers, 11-C-acetate has a short half-life (20.4 min) and can only be used if prepared onsite.

6.9.11 **18-F-Acetate**

Methods for safe and efficient synthesis of this radiotracer are still under investigation. Data from animal experiments suggest that it could be more useful than carbon-labelled acetate for prostate cancer imaging (304).

6.9.12 **11-C-Methionine**

The accumulation of L-methyl-C-methionine in cancer cells is attributed to an increased amino acid transport and in part to protein synthesis (305). Nilsson *et al.* described this high uptake in a considerable number of malignant lesions in patients with androgen-resistant prostate cancer (305). Recently, Toth *et al.* (306) published results using 11-C-methionine PET detection of prostate cancer in 20 patients with a PSA levels between 3.49 and 28.6 ng/ml and 1–5 previous negative biopsies. In 15 patients, 11-C-methionine accumulated suspiciously in the prostate, and biopsies of these zones revealed prostate cancer in 7 patients. The prostatic biopsies in the other 5 patients were negative. That still makes 8 (the patients with 11-C-methionine accumulation but negative biopsies) to 13 (plus the non-accumulating patients) in whom there was no clear diagnosis.

6.9.13 **11-C-Choline**

The metabolism of cell membrane components of malignant tumours with high proliferation rates is also increased. This leads to a higher uptake of choline, one of the components of phosphatidylcholine, an essential element in the cell membrane. The intracellular choline is rapidly metabolized to phosphorylcholine (PC). Experiments with magnetic resonance spectroscopy (MRS) revealed that prostate cancer cells have a high uptake of PC, whereas normal tissue does not (296). Unfortunately, as the uptake in BPH is also elevated, it is difficult to distinguish between cancer and BPH in individuals (307). As the isotope is not excreted in the urine, PET imaging with 11C-choline has an added benefit of not requiring diuretic administration or bladder irrigation (294). 11C-choline PET does not, however, avoid the problem of differentiating BPH from prostate cancer. Despite the mean standard uptake value of 5.6 for prostate cancer and 3.5 for BPH, crossover does occur, which makes it difficult to determine tissue type from this imaging alone (297). Also, there is no correlation of the standard uptake value with Gleason score, prostate size, or PSA level (297).

C-choline PET can show clear images of the prostate and the pelvic lymph nodes in the absence of bladder activity (289,308,309).

With all choline compounds an intensive bowel activity is observed and can cause false-positive findings (293). As the blood clearance is approximately 7 minutes, imaging should be done as early as 3–5 minutes after the injection.

Currently, it is still unclear whether the choline uptake in prostate cancer lesions can serve as a marker for their biologic aggressiveness. Studies to date show no correlation (307).

The feasibility of 11-C-choline PET for the diagnosis of recurrent disease after radical prostatectomy or external beam radiation for localized prostate cancer was investigated by de Jong *et al.* (293). Of 36 patients, 20 operated and 16 irradiated, 14 (7 in each group) had no biochemical evidence of disease and C-choline PET was negative in all. In the group of 22 patients with biochemical failure, 12 had positive findings on 11-C-choline PET.

Histologic confirmation of recurrent disease was obtained in 6 patients with local lesions and 4 patients with suspicious lymph nodes. Three patients had suspicious bone lesions on 11-C-choline PET, confirmed in 2 patients by a positive bone scan. However, a comparison of the PSA values in the biochemical-failure group shows that only patients with PSA relapse above 4.3 ng/ml had positive findings on 11-C-choline PET (see **Table 8**).

Furthermore, in the group of operated patients, all lesions recognized on 11-C-choline PET were also identified by conventional TRUS and CT scan. Not being able to identify tumour recurrence below a PSA of 4.3 ng/ml, 11-C-choline does not appear to add something to the conventional imaging techniques in this setting. But as stated by the authors, this group is too small and too heterogeneous to draw a final conclusion.

Picchio *et al.* (310) compared 11-C-choline PET with FDG PET in 100 men with biochemical relapse after radical prostatectomy (n=77) or external radiation (n=23). Besides a significantly better agreement with conventional imaging overall, 11-C-choline also detected 10 of 16 local recurrences demonstrated by conventional imaging, whereas 18-FDG only detected 6.

11-C-choline has some advantages over 18-FDG and 11-C-acetate, and this is reflected in the results of the clinical studies, but there are drawbacks such as the rapid bowel excretion and a very short half-life.

6.9.14 **18-F-Choline**

F-labelled choline could be a good alternative for C-labelled choline owing to its longer half-life. Unfortunately, this isotope is characterized by a rapid urinary excretion, the compound appear in the urinary bladder three to five minutes after injection, and meets the same restrictions as FDG (311,312).

TABLE 8 PSA relapse in patients treated for localized prostate cancer by radical prostatectomy (RP) or external beam radiation (EBR). The values in bold go with positive findings on 11-C-choline PET (310).

RP	0.5	0.9	0.9	1.0	1.9	3.5	4.3	4.5	4.5	4.9	8.5	22.3	35.7
EBR					2.3	5	7	16.1	22.8	27	31.4	103	120

6.9.15 18-F-Fluorodihydrotestosterone

18-F-fluorodihydrotestosterone (18F-FDHT) in the form of 16-beta-18-fluoro-5 alpha dihydrotestosterone is a radiolabelled analogue of dihydrotestosterone, the primary ligand of the androgen receptor (313). In a pilot study by Larson *et al.*, 18F-DHT was found to localize to tumour sites in patients with progressive clinically metastatic prostate cancers (298); however, the appropriate use of this modality still remains to be determined. Ongoing studies are conducted to find out whether 18F-FDHT uptake in prostate cancer cells is indicative for well differentiated disease, likely to respond to androgen withdrawal.

6.9.16 99mTc-labelled bombesin

Another novel radiotracer under investigation is 99mTc-labelled bombesin. Bombesin is a neuropeptide that is produced by several adenocarcinomas, including prostate cancer. De Vincentis *et al.* demonstrated increased uptake when scanning with bombesin in 12 of 12 patients with biopsyconfirmed primary prostate cancer, and identified 4 patients with positive lymph nodes, all of which were confirmed on pathologic analysis after surgery (297).

Positron emission tomography imaging, either with FDG or one of the newer isotopes, can be further enhanced by fusion of the images with more traditional axial images. Computerized tomography has been the most widely used for PET fusion imaging with encouraging initial results (314-316).

6.9.17 Conclusion

Positron emission tomography is an appealing new imaging technique for prostate cancer due to its ability to view the whole body with reduced irradiation, which is particularly interesting in a disease that may spread anywhere in the body. The radiation dose for a PET scan is about equal to that of a conventional CT, whereas the information obtained on PET scan may demand for several CT scans, e.g. chest, abdomen, pelvis, and brain.

The basic biophysical principles of PET sustain its application for early diagnosis of prostate cancer and for detection of early local recurrence of prostate cancer. Clinical research with different radiotracers shows that there are still many obstacles to its introduction in the clinical setting: the availability of the isotopes, some with a short half-life, their applicability in the first region of interest being the small pelvis, and the 4–5 mm limited spatial resolution of the images. But it is clear that based on the preliminary results, PET deserves further attention with more clinical trials. F-labelled tracers suffer from a rapid urinary excretion, C-labelled tracers from a rapid intestinal excretion. These problems might be solved in the future. Attempts have already been made to reduce the bladder activity by forced diuresis or by constant bladder irrigation with an indwelling catheter, but with no improvement in results. Problems in recognizing the landmarks or the exact anatomic localization of PET hotspots can be solved my PET-CT or PET-MRI fusion technology.

Until further clinical research has shown much better results, PET cannot be regarded as a useful tool for initial detection or local staging of prostate cancer.

But the most interesting application in the future could be the identification of recurrent disease after treatment with curative intent.

6.10 Indium-111 Capromab Pendetide Scanning (ProstaScint®)

6.10.1 Introduction

The ProstaScint (In-111 capromab pendetide) scan (Cytogen Corporation, Princeton, NJ, US) uses a radiolabelled murine monoclonal antibody targeted at the intracellular epitope of the prostatespecific membrane antigen (PSMA) molecule. Prostate-specific membrane antigen is expressed on both benign and malignant prostate epithelial cells. Approximately 95% of prostatic malignancies express PSMA, including those that have lost the ability to express prostate specific antigen (317-319). ProstaScint imaging is approved by the United States (US) Food and Drug Administration (FDA) for the diagnostic imaging and staging of newly diagnosed prostate cancer patients who are deemed at high risk for pelvic lymph node metastases. This indication is bolstered by the inability of standard cross-sectional imaging techniques such as CT and MRI to detect prostate cancer spread to lymph nodes that are not pathologically enlarged (320-327). In addition, ProstaScint is approved for postprostatectomy patients with a rising PSA level, for whom there is a clinical suspicion of metastatic disease (328-333). Uptake in the prostatic fossa on ProstaScint imaging can differentiate recurrent/ residual disease from benign post-operative changes and obviates the need for TRUS guided biopsies of the prostatic fossa to confirm the presence of malignancy. ProstaScint does not, however, distinguish between recurrent malignancy and iatrogenic residual benign prostatic tissue remaining in the prostatic fossa.

6.10.2 Technique

Patients receive an IV infusion of 5 mCi of radiolabelled antibody followed by planar and crosssectional single photon emission computerized tomography (SPECT) (317-319). Normal biodistribution of capromab pendetide includes the most intense activity in the liver, spleen, bone marrow, and blood pool. Varying levels of activity are observed in the kidneys, nasopharynx, spermatic cord, and genitalia. Prostatic soft tissue metastases are typically located more often in pelvic lymph nodes, but these tumour foci can be difficult to identify by ProstaScint scanning, due to masking by the bone marrow in the pelvis. As a result, detection of pelvic nodal disease requires careful evaluation with tomographic imaging and is further optimized by additional imaging adjustments. One adaptation employed to minimize false-positive ProstaScint readings is the performance of dual isotope imaging. Dual imaging using both ProstaScint and radiotracer-labelled RBCs allows for differentiation between true ProstaScint uptake and non-specific isotope collection in the vascular spaces and marrow (334). More recently, delayed images have been employed to avoid the confounding blood pool activity. Delayed images are acquired 3–5 days following administration of the isotope in order to allow for mobilization of the non-specifically bound isotope from the blood vessels and bowel while persistent uptake due to malignancy remains (335).

6.10.3 **Results**

In most studies to date, the predictive ability of ProstaScint is superior to that of CT/MRI in detecting lymph node metastases prior to therapy. Rosenthal *et al.* evaluated 152 men with high-risk disease (defined by Gleason score, PSA, and clinical stage) with ProstaScint prior to surgical staging (322). Of 64 patients with positive lymph nodes, 40 were read as positive by ProstaScint scan (PPV, 62%). Of 88 patients without lymph node metastases, 63 were read as negative by ProstaScint (specificity, 72%). Overall, the sensitivity for detection of lymph node metastases was 62%. In this study, CT and MRI demonstrated a PPV of only 4% and 15%, respectively (323).

Prostate-specific agent level, Gleason grade, and other clinical data have been incorporated into algorithms or nomograms to aid in the prediction of lymph node metastases in prostate cancer. Polascik and colleagues (324) compared the ability of several clinical algorithms and ProstaScint scans to predict lymphatic metastases in 198 men with clinical T2-3 disease undergoing radical prostatectomy. A total of 39% of patients in this high-risk cohort were found to have lymph node metastases at surgery. From 40.5% to 45.4% of lymph node–positive patients were predicted by clinical algorithm compared with 66.7% by ProstaScint alone. When integrating ProstaScint with clinical algorithms based upon Gleason score, disease volume, and pre-operative PSA level, a PPV of 72.1% could be achieved.

Several studies support the use of ProstaScint for prostatic fossa imaging (328-333). In one of the largest series published by Raj *et al.*, the authors found that of 255 men with PSA levels between 0.1 and 4.0 ng/ml after radical prostatectomy, uptake was noted in 72% (184 patients) (328). A total of 31% (78 patients) were noted to have local uptake (prostatic fossa) only. No minimum serum PSA value was needed to detect disease.

ProstaScint has also been evaluated for its role in demonstrating a durable response to salvage radiation (SRT) for isolated uptake to the prostatic fossa but with variable results (333, 336-339). Kahn and colleagues compiled the results of a multicentre study of men who underwent SRT after radical prostatectomy (336).

Of the 32 patients evaluated, 70% demonstrated a durable response to SRT with a normal extraprostatic scan compared with 22% with a scan positive outside the prostatic fossa. The median follow-up was 13 months after SRT. In contrast, in a study of 30 men, Thomas *et al.* found no significant difference in biochemical control, with a median follow-up of 34.5 months, between men who had a negative scan (31%) compared with men who had a positive scan in at least one location (either within or outside the prostate fossa) after SRT (337). More recently, Wilkinson and Chodak found only 7 of 15 men (46.7%) demonstrated a durable response to SRT with positive ProstaScint uptake to the prostatic fossa (332) (see **Figures 42** and **43**).

FIGURE 42

Early ProstaScint image showing pelvic lymph node metastasis (arrow), which is difficult to distinguish from background pooling of isotope in pelvic bone marrow and vasculature.



FIGURE 43

Posterior ProstaScint image (**Panel A**) show a focus of uptake in the left upper quadrant. RBC imaging (**Panel B**) shows this area has intense blood pool activity, ruling out malignant uptake. CT (**Panel C**) confirms this finding to be a splenule.



6.10.4 Limitations

As mentioned above, a major limitation of ProstaScint historically has been the collection of the isotope in blood pools and bowel. Recent improvements, particularly delayed imaging and fusion with cross-sectional imaging techniques, have significantly improved the previously low PPV of the technique (335,338).

Another fundamental limitation of the ProstaScint imaging is the necessity for an experienced interpreter (317-319). As the findings of the study are often subtle, with a high risk of false positive due to bowel or blood vessels overlying the lymph nodes, there may be an improvement in interpretive accuracy as the reader becomes more experienced. The importance of reader experience in interpretation of ProstaScint scans is made evident by the reported data regarding staging. Initially, the test had a reported sensitivity, specificity, and overall accuracy of 62, 72, and 68%, respectively (328); however, higher values have been reported in more recent studies (75, 86, and 81%, respectively) (327). The discouraging initial results experienced at most facilities has limited the widespread

use of this imaging technique in the past. To overcome the obstacle of the learning curve, Cytogen Corporation has developed a rigorous training program, called Partners In Excellence (PIE), and will not allow nuclear medicine specialists to purchase the isotope if they have not been trained through this program (340). A panel of expert consultants has also been convened by the company to provide nuclear radiologists with rapid second opinions at no charge.

Fusion of capromab pendetide uptake with anatomically detailed CT or MR images provides information on risk factors that strongly influence the prognosis and staging of prostate cancer, which includes factors both within and beyond PZ and TZ cancer, the implications of which have been discussed by Augustin *et al.* (341). Similarly, capromab pendetide uptake can be used to identify whether ECE and perineural invasion (342) or involvement of the seminal vesicles (343,344) has occurred. Risk factors beyond the prostate include the United States FDA-approved application of identifying lymphatic metastases. A representative example from a man evaluated with capromab SPECT/CT prior to surgery is provided in **Figures 44A** and **44B**.

6.10.5 Future study

Progress in optimizing techniques for fusing ProstaScint images with CT and MRI has the potential to vastly improve the utility of this imaging technique (339). Other monoclonal antibodies, such as human J591, are being investigated as a molecular-based imaging tool (345). Human J591 targets the extracellular domain of PSMA and has been accurate (>90%) in identifying metastatic prostate cancer in preliminary studies. Employing these PSMA antibodies for therapeutic purposes is another emerging application with wide-reaching implications (345).

6.11 Lymphotropic Magnetic Nanoparticle MRI

6.11.1 Introduction

The primary limitation of cross-sectional imaging techniques such as CT and MRI in the identification of lymph node metastases is the inability to identify disease within smaller (5-mm to 10-mm) lymph nodes. The infusion of lymphotropic magnetic nanoparticles prior to MRI provides a potential means for molecular imaging to discern normal lymphatic tissues from malignant deposits in lymph nodes that are not pathologically enlarged by standard imaging (346-348). These nanoparticles have a monocrystalline, inverse spiral, superparamagnetic iron oxide core, and contain a dense packing of dextrans to prolong their time in circulation and increase uptake by lymph nodes (347). The nanoparticles themselves measure an average of 2–3 nm in length (202). The mean overall particle size of the 10-kD dextrans is 28 nm (202). The nanoparticle-dextrans comprises the agent ferumoxtran-10, manufactured by Advanced Magnetics, Incorporated (Cambridge, MA) and marketed as Combidex by Cytogen Corporation (Princeton, NJ) in the United States and as Sinerem by Guerbet Group (Aulnay-sous-Bois, France) in Europe. In the literature, these nanopartiles are also termed monocrystalline iron oxide nanoparticles (MION), lymphotropic supermagnetic nanoparticles, lymphotropic superparamagnetic nanoparticles, ultrasmall superparamagnetic iron oxide (USPIO), superparamagnetic iron oxide (SPIO), and quantum dots (202,348-351).

FIGURE 44

A and B: An example case of SPECT/CT images of capromab activity in a patient prior to radical prostatectomy. Enhanced uptake in upper prostate (coronal and axial images). Panel:

- A demonstrates region of activity in the left base of the prostate gland.
- **B** provides all axial images from the region of the prostate taken from the same case.



6.11.2 Technique

After administration of ferumoxtran-10 (2.6 mg Fe/kg in 100 ml saline infused intravenously over 30 minutes), the lymphotropic nanoparticles are slowly extravasated from the intravascular space into the interstitial space, from which they are transported by way of lymphatic vessels, through interstitial lymphatic fluid transport, into the lymph node tissue (316). Within normal lymph nodes, nanoparticles are internalized by macrophages, and these intracellular iron-containing particles reduce the signal intensity of normally functioning nodes on post-contrast T2-weighted fast spin-echo or gradient-echo images through the magnetic susceptibility effects on iron oxide (348). Metastatic nodes, in which macrophages are replaced by tumour cells, show no significant change in signal intensity on post-contrast T2-weighted fast spin-echo or gradient-echo sequences. Even in lymph nodes with small foci of tumour, disturbances in lymph flow or in nodal architecture caused by the tiny metastases lead to abnormal patterns of accumulation of the nanoparticles that are detectable by MRI performed 24 to 36 hours after dosing (352).

By conventional MRI criteria, lymph nodes are classified as malignant if the short-axis diameter is elongated and exceeds 10 mm or is rounded and exceeds 8 mm. On MRI with lymphotropic magnetic nanoparticles, several criteria have been suggested by which nodes should be considered malignant on T2-weighted fast spin-echo or gradient-echo sequences after the administration of lymphotropic magnetic nanoparticles:

- A decrease in signal intensity by at least 30%; (202) (see Figure 45)
- 2. A heterogeneous signal (giving the entire node a mottled appearance), discrete focal defects (isolated islands of high signal intensity), or both; (202,349).
- **3.** Nodes with a central area of hyperintensity (excluding a fatty hilum identified on T1 sequence) but a peripheral decrease in signal intensity; (202,352)
- 4. Partial decreased signal intensity in more than 50% of the node area (352).

MRI nodal abnormalities in three patients with prostate cancer. As compared with conventional MRI (**Panel A**), MRI obtained 24 hours after the administration of lymphotropic superparamagnetic nanoparticles (**Panel B**) shows a homogeneous decrease in signal intensity due to the accumulation of lymphotropic superparamagnetic nanoparticles in a normal lymph node in the left iliac region (arrow). **Panel C** shows the corresponding histologic findings (hematoxylin and eosin [H&E], x125). Conventional MRI shows a high signal intensity in an unenlarged iliac lymph node completely replaced by tumour (arrow in **Panel D**). Nodal signal intensity remains high (arrow in **Panel E**). **Panel F** shows the corresponding histologic findings (H&E, x200). Conventional MRI shows high signal intensity in a retroperitoneal node with micrometastases (arrow in **Panel G**). MRI with lymphotropic superparamagnetic nanoparticles demonstrates two hyperintense foci (arrows in **Panel H**) within the node, corresponding to 2-mm metastases. Corresponding histologic analysis confirms the presence of adenocarcinoma within the node (**Panel I**, H&E, x200)



6.11.3 **Results**

The vast majority of studies investigating the clinical use of lyphotropic nanoparticles have grouped pelvic malignancies, including prostate cancer, into a single category for analysis (353-358). In the only prostate cancer series to date, published by Harisinghani *et al.*, 80 men with stage T1-3 prostate cancer had improved detection of nodal metastases by high resolution MRI following the administration of ferumoxtran-10 (202). In this series, 334 lymph nodes were resected at surgery; 63 nodes in 33 men were found to contain metastatic disease on histologic analysis.

Only 15 of 33 patients with lymph node metastases were detected by conventional MRI size criteria, while all 33 were detected by MRI following ferumoxtran-10 infusion. Overall, 90.5% of all positive lymph nodes, and 96.4% of metastases in lymph nodes 5–10 mm in size were identified by ferumoxtran-10 infusion. Only a 5% false-positive rate was observed. Unexpectedly, even very small metastases, less than 2 mm in diameter, were occasionally identified within normal-sized lymph nodes. Such microscopic tumour deposits are below the threshold of detection of any other imaging technique.

6.11.4 Limitations

The primary side effect of ferumoxtran-10 is an anaphylactoid reaction described as being similar to iodinated contrast. The Advanced Magnetics' January 2005 submission to the US FDA states that of the initial 131 patients receiving a bolus injection of undiluted Combidex, 3 (2.3%) had serious adverse events in the form of anaphylactoid reactions; one of these patients died of the anaphylactic reaction (352).

The company has foregone the prior bolus injection method of administration and now recommends dilution of the standard 2.6 mg Fe/kg dose in 100 ml saline to be infused over 30 minutes, stating that this technique not only significantly reduces the incidence of adverse events, but it also facilitates prompt intervention. The bolus technique was necessary to provide adequate liver/spleen imaging, but due to the adverse events, an indication for use of the agent in liver/spleen imaging is no longer being sought by the company. Since the introduction of the infusion technique, the rate of serious adverse events has dropped to 0.3% (5 of 1,930 subjects), which is less than a third of the rate seen with administration of iodinated contrast agents (352). The most frequent adverse events with the infusion technique were vasodilation (3.4%), rash (3.0%), back pain (2.4%), and pruritis (2.2%) (352). In patients complaining of back pain during infusion, the discomfort was alleviated by cessation of the infusion and restarting at a slower rate (202). Less common adverse reactions were urticaria, dyspnea, nausea, chest pain, sweating, and headache (352).

A dose-dependent sequestration of the particles in the liver has been demonstrated in rat models that persists for up to 63 days (359). This has been suggested to be the result of particle breakdown products and the induction of ferritin and hemosiderin with increasing iron cores/loading factors. No long-term sequelae of this sequestration has been described.

6.11.5 Future studies

In the US, a conditional approvable letter was received from the FDA for Combidex on March 24, 2005. Final approval depends on publication of data for specific tumour sites rather than including all pelvic tumours into a single category. Ongoing studies are also taking place to optimize acquisition strategies, such as the timing of contrast material-enhanced imaging, the section thickness, the imaging plane, the imaging parameters for T2-weighted sequences, particle coating, and particle size (360,361). Alternative agents, particularly anionic iron oxide nanoparticles, are also being evaluated (362).

While there are great implications for improved imaging with this technology, there is an even greater amount of excitement in the development of fluorescent nanoparticles to aid in node dissection, antibody-conjugated nanoparticles, and nanoparticle-linked therapeutic agents (350,363).

6.12 Bone Scintigraphy

Bone scintigraphy utilizing 99mTc-labelled phosphates and phosphonates shows gradual accumulation in metabolically active bone with increased uptake in areas of greater metabolic activity. This includes not only areas of malignancy, but also inflammatory changes such as fracture healing. It is well recognized that these studies are useful in the assessment of patients with carcinoma of the prostate to determine the presence of metastatic disease, but it is also well recognized that not all patients require this study either during their initial assessment or during treatment and monitoring. The study is sensitive for the detection of osteoblastic bone metastasis, which commonly occurs in patients with metastatic prostate cancer (see **Figure 46**).

Though bone surveys have been used in the past, studies have indicated that of those with normal findings, 23% demonstrate bone metastasis on scintigraphy (364). Prior to the use of PSA, studies also demonstrated the value of routine use of bone scintigraphy in categorizing patients. Sixteen percent of patients having clinically localized disease were upstaged to having metastatic disease.

With the widespread use of PSA in both the evaluation and staging of patients with carcinoma of the prostate, there has been a decreased utilization of bone scintigraphy in the assessment of these patients. In those with clinically localized disease based on PSA and biopsy characteristics (Gleason grade, tumour volume), it is evident that bone scintigraphy is not useful in those having a low likelihood for tumour metastases. Chybowski and associates demonstrated that those patients with positive bone scans have significantly higher PSAs (median, 158.0 ng/ml) than those with negative studies (median, 11.3 ng/ml). Of those men with a PSA >20 ng/ml, 1% had a positive bone scan (365).

FIGURE 46

Bone scan demonstrating metastatic disease from carcinoma of the prostate.



Others have also tried to determine the indications for performing bone scan studies, and Lee and associates demonstrated on a multivariant analysis that Gleason score, PSA level, and clinical stage were significant independent predictors for positive bone scintigraphy in patients with carcinoma of the prostate. For instance, of 308 men with Gleason 2–7, PSA level of \leq 50 ng/ml, and clinical stage T2b, only 3 were found to have a positive bone scan. The incidence of positive scans increase as these parameters increase and for those men with PSA level >50 ng/ml, almost half had positive bone scans (366).

Though several decades ago, bone scans were used routinely in all patients with newly diagnosed prostate cancer, and these studies were also used in the follow-up of patients, oftentimes on an annual basis, it is now recognized that they can be performed more selectively. Those patients in a low-risk category for presence of advanced disease do not require bone scans. Similarly those patients with a stable PSA levels and lack of symptoms of bone pain or elevation of alkaline phosphatase, either at the time of diagnosis or during the periods of follow-up, do not require these studies either. Should a rapid change occur in PSA levels with a short doubling time or the patient develops bone pain consistent with metastatic disease, bone scans are certainly indicated. Finally, bone scans are occasionally obtained during clinical trials or in those patients in whom a baseline evaluation is required.

6.13 Recommendations

Randomized controlled trials assessing the value of each of the imaging modalities regarding diagnosis, staging and treatment assessment are limited to non-existent. Most reports are of individual or institutional experience. *The Committee is therefore unable to make definitive recommendation based on evidence-based medicine grading systems.*

ULTRASONOGRAPHY

- No evidence to demonstrate the role of ultrasound in the diagnosis of prostate cancer.
- Transrectal prostate ultrasonography is not helpful for detection of microscopic involvement of capsule or seminal vesicles in patients diagnosed with carcinoma of the prostate.
- TRUS is helpful in assisting in prostate biopsy and permitting sampling of specific zones within the prostate or biopsying ultrasound abnormalities. Costs need to be considered in the processing of biopsy cores. A specific number of cores to be obtained with each biopsy cannot be recommended, although data suggests that increasing the number of cores taken during biopsy increases grading accuracy.
- New developments in the use of contrast agents and the role of colour and power Doppler appear to be helpful in identification of malignancies, but more studies correlating imaging and anatomical findings are needed.
- Transrectal prostate ultrasound is useful in the assessment of total prostate and specific zonal size. These measurements are useful in determining PSA density.

СТ

- Has a limited role for local and/or distant staging.
- The applications are based on biopsy information and prostate-specific information.
- Internal architecture of the prostate is not seen, and microscopic invasion cannot be visualized.

MRI

- Provides excellent identification of prostate zonal anatomy.
- Microscopic invasion of the seminal vesicles and prostatic capsule cannot be reliably identified.
- Magnetic resonance imaging has limitations for clinical staging, although the finding of ECE on MRI is associated with greater risk for locally advanced disease.
- Diffusion-weighted MRI images may add to the ability to distinguish and characterize tumours in the anterior and central zones of the prostate.
- The role of MRI in the evaluation of men with suspicious clinical features prior to planned re-biopsy with targeting of suspicious regions detected with MRI is under investigation.

MRS

- Magnetic resonance spectroscopy offers much potential for identification of specific abnormalities with the prostate.
- The technique will potentially assist in biopsy and local therapy, but greater experience is needed.

PET

- Positron emission tomography is helpful in identifying local recurrence following local therapy (*e.g.* radical prostatectomy, radiation therapy).
- The technique offers potential in detection of metastatic disease, particularly lymph node involvement.
- Positron emission tomography is useful in identifying abnormal areas within the prostate.

SPECT

- Single photon emission computerized tomography offers potential in the detection of metastatic disease.
- The technique is able to potentially identify abnormal areas within the prostate, which has the potential for local therapy and assisting in biopsy.
- As with PET, SPECT offers the potential of identifying local recurrence and differentiating from metastatic disease in patients with PSA elevation following local therapy.

BONE SCINTIGRAPHY

- Bone scintigraphy is useful in detecting bone metastases. It is helpful in selecting patients for the study who have a reasonable likelihood for bone involvement based on clinical information (*e.g.* bone pain, elevation of PSA levels (0.10 ng/ml), grade, and volume obtained of tumour on biopsy).
- The use of bone scintigraphy after treatment in asymptomatic patients with low/stable or undetectable PSA is not necessary unless participating in a research protocol.

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A Brief History of Prostate Carcinoma Treatments

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7.1 Introduction

The history of the understanding and management of prostatic diseases is a remarkable story. Leonardo da Vinci (1452-1519) was the master of anatomical and medical illustration, but he never gave a description of the prostate gland, which can be explained by the fact that most of his knowledge was drawn from anatomical dissections of castrated oxen that only had small and atrophied prostates. Andreas Vesalius (1514-1564) produced the first illustration of a prostate but did not describe the seminal vesicles. Ambroise Paré (1510-1590) recognized obstructive symptoms in the prostate and related them to what he called "caruncles". Paré even suggested that catheters or sounds with sharp-ridged surfaces be used to remove these "carnosities" or "caruncles" by repeatedly passing these instruments through the urethra. The first authentic description of the prostate is in fact attributed to Niccolo Massa, a Venetian physician who died in 1563. It was Regnier de Graaf (1641-1673) who gave the first detailed anatomy of the prostate, the seminal vesicles and the ejaculatory ducts in his 1668 Tractus de virorum organis generationi inservientibus, de clysteribus et de usu siphonis in anatomia. Jean Riolan (1577/80-1657) was the first to suggest that the neck of the bladder could be obstructed by the prostate in 1649. John Hunter (1728-1793) described the symptoms due to a large prostate and its effects on the bladder and kidneys. He was also aware that these symptoms did not occur in castrated individuals. The potential influence of hormones on symptoms related to benign prostatic enlargement was also later recognized by Mansell Moullin from the London Hospital in the 1890s, as well as by William White from Philadelphia who showed some symptomatic improvement in a small number of patients after castration. However, this practice was never universally accepted. Vasectomy also enjoyed a short period of popularity for the treatment of prostatic disease. Most men at that time had to rely on a catheter (often kept in a gentleman's walking cane) to give them relief from prostatic obstruction. It was said that your outcome was better if you could afford to engage someone to catheterize you, or your stature was such that you could successfully see what you were doing.

7.2 **The Beginnings of Surgical Treatments for Prostate Diseases**

By the end of the 19th century, with developments in anesthesia and Joseph Lord Lister's contribution to anti-sepsis and asepsis, open surgery suddenly became possible and the quest to find the ideal treatment for the management of prostatic obstruction and, later, prostate cancer has by now become part of the urological folklore.

The prostate is situated deep within the bony pelvis and the position of the prostate gland necessitates intricate operative surgery. The gland surrounds the posterior urethra bound at both ends by sphincters. It lies close to the lower end of the ureter and rectum, and critically close to those structures concerned not only with continence but erectile function as well. Blood supply is not readily accessible and the regional lymph nodes can be difficult to dissect. Prior to antiseptic surgery, direct surgery on the prostate gland was seldom attempted, although portions of the gland had already been removed during the course of operations for stones.

In the period between 1834 and the early part of the 20th century, attempts were made to evaluate what had become nine surgical approaches to the prostate. Of the great surgeons of the day, Theodor Billroth (1829-1894) performed the first trans-pubic prostatectomy in 1867. Bernhard von Langenbeck (1810-1887) divided the suspensory ligament of the penis to perform an infra-pubic prostatectomy compromised, of course, by the arch of the pubis with limitations of space and the venous plexus of Santorini. This technique was quickly abandoned. In 1873, Jean-Nicolas Demarquay (1814-1875) practised trans-rectal prostatectomy for both benign hyperplasia and carcinoma of the prostate. The disadvantages were limited exposure and the dangers inherent to working in an infected field, and the likelihood of an urethro-rectal fistula as a postoperative complication. Another obsolete method that enjoyed extensive use was the ischiorectal prostatectomy. This technique was first evaluated in 1890 by the Viennese surgeon Leopold von Dittel (1815-1898). With the patient in a prone position, an incision was made from the coccyx to the right of the anus, the rectum retracted to the left, and the prostate exposed by way of the right ischiorectal fossa. In Dittel's procedure he excised portions of the lateral lobes, leaving a cuff of tissue surrounding the prostatic urethra, through which a catheter was placed. In 1919 Friedrich Voelker (1872-1955) reported using this approach in 56 cases. An isolated reference to sacral prostatectomy was made by J. Boeckel in 1908. All these methods became obselete very quickly. The suprapubic, retropubic, transurethral and perineal approaches were the ones that endured and became established.

7.3 Suprapubic Approach to the Prostate

In this period, with the race on to perfect open prostate surgery, there were those such as Sir Henry Thompson (1820-1904) of London who felt that there was no future in prostate surgery, certainly for benign disease, as the bladder function had been irreversibly damaged by the obstructive process. There was no doubt that the operations before 1895 were only partial prostatectomies. Towards the end of the 19th century there developed a race and a controversy as to who defined and performed the first successful supra-pubic approach to prostatectomy. William Bellfield in Chicago in 1886 probably removed a large middle lobe only. Arthur McGill in Leeds in 1887 operated for bladder tumour but almost certainly performed enucleation of the prostate. However, the credit for establishing the supra-pubic trans-vesical approach for prostate surgery and removing the whole prostate goes to Eugene Fuller (1858-1930) of New York. He described the operation in 1895 to the American Association of Genito-Urinary Surgeons in a paper entitled "Six successful and successive cases of prostatectomy". His boxing partner and fellow professor, Ramon Guiteras (1858-1917), apparently modified the technique by inserting two fingers in the rectum to apply counter-pressure during the prostatectomy. However, one of the legends of urology is that Guiteras stayed with Sir Peter Freyer (1852-1921) in London on his way to the International Urology meeting in Paris where he was presenting a paper entitled "The present status of the treatment of prostatic hypertrophy in the United States". Sir Peter Freyer reported in 1901 that he performed a new-and what appeared

to be a formidable–operation for the radical cure of prostate hypertrophy by what he described as total enucleation of the enlarged prostate. This was published in the British Medical Journal in July 1901. His technique was very similar to Fuller's technique except that he scored the urothelium with his fingernail rather than scissors (unlike Fuller's), and applied rectal counter-pressure like Guiteras. Freyer gave no credit or mention to either Fuller or Guiteras. There were heated exchanges in the journals about Freyer's plagiarism of a technique without due acknowledgement, which divided the profession. However, there is no doubt that Freyer single-handedly popularised the operation. By 1920 he had performed 1,600 operations with this technique and erroneously believed that he was performing a total prostatectomy, which could have had implications for the management of prostate cancer.

7.4 Perineal Approach to the Prostate

In parallel to the development of the open supra-pubic prostatectomy was the alternative of perineal prostatectomy. These were performed in the US by Francis S. Watson in 1889, William Wishard in 1890, and George Goodfellow in 1891. Most of these procedures were essentially traumatic, blind transurethral avulsions of the prostate gland, although George Goodfellow (1855-1910), from Tombstone and Tuscon, performed the first perineal enucleation of the enlarged prostate in 1891. In the July and November 1904 issues of JAMA, he first reported on 72 cases which he had operated with only two fatalities. Many surgeons followed him and contributed various technical aspects to perineal prostatectomy. Goodfellow's definition of a good surgeon was one who had "the eye of an eagle, the heart of a lion, and the touch of a woman."

Hugh Hampton Young (1870-1945) from Baltimore performed the first perineal prostatectomy for benign prostatic hypertrophy in l898 exerting counter-pressure on the gland through a suprapubic incision. In 1903, Young carried out his first careful dissection of the perineum and enucleation of the hypertrophied gland under direct vision. There was a morbidity and mortality with hemorrhage and sepsis. However, in 1923 he was able to report a series of 1,049 prostatectomies over a 20-year period with a commendable mortality rate at the time of 3.4%. In fact, 144 patients from this group were between 75 and 95 years of age!

On the basis of his mastering the perineal prostatectomy for benign disease, Young carried out in 1904 what is believed to have been the first radical perineal prostatectomy for prostate cancer. He improved the technique and was able to develop adequate retraction by the use of a special prostatic retractor which he described. The perineal approach by Young in 1904 was standard for over forty years and was the surgical treatment for prostate cancer. Rigid criteria for operability evolved and were defined in time. In 1965 a total of 466 operations were performed at Johns Hopkins Hospital with, in fact, few changes to Young's original technique. The changes that had evolved included better anesthesia, hemostasis, and tissue diagnosis with frozen section allowing transection of the membranous urethra to leave as much urethral length as possible.

7.5 Retropubic Approach to the Prostate

Not much had really changed in surgical technique, with transvesical prostatectomy performed for benign disease and radical perineal prostatectomy for prostate cancer described by Young. "Prostatectomia suprapubica extravesicali" had already been performed in 1908 by W. J. van Stockum (1860-1913) from Rotterdam, The Netherlands, and published one year later in the German journal, *Zentralblatt der Chirurgie*.

However, the wide clinical establishment of the retropubic approach to the prostate after 1945 must be credited to the Irish surgeon Terence J. Millin (1903-1980) from All Saints Hospital, London. Millin devised a new approach of retropubic prostatectomy for benign disease and published a report of 20 cases in *Lancet* in 1945. He comments on the high mortality of the transvesical operations, their lengthy postoperative stay and sepsis. He criticises the perineal operation for needing a long apprenticeship before achieving good outcomes. He also refers to the dreaded complication of urethrorectal fistula. From Millin's description, William W. Scott and Charles B. Huggins performed the first retropubic prostatectomy for benign disease at Johns Hopkins.

The retropubic approach for radical prostatectomy was therefore a natural development to Millin, and he, in fact, probably performed his first case for chronic prostatitis rather than cancer. He was aware of the risk to urinary continence postoperatively, but felt strongly that the alternatives of estrogen or sub-capsular orchidectomy were not going to cure prostate cancer, and that early diagnosis and surgery offered the best chance of cure. There were no details of his results, but for the incontinent patient, he describes encircling loops of catgut around the corpus spongiosum.

Richard Chute (1954) recognized that Hugh H. Young, Hugh J. Jewett and others obtained a 44-51% five-year cure rate of prostate cancer by radical perineal prostatectomy. It was recognized that cancer control was related to tumour stage, and that the ideal patient was someone with a discrete palpable nodule upon digital examination, and organ-confined disease upon histopathological examination. The retropubic approach was favoured, as it provided a valuable opportunity for lymph node staging. Nevertheless, few surgeons performed radical prostatectomy. Surgery had a mortality of almost 3% and the complications–which included haemorrhage, stricture and fistula, as well as incontinence and impotence–meant that many surgeons preferred the alternatives of hormone treatment or radio-therapy. In the 1950s, the leading protagonists of radical retropubic prostatectomy for prostate cancer had done no more than 50 cases each. Few patients were thought to be suitable for radical prostatectomy, and by the late 1970s only 7% of men with localized disease underwent surgical treatment.

7.6 Modern Radical Prostatectomy

Born in 1938, Patrick C. Walsh was appointed Professor and Director of Surgery at the James Buchanan Brady Urological Institute at the Johns Hopkins Hospital in 1974, taking over from Dr. Scott. At that time, Millin's retropubic operation for benign disease was extremely popular, but his description of radical prostatectomy for treatment of prostate cancer was less widely accepted because of the blood loss and the morbidity. Walsh was instrumental in bringing about a formal understanding of the anatomy of the dorsal venous complex and the course of the pelvic nerves, which helped circumvent these complications.

Based on anatomical studies of Santorini's plexus, Walsh, together with W.G. Reiner, reported a technique to reduce blood loss. Their landmark paper published in the *Journal of Urology* in 1979 described the trifurcation of the dorsal vein of the penis and the relationship of the pubo-prostatic ligaments, with which the modern surgeon is now so familiar, although there were to be modifications over the next 20 years. The understanding of anatomy was the basis upon which hinged the understanding and safety of the procedure. Once he understood the vasculature of the prostate, Walsh's next objective was to preserve potency and continence. It was known that the pelvic nerves travelled between the rectum and the prostate, but the relationship to the prostate was not known. Walsh had a chance meeting with Pieter J. Donker at the American Urological Association Meeting in Miami in 1977 and visited him in Leiden, The Netherlands. Donker demonstrated the pelvic nerves in an infant cadaver and showed that the nerves passed outside the prostate and Denonvilliers fascia. The possibility of removing the prostate without injury to the nerves was now recognized. The first successful nervesparing operation was performed in 1982 on a 52 year-old man. The second landmark paper was published in 1983 and described the nerve-sparing operation. Walsh's description therefore forms the basis from which evolved the modern technique of radical retropubic prostatectomy.

The evolution of radical prostatectomy for prostate cancer is just over a century old. Initially feared because of its complications and difficulty, we have found that the operation can be carried out safely, thanks principally to advances in surgical anatomy. Refinements have been developed, and morbidity progressively reduced. Over the last two decades, we have seen the impact of laparoscopy and robotic surgery that follow the same surgical principles.

7.7 Radiation Therapy for Prostate Cancer

As early as 1897, it was concluded that X-rays could be used for therapeutic, as well as diagnostic purposes. In 1904, A. Imbert and L. Imbert used X-ray therapy to treat an advanced prostatic malignancy and claimed an excellent result. In 1908, both Minet and Desnos employed radium carried to the prostatic urethra embedded in a catheter. Paschkis from Vienna devised the first cystoscopic radium applicator in 1911. The radium capsule was situated at the very tip of the instrument and no external fxation of the cystoscope holding it in the correct position was used. In 1913, Pasteau and Degrais from Paris reported several cases of prostate cancer which had been successfully treated by the use of radium introduced through a simple coudé gum catheter.

In 1912, Marie Curie published the "Theory of Radioactivity". The investigation of X-ray radiation for patient therapy moved into the clinical routine in the early 1920s. Prostate cancer radiation treatment has been used in the United States since 1915. Benjamin Barringer (1877-1953), Chief at New York Memorial Hospital, was the first to perfom transperineal implantation of radium into the prostate in hundreds of cases between 1915 and 1930, first published in JAMA in 1917. Initially, Barringer used radon-tipped needles introduced through the perineum and left for several hours. Later, gold-encapsulated radon seeds were applied by the same route as permanent implants. In the 1930s, Barringer also experimented with the open approach for radon seed application using a template for controlled placement of the seeds, much like today's technique. He even combined the perineal and suprabupic approaches for brachytherapy of the prostate.

The next technique used in radiotherapy was by electron beam X-rays, but the latter could not penetrate deeply enough to irradiate the affected tissue, and physicians soon realized the significant risk of skin cancer. In 1923, Waters and Pierson used "deep X-ray therapy" for the treatment of bony metastasis, producing effective relief of pain. This was the first-ever report of using X-rays for pain relief in prostate cancer. With the introduction of androgen control therapy, the use of radiation therapy was largely abandoned for many years. After World War II, there was renewed interest in radiotherapy. In 1952, Rubin Flocks (1906-1975) introduced a new method which consisted of an injection of radioactive gold (198Au) into the malignant prostate, regional lymph glands and adjacent tissues via suprapubic exposure.

Physicians were able to use megavoltage in prostate cancer treatment. They used radioactive isotopes from cobalt-60. But by the 1980s, radiation oncologists began using the linear accelerator, which increased the speed of particles and allowed for the most process aiming of the beam. Today, we have many refinements in radiotherapy including conformal techniques and brachytherapy, and constant progress is being made in rendering radiotherapy safe and effective.

7.8 Hormonal Therapy of Prostate Cancer

It was John Hunter in the 18th century who first discussed the association between prostatic growth and testicular function. He demonstrated that castration in young male animals prevented the further growth of the prostate, while in the adult, it caused atrophy. His findings were published by his brother-in-law, Everard Home, in his 1811 textbook, *Practical observation on the treatment of the diseases of the prostate gland*. Hunter saw further evidence for his theory of a functional interaction between the testicles and the prostate in the fact that eunuchs never suffered from symptoms of an enlarged prostate. Based on these early investigations, the turn of the century saw a growing interest in surgical removal of the testicles, or castration as treatment for enlarged prostates.

According to Ricketts, it was Louis Auguste Mercier who in 1857 first performed orchidectomy for the treatment of enlarged prostate. In 1893, William White and others strongly advocated the procedure, but its lack of effect in benign prostatic hyperplasia, and the high mortality rate of the operation at that time led to its abandonment. But for the high mortality rate, its beneficial effect on prostatic carcinoma might have been discovered fifty years earlier. In 1890, James Ewing Mears proposed vasectomy to shrink the enlarged prostate. This method was later endorsed by Mears, who advocated it as an alternative to castration because of the high mortality of the latter. Without any effect, vasectomy too, promptly fell into oblivion.

The experimental studies which established the knowledge about androgen control of malignant prostatic growth were initiated by Charles Brenton Huggins (1901-1997) in 1939. Huggins was born in Halifax, Nova Scotia, in 1901–the same year the first Nobel Prize was awarded. At the age of 23, he obtained his M.D. from Harvard Medical School and became a surgical resident at Ann Arbor, Michigan. After this training, Huggins was invited by Phemister, Chairman of Surgery at the new University of Chicago Medical School and Billings Hospital, to join the faculty. The credo of this new school was scientific scholarship as the basis of clinical excellence. Despite the fact that he had no specialized knowledge of urology, Huggins was soon asked to organize a urology service. Phemister obviously preferred to appoint a surgeon with a scientific background to learn urology, rather than a urologist with little scientific training to learn science. Huggins travelled abroad to acquire further experience, and it was during a stay at the Lister Institute in London that he first came across the role of phosphate esters in osteoblastic activity, and the related increase in serum alkaline phosphatase. This phenomenon later became a crucial point in his research on prostate cancer. Huggins finally concluded that "Evidence derived from castration on benign prostatic hypertrophy supports the view that the prostatic epithelium at least is under control of the testis".

He demonstrated that castration in man decreases the height of prostatic epithelial cells in normal prostatic tissue, that the male hormone, testosterone, stimulates secretory activity of dogs' prostatic cells, and that the female hormone, diethylstilbestrol, inhibits this activity. He further proved that acid phosphatase was elevated in metastatic prostate cancer, and that castration relieved pain and caused stabilization or regression of local and metastatic osseous lesions. Huggins believed that

continued reduction of androgen levels was necessary to keep tumour growth under control and advocated castration as the method of choice. During the next 50 years, Huggins reported more than 230 scientific articles.

Huggins' fundamental investigations into the influence of the endocrine system on the development of human malignancy were honoured by the Nobel Prize for Medicine and Physiology in 1966, which he was awarded together with Peyton Rous (1879-1970). Rous developed the first virally induced solid tumours in animal experiments, the Rous-chicken sarcoma. He was one of the first scientists to realize and estimate the importance of Huggins' findings.

7.9 Radioorchiectomy

Another form of castration, the technique of radioorchiectomy (castration by irradiation) is historically connected mainly with Arbor D. Munger. During the 1941 Annual Meeting of the American Urological Association in Colarado Springs, it was Munger who reported on 11 patients out of 76 treated with a combination of resection and combined irradiation of the prostate and the testicles. The testicles were irradiated with 500 Roentgen. Eight of these 11 patients survived, whereas the percentage of men dying under the other therapeutic regimes was much higher. This work began in 1935, so that Munger is generally regarded as the pioneer of radioorchiectomy in prostate cancer therapy.

More surprising still is a rather obscure report by Edward L. Keyes and Russell S. Ferguson from New York City, who had been performing radioorchiectomies in several patients since 1932 and published the following statement in the 6th edition of their textbook, *Urology*, in 1936: "Extension of the life of the patient in comfort, even in the face of widespread metastatic disease, may be accomplished by taking advantage of our present theoretical knowledge of the physiology of growth of neoplastic prostatic epithelium. To this end, we have combined roentgen castration with local irradiation to good effect in a number of cases. The apparent influence of the castration is to decrease the rate of growth and even in some instances to arrest the growth entirely in both the primary tumour and in the metastatic lesions of the disease."

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Treatment of Low- and Intermediate-Risk Prostate Cancer: Definition, Treatment Options and Outcomes of Care

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8.1 Scope of Problem Worldwide

Prostate cancer is a major health concern worldwide. Internationally, prostate cancer is the second most frequently diagnosed cancer in men, accounting for 14% (903,500) of the total new cancer cases in 2008. (1) Older age, race and family history are well-established risk factors for prostate cancer. (1) Incidence rates of prostate cancer vary by more than 25-fold worldwide. The highest rates are in North American, Australia/New Zealand and Europe, while the lowest incidence are seen in South-Central Asia. (2) This variation is thought to be multi-factorial. PSA testing and completeness of cancer registration are thought to contribute to discrepancies. (3) As Western influences become more pronounced in less developed countries, prostate cancer incidence rates in those countries are tending to increase, even though the prevalence of PSA testing may be relatively low. (3) The PSA test was first introduced into clinical practice in the United States (US) in the mid-late 1980s. (4.5) It was then used in Canada, the United Kingdom (UK) and Australia soon thereafter. (3) Looking at temporal trends in prostate cancer incidence, rates rose rapidly in the early 1990s, soon after the introduction of PSA testing, followed by a sharp decline due to a smaller pool of prevalent cases. (1) Estimates of the prevalence of PSA testing were highest in the US as of 2001, 75% of men over 50 reported ever having a PSA test. Similar rates were reported in Canada and Australia. (3) While PSA testing has been shown to increase prostate cancer detection, its use remains controversial. Interestingly, increases in incidence have been observed in countries with a lower prevalence of PSA testing, such as Japan and other Asian countries, and thought to be consistent with the increasing influences of Western culture dietary and exercise practices. (3)

Race also affects prostate cancer incidence. This is evident in the United in 2004, 165.8 per 100,000 men of African-American descent were diagnosed compared to 105.5 of European descent. (3) It is thought that genetic susceptibility to prostate cancer, different levels of androgenic activity within the prostate gland, differences in diet, socioeconomic status, environmental and other lifestyle factors may contribute. (6)

With an estimated 6% (258,400) of deaths, prostate cancer is the sixth leading cause of death from cancer in men. (1.2) There is less variation in mortality rates worldwide (10-fold), relative to incidence, presumably due to PSA testing. (2) Race has been found to affect mortality rates. Mortality rates are generally high in predominantly black populations (Caribbean, 26.3 per 100,000 and sub-Saharan Africa, 18-19 per 100,000), very low in Asia and intermediate in Europe and Oceania. (2,3) Decreasing mortality rates are noted in more developed countries, such as Australia, Canada, the UK, the US, Italy, and Norway likely due to a combination of earlier diagnosis with PSA testing, improved treatment, or some combination of these or other factors. (1,3)

The relative proportions of men in the low- and intermediate-risk groups at presentation vary across continents with higher proportions in the US and other countries where screening with serum PSA is more common.

8.2 **Definition of Disease States**

Defining prostate cancer risk (i.e. risk of progression, recurrence and/or metastases) is critical in aiding practitioners and patients in treatment comparison and planning. Risk of disease progression is stratified based on success of definitive local therapy and/or disease progression in the absence of treatment. (7) Risk stratification schemes consider prostate specific antigen (PSA), Gleason grade clinical (T) stage and, sometimes, disease volume as assessed by biopsy. The National Comprehensive Cancer Network (NCCN) has created guidelines that incorporate these variables which then assigns patients to either low-, intermediate- or high-risk disease groups. (8)

While there are several different clinical staging systems for prostate cancer, a widely used system is the American Joint Committee on Cancer (AJCC) Tumour Node Metastasis (TNM) System. This system considers extent of primary tumour, presence/absence of spread to lymph nodes and presence/absence of distant metastasis. Notably, the 1992 AJCC guidelines defined T2 disease as palpable organ confined prostate cancer. Subdivisions of T2 disease included T2a (tumour involving half of a lobe or less), T2b (tumour involving more than half of a single lobe but not both lobes) and T2c (tumour involving both lobes). In 1997 these were redefined as the subdivision of T2 disease was reduced from 3 (T2a, T2b and T2c) to 2 substages by combining single lobe disease (T2a and T2b) into a single stage, now termed T2a. (10) While this was found to negatively impact outcome (10), current guidelines remained unchanged. Patients may undergo radiographic staging with CT and bone scan if the Gleason score is >7 or the PSA is > 20 ng/mL. (11) There are concerns of widespread overuse of imaging tests for staging clinically localized prostate. While Cooperberg *et al* did find that the rates of testing have decreased for all risk groups, patients in the low- and intermediate-risk categories continues to undergo unnecessary testing. (12) It is estimated that inappropriate use of radiographic imaging occurs in 22.7% of men diagnosed with low-risk disease. (13)

The most commonly used histological grading system is the Gleason score. (11) The score is obtained when the two most predominant patterns are added. Low-grade cancers are those with no pattern 4 or 5 score. Intermediate grade cancers are those with a primary pattern 3 and a secondary pattern 4 score. High-grade tumours are generally those with primary patterns 4 or 5 (Gleason score 4/3, 8-10).

Partin *et al.* first described a predictive method which achieved widespread use for counselling men with clinically localized prostate cancer. (14) Subsequently, two popular risk assessment schemes were separately introduced in 1998 by D'Amico and Kattan. D'Amico *et al.* first described a three-level risk classification system, i.e. low-, intermediate- and high-risk. (8) Low-risk disease was defined as up to stage T2a, PSA level ≤ 10 ng/mL and total Gleason score ≤ 6 while intermediate-risk was described as stage T2b or Gleason score of 7 or PSA level >10 and ≤ 20 ng/mL. Similarly Kattan *et al.* created a nomogram based on similar preoperative disease characteristics. These tools are relatively easy to use by both practitioners and patients, and the clinical validity of these tools has also been extensively evaluated. (15-17)

Several factors such as accuracy, generalizability and validity must be considered prior to widespread clinical implementation of risk stratification tools. (18,19) Mitchell *et al.* found that stratifying a community-based cohort, Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE),

to either D'Amico or Kattan nomogram resulted in statistically significant differences in predicting 5-year freedom from progression (FFP) especially for the intermediate and high risk groups. (20) No current model can predict risk with perfect accuracy. Only a few models predict metastasis (21-23) and cancer-specific death. (24,25) Current research is underway to improve risk estimation accuracy by way of independent prognostic factors,(26) novel biomolecular markers and advanced imaging techniques. (27, 28) While more than 100 predictive tools have been published, and fewer both internally and externally validated (14,18,19,29,30), the American Urological Association (AUA) currently endorses the 3-level classification described by D'Amico *et al.* (19) The NCCN, recognizing increasing concerns of over-treatment secondary from over-diagnosis, recently defined a new risk category termed "very low risk." This refers to T1c disease, Gleason score \leq 6, PSA <10 ng/ml, fewer than three biopsy cores positive with \leq 50% cancer in each core and a PSA density of <0.15 ng/ml/g. (7)

In 2005, the University of California, San Francisco (UCSF) developed the Cancer of the Prostate Risk Assessment (CAPRA) score to assist in predicting recurrence-free survival and pathological tumour stage after radical prostatectomy. The CAPRA score, which ranges from 0-10, considers age, preoperative PSA, Gleason sum, clinical T stage and percent positive biopsy cores. (31) This tool is not only externally validated by both national and international institutions (32,33), but is also simple to apply. (32) Similar to the D'Amico classification scheme, (8) UCSF's CAPRA score can be collapsed with three risk groups. (31) The CAPRA was used to evaluate clinical endpoints in a cohort of over 10,000 patients with clinically localized prostate cancer where treatment included either primary radical prostatectomy, radiation therapy (external beam or interstitial), androgen deprivation monotherapy, or watchful waiting/active surveillance. Importantly, this tool was accurate in predicting both cancer-specific mortality (CSM) as well as overall mortality (OM). (34)

8.3 Treatment Options and Decision Support

Primary treatment for clinically localized prostate cancer is a complex decision as there are various therapeutic options available often with equal oncologic efficacy but differing adverse effects. (35) There is insufficient evidence to recommend one treatment option over another for most prostate cancer disease states. (36) Important factors in deciding primary treatment include probability of cure, life expectancy, medical comorbidities, potential adverse effects and patient preference. (7)

Contemporary management of low- and intermediate-risk prostate cancer often involves decision support, and these tools to enhance clinical and shared decision making are widely available for both urologic clinicians and patients. For clinicians, predictive models have been developed to estimate risk of recurrence of disease with and without active treatment. (14,31,37) Other statistical analytic approaches use Markov models to provide estimates of the best management approach. (38) While evidence is available to support the use of models based on clinical features, the evidence for the feasibility of incorporating patient preferences in clinically-based algorithms is incomplete. (39)

Because of the often small differences in survival time among management strategies for low- and intermediate-risk prostate cancer, shared decision making involving both patient and clinician is of great interest. (40) Patient values, goals, and preferences in these decisions are considered to be especially important because the selection of the best strategy involves complex trade-offs among side effects and long term life impacts. A variety of patient decision aids have been developed to facilitate shared decision making for prostate cancer. Most provide extensive information about the characteristics of treatments and their expected outcomes. Evidence suggests that decision aids focused on prostate cancer treatment choices increase patient knowledge and involvement in decision making, and decrease patient distress. (41) Additional work is needed to determine whether decision aids improve the alignment of prostate cancer management choices with patient preferences.

8.4 Treatment Modalities and Outcomes

8.4.1 Active surveillance

An increasing divergence in localized prostate cancer incidence and mortality is causing concern about overdiagnosis and subsequent overtreatment of low-risk disease. (11) Overdiagnosis of prostate cancer with PSA-based screening has been estimated to occur in 23 to 67% of cases, (42,43) leading to high rates of overtreatment. (44) Furthermore, fewer than 10% of low-grade prostate cancers managed conservatively may experience a cancer-specific death after 20 years of follow up. (45,46) Many advocate that treatment should be selective, reflecting each patient's comorbidities, disease characteristics and preferences. (47,48) Currently, active surveillance (AS) is an initial management strategy comprised of close monitoring of PSA levels combined with periodic imaging and serial prostate biopsies. (47) This scheme is likely to change as new surveillance strategies are refined. AS fundamentally aims to provide definitive treatment for men if localized disease progresses, but ultimately reduces the risk of treatment related complications in the proportion of men whose disease does not progress. (11) As the percentage of men diagnosed with low-risk disease is increasing (13,49), AS is increasingly considered in treatment planning.

Current guidelines recommend patients with low risk disease be considered for AS. (7,11) While little is known about disease progression in patients who have intermediate-risk disease, AS may be a viable option for carefully selected men with intermediate-risk prostate cancer. (50) Patients with relatively short life-expectancy or certain comorbid conditions may also be appropriate candidates. (47) For a variety of reasons, relatively few men who are appropriate candidates are managed with AS. (13,44,51,52)

Although the exact criteria for undergoing AS is inconsistent, generally those with low, stable serum PSA measurements (<10 ng/ml), no Gleason pattern 4 or 5, clinical stage T1-2a, and \leq 33% of cores positive using an extended core biopsy scheme are appropriate. Disease progression is evaluated with serial PSA testing, digital rectal examination (DRE) and prostate biopsies. If the tumour shows evidence of progression (i.e. increased grade, volume, or stage), patients may then undergo

intervention (i.e. surgery or radiation). (53) A recent review found that men who initially opt for AS ultimately undergo intervention in 14% to 41% of cases. (47) As no marker of disease progression has been well-validated (11,47), discovery of novel biomarkers or imaging is a major goal of current research. Improvement in disease-progression markers and continued integration of clinical data will allow practitioners to better define and educate patients about the significant role AS plays in prostate cancer management. (48)

Risks associated with AS include patient anxiety over disease progression, inherent risk of serial prostatic biopsy (54,55), and most concerning, disease progression. Multiple studies have revealed significant pathology upgrading but less upstaging among men who underwent radical prostatectomy but met criteria for AS. (56,57) Given the interval between initial diagnosis and progression, this likely reflects a sampling artifact as opposed to true tumour progression. (58)

A growing body of evidence supports the use of AS for men with low-risk (47,53,59,60) and very selected patients with intermediate-risk disease. (50) It appears to be a safe, cost-effective treatment strategy for selected men with localized prostate cancer. (47) Delayed treatment does not appear to risk significantly poorer outcomes in those who elect AS versus immediate treatment. (61) A recent meta-analysis (47) found that several academic institutions are currently evaluating cohorts of men treated by active surveillance protocols (see Table 1). (50,59,62-64) Follow up of these cohorts ranges from 22 - 82 months. The weighted mean overall survival, cancer-specific survival and PSA-free survival was 92%, 99% and 67%, respectively. The proportions of men moving from surveillance to active treatment range from 14-41%. (47) Active surveillance was associated with greatest quality-adjusted life expectancy when compared to open prostatectomy, RT and brachytherapy. (65) No report has published evidence that has disproved possibility of cure after a period of active surveillance. (50,61,63) As the median follow-up in the current literature is about a decade, it is unclear if AS is appropriate in men with very long (>15 year) life expectancies.

The much anticipated results from the large randomized controlled trial, Prostate Cancer Intervention Versus Observation Trial (PIVOT), were recently presented at the 2011 American Urological Association (AUA) meeting. It was revealed that there was no prostate cancer-specific mortality benefit associated with surgery compared to observation for patients with low-intermediate-risk disease. (Of note, a difference was noted in men with PSA >10 or Gleason score 8 to 10, which may include intermediate-risk patients). (66) This contrasts with previous reports of a European study which found that prostatectomy offered survival advantage. (67) However, those in this later study likely had higher risk disease, at least by volume.

Further prospective trials on active surveillance outcomes are underway. The START (Surveillance Therapy Against Radical Treatment) trial currently randomly assigns patients to surveillance versus patient choice for surgery or radiation. This study is sponsored jointly by the National Cancer Institute of Canada and four US oncology groups. (68) The ProtecT (Prostate testing for cancer and Treatment) study is sponsored by nine centres in the United Kingdom. Between 1999 and 2008, around 2,000 patients were randomly assigned to surgery, radiation therapy or active surveillance. (69,70) It is expected that these studies will provide future information on safety and efficacy of active surveillance.

TABLE 1 Active Surveillance

Author	Study Date	No. of Patients	Median Age	Mean Follow- up (months)	BCFS	Weighted Average	
Low Risk							
Soloway <i>et al.</i> (62)	2010	230	64	32	86	64.807302	
Tosoian <i>et al.</i> (63)	2011	633	66	32	54		
van den Bergh <i>et al.</i> (64)	2009	616	66	52	68		
Adamy <i>et al.</i> (178)	2011	238	64	22	NA		
van As <i>et al.</i> (179)	2007	326*	67	22	73		
Dall'Era <i>et al.</i> (180)	2008	208*	63	43	74		
Klotz <i>et al.</i> (59)	2010	453*	70	82	70		
*Combines low-/intermediate-risk, data not used for weighted average calculation							
Intermediate Risk							
Cooperberg <i>et al.</i> (50)	2011	90	65	51	61	61	

Table modified with permission from "Active Surveillance for Prostate Cancer: Progress and Promise" by Cooperberg et al.

8.4.2 Surgery

Radical prostatectomy (RP) is a common and effective option for patients with localized prostate cancer who have a life expectancy of 10 years or more. (7) Radical prostatectomy can be performed using either retropubic or perineal incision or by using a laparoscopic with or without robotic-assisted technique. Lymph node dissection appears to be unnecessary in those with low-risk disease. (71) An extended pelvic lymph node dissection (PLND) may be preferred to limited PLND in those with intermediate- and high-risk disease. This would include removal of all node-bearing tissue from an area founded by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the pelvic floor posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. (7) The decision to include nerve-sparing procedure is largely dependent on tumour characteristics and, to a lesser extent, a patient's sexual function. Urinary incontinence can be reduced by preservation of urethral length beyond the apex of the prostate and avoiding damage to the distal sphincter in addition to bladder neck preservation. (7)

Robotic-assisted radical prostatectomy (RARP) was introduced in 2000 for treatment of localized prostate cancer. Much controversy exists regarding the cost-effectiveness of robotic technology. Despite this, there has been a major shift towards use of this modality. (72) Media coverage and internet marketing of robotic-assisted surgery is widespread and thought to contribute to increased use. (72)

Data on long-term prostate cancer specific mortality after radical prostatectomy has been assessed. When compared to watchful waiting strategy, RP was associated with lower risk of cancer recurrence, cancer-related death, and improved survival for patients with low-intermediate-risk disease after 15-year follow-up. (67) High volume surgeons in high volume centres generally appear to provide better oncologic and morbidity outcomes. (7,73,74) Eggener *et al.* reported 15-year outcome data from a large cohort of patients who underwent radical prostatectomy. Two thirds of the cohort had organ-confined disease; overall mortality for this group was 0.8%. A Gleason score 8–10 and seminal vesicle invasion were found to be the strongest predictors of mortality. (75) As radical prostatectomy is increasingly performed on younger men with lower risk disease (76), these findings question the appropriateness of immediate surgical treatment in men with pathologically well-differentiated, limited volume and organ confined cancer; even for those with advanced stage (T3, N+) and/or high-score disease (Gleason score 8-10) mortality varied betwenn 63 to 74%.

Unfortunately, most literature comparing different forms of prostatectomy is observational and retrospective. Data comparing open (ORP), laparoscopic (LRP) and robotic assisted (RARP) prostatectomy found that while there was less blood loss associated with minimally invasive procedures, no functional or early oncologic outcome data could be established with certainty. (77) Similarly, Medicare-linked data from the Surveillance, Epidemiology and End Results (SEER), compared minimally invasive (robotic and laparoscopic) to open prostatectomy and found that minimally invasive surgery was associated with a shorter hospital stay, less risk of blood transfusion and fewer surgical complications. However, rates of genitourinary toxicity, such as incontinence as well as erectile dysfunction, were higher in the minimally invasive treatment group. (78) A large systemic review identified 37 studies comparing open, laparoscopic and robotic-assisted prostatectomy. The authors found few differences in oncologic or HRQL outcomes, further reiterating the need for long-term prospective data. (79) Table 2 demonstrates weighted biochemical-free survival rates for differing modalities.

Increasing use of robotic-assisted prostatectomy has prompted questions regarding efficacy of this procedure over open prostatectomy. Use of open prostatectomy is decreasing; perineal prostatectomy accounted for only 2% of all prostatectomies in 2007 according to data linked from SEER-Medicare. (80) The Institute of Medicine comparative effectiveness research (CER) report specifically lists open versus robotic prostatectomy on a list of 100 research priorities. (81)

8.4.3 Radiation

8.4.3.1 External beam radiotherapy

External beam radiation therapy (EBRT) is one of the principal treatment options for patients with clinically or regionally localized prostate cancer. There have been recent technological advances in EBRT since it was first utilized in the 1930s. Computed tomography (CT) scan-based treatment planning has allowed for improved accuracy in radiation delivery, more precise targeting of the prostate, seminal vesicles and lymph nodes. Since the 1990s, intensity modulation radiotherapy (IMRT) further refined treatment delivery. Improved dose localization allowed for increased doses without increased toxicity. Dose escalations have been shown to improve biochemical outcomes. (82-85) Use of 3D conformal and IMRT techniques are now considered standard of care.

While the previous standard dose EBRT was 70 Gy, higher doses to 80 Gy can be delivered safely. Doses of 75.6-79.2 Gy are appropriate in patients with low- and intermediate-risk disease. (7,83,84) Image-guided radiation therapy (IGRT) is required if 78 Gy or higher is used. (7) For patients at intermediate-risk, RCTs have shown that a short-course (i.e. 4-6 months) of hormonal therapy and

standard or dose escalation EBRT should be considered. Patients with intermediate-risk cancer may benefit from pelvic lymph node irradiation. (7) Contraindications to pelvic radiation include prior pelvic irradiation, active inflammatory bowel disease and permanent foley catheter placement.

Multiple studies have demonstrated survival benefit when short courses of ADT are added to radiotherapy in patients with intermediate- and high-risk disease. (86-89) Jones *et al.* recently published data on a large prospective cohort of low- and intermediate-risk patients who were randomly assigned to radiotherapy alone or radiotherapy with four months of ADT. Secondary analysis of data according to risk group revealed that overall survival and improvement in disease-specific mortality was limited to intermediate-risk group (NNT = 14). (90) While there was no survival advantage in men with low-risk disease, the addition to ADT was found to significantly lower the incidence of biochemical failure and positive findings on repeat biopsy at two years (see Table 2). These findings have prompted the initiation of the RTOG 08-15 trial which will further address the efficacy of short term ADT combined with radiotherapy for patients with intermediate-risk disease. (90) Hormonal therapy, in both limited duration as well as primary treatment, negatively impacts the HRQOL. (91)

Modern use of external beam radiotherapy is assisted by 3DCRT or IMRT, allowing for safe administration of higher doses of radiation and improved recurrence-free survival. (84) Despite this, there is no evidence that demonstrates improvement in cancer-specific mortality (CSM) or all-cause mortality (ACM). (36,92,93) Data comparing effectiveness of 3D-CRT versus IMRT is limited. IMRT has been associated with reduced rates of biochemical recurrence, but with concurrent rise in urinary toxicity rates (Table 2). (94)

Proton beams can be used as an alternative radiation source, since theoretically, protons may reach deeply-located tumours with less damage to surrounding tissues. However, proton therapy has yet to demonstrate superiority over contemporary photon therapy. (7)

Stereotactic body radiotherapy (SBRT), such as the CyberKnife has recently emerged as an alternative, non-invasive technique to deliver hypofractionated radiotherapy to the prostate, comparable in many respects to HDR brachytherapy. (95) It has been shown to be efficacious for the treatment of localized prostate cancer in the UK since the 1980s. (96) The CyperKnife is reported to provide excellent dose coverage of the prostate and was well tolerated. (97) Recent data on this modality reveals that it is safe (98) and efficacious in treating low- (95,99,100) and intermediate-risk (100) disease. Several studies have demonstrated favourable biochemical outcomes in patients with localized disease. (98,101)

8.4.3.2 Brachytherapy

While permanent interstitial brachytherapy (BT) of the prostate has been performed since the 1960s, it was not until the 1980s that a transperineal approach was employed for definitive treatment of prostate cancer. (11) Typically, a preoperative transrectal ultrasound-based volume study is performed. Radioactive needles can be implanted under either ultrasound or MRI guidance. The recommended dose for BT when used as monotherapy is 145 Gy for 125 Iodine and 125 Gy for 103-Palladium. When used in combination with external beam radiotherapy (40-50 Gy standard), 110 Gy and 100

Gy should be given respectively. (7) Subsequent post procedure dosimetry is standard. An excellent implant is defined as one in which 90% or more of the prostate gland volume receives at least 100% of the prescription dose. (102)

Both low- and many intermediate-risk patients are considered appropriate candidates for this therapy. (103) Several guidelines state that permanent BT as monotherapy is appropriate for patients with low-risk disease. (7.35) Cancer control rates compare to surgery (>90%) for patients with low-risk disease. (104) Few studies report outcomes comparing EBRT and BT. Brachytherapy alone has been shown to be superior to EBRT in terms of biochemical recurrence but at the cost of higher late urinary toxicity. (105,106) More commonly, men are treated with combination EBRT and BT. A systematic review found a survival benefit when EBRT is combined with brachytherapy. (107) Combination therapy is also associated with increased morbidity. (108)

Patients with intermediate-risk disease may benefit from combination BT/ EBRT with or without a short course of hormone therapy. (7)

It can be difficult to implant patients who have very large or very small prostates, a high International Prostate Symptom score (IPSS), or have had previous transurethral resection of prostate (TURP). Neoadjuvent androgen deprivation (either with the use of LHRH agonists or 5 alpha reductase inhibitors) may be used to decrease the size of the prostate if necessary. (7)

Temporary high-dose rate (HDR) brachytherapy was first performed in the mid 1990s for treatment of prostate cancer. Radiation is delivered through transperineal-placed hollow needles with subsequent removal of the radioactive substance at the end of each treatment. High-dose rate BT has most commonly been given in conjunction with external beam therapy in those with intermediate- and high-risk disease. However, it has also been used selectively as monotherapy. Long-term outcomes are limited as only a few publications describing this option since the year 2000 have shown promising outcomes (109). Barkoti *et al.* recently reported results of a Phase II, single-institution, prospective study using HDR brachytherapy as a monotherapy for low- and intermediate-risk prostate cancer patients. While this study demonstrated favourable morbidity profiles, longer follow-up and application in a multi-institutional setting are necessary to determine efficacy. (109)

Recent studies have showed promising outcomes of combined HDR BT and EBRT treatment. It was found that HDR BT combined with EBRT versus EBRT alone allows for greater improvement in biochemical relapse-free survival in low- and intermediate-risk patients. (110,111) Several studies have also evaluated the efficacy of IMRT when combined with HDR. Deutsch *et al.* found an improvement in 5-year PSA relapse free survival in patients treated with IMRT combined with HDR BT versus IMRT alone. The most significant benefit was found in the intermediate-risk patients. (112) In a prospective, randomized trial, Wilder *et al.* reported similar biochemical disease-free survival outcomes and toxicity rates for HDR combined with IMRT compared to IMRT alone in patients with low- and intermediate-risk disease. (113) Table 2 depicts biochemical outcomes from multiple studies.

8.4.4 **Primary hormonal therapy**

Primary hormonal therapy is not considered "standard" treatment for localized disease according to national guidelines. (11) Overall use of androgen deprivation therapy (ADT) has leveled and may be starting to decline. (114) Other sections discuss the roles of androgen deprivation therapy (ADT) as neoadjuvant or adjuvent therapy.

8.4.5 Cryotherapy

Cryosurgery is a percutaneous, transperineal approach that achieves tumour control by damaging tissue by local freezing. Since its earliest application in the treatment of localized prostate cancer in the 1960s, (115) important advancements have been made in this approach. The introduction of third generation cryosurgical machines in 2000 has allowed for improved intraoperative treatment planning and monitoring as well as reduced morbidity and complication rates according to the 2008 AUA "Best Practice Statement on Cryosurgery for the Treatment of Localized Prostate Cancer". (116) In the mid-1990s, when cryosurgery began to emerge as salvage therapy option for patients who had failed radiation therapy, the AUA removed cryosurgical ablation from investigative therapies list. (116) Cryosurgery has since been employed as primary treatment for localized prostate cancer, as both primary whole gland and focal ablation.

Attempts have been made to define biochemical recurrence for whole gland cryosurgery. Several reports have used PSA levels to assess treatment success for patients with low- and intermediate-risk disease. (117-121) Prognostic factors for favourable PSA outcomes such as number of positive biopsy cores have been investigated. (122)

The reported 5-year biochemical disease-free rates defined by various PSA endpoints is reported to be as high as 92% for patients with low- and intermediate-risk disease (see Table 2). (123) Cheetham *et al.* recently reported 87% overall 10-year prostate-cancer specific survival. (124) These results suggest that cryotherapy is reasonably safe and is associated with at least short-term oncologic efficacy. (125) Very low rates of urinary retention, rectal fistula and urinary incontinence were reported. (120) However, rates of impotence appear high. (126)

8.4.6 High intensity focused ultrasound (HIFU)

There is increasing interest in the use of high intensity focused ultrasound (HIFU) as a minimally invasive approach for treatment of localized prostate cancer. While thermal ablative technology was initially developed in the 1940s, HIFU is a relatively novel modality used for primary treatment of localized prostate cancer. (127)

High intensity focused ultrasound employs a probe that emits a beam of focused ultrasound to generate areas of intense heat to destroy cancer tissue. The probe has a cooling balloon around it to protect nearby areas from the high temperature. (128) Popular devices include the Sonoblate[™] device (Focus Surgery Inc.) and the Ablatherm[™] device (EDAP TMS). While neither device is currently FDA-approved in the US, both are approved for commercial distribution in Canada, the European Union, South Korea and Russia. (128)

Overall very little data on cancer-specific outcomes related to use of HIFU exist. A recent report by Lukka *et al.* of the Genitourinary Cancer Disease Site Group (GU DSG) found that only case series exist (see Table 2). These report relatively short follow-up times and only biopsy or PSA-related outcomes. Data from a 176 cohort of Japanese men found that over half of patients experienced a rapid-rise in PSA after undergoing primary HIFU for treatment of clinically localized prostate cancer. A significant association between the presence of rapid-rise PSA and the risk of biochemical failure was found only in the low- and intermediate-risk group. (129) This group further found that while retreatment with HIFU was relatively common and varied among series, retreatment outcomes were generally not investigated.

Because of the lack of outcomes data, it is difficult to draw conclusions about long-term efficacy. (128) Overall, preliminary results describe 5-year disease-free survival rates ranging from 55 to 95% in five of the series reviewed. (128)

	RARP (181-184)	ORP (183-194)	LRP (184,188, 195-199)	IMRT (200-205)	BT (204-213)	3D-CRT (84,203, 204,206)	EBRT+BT (204,210, 214-217)	EBRT + ADT (88-90, 218, 219)	Cryo- therapy (117-121, 220, 221)	HIFU (222-225)
Low-Risk Patients										
Weighted 5-year BCFS^	91.3	87.7	91.7	88.2	84.5	84.3	92.4∞	73.6	84.0ª	79.5
Ranges	87.5-98.1	82-96.7	88.1-98.2	74.1-100	59-94	74-90	80-100	(70-74)	69-91.8	(60-92)
Weighted 10-year BCFS*	92.6*	76.0	77	84.2	89.4**		88.0∞		89.0ª	
Ranges	92.6	72-83.1	77	81-89	79-99		85.8-90		81-92	
Intermedia	ate-Risk Pat	ients								
Weighted 5-year BCFS^	78.2	78.2	89.1	87.7	77.2	85.7	92.0∞	69.2	74.0ª	75.3
Ranges	74.8-89.6	59-93.5	74-98.2	74.1-99.5	59-94	74-91.3	80-96.1	56-72	71-89	69-79
Weighted 10-year BCFS*	69.8*	71.0	50	79.6	77.3		85.0∞		86.5ª	
Ranges	69.8	59.7-77	50	78-81	61-96		83-87		81-89	

TABLE 2 Estimates of Biochemical Recurrence-free Survival

^ includes 3-year outcome data

* Includes 8- and 12-year outcome data

∞ includes studies with high dose rate (HDR) BT

^a includes Phoenix, ASTRO definitions

Abbreviations (for Tables 2 to 5): 3D-CRT = 3D conformal radiation therapy , BT = brachytherapy, EBRT + BT = external beam radiation therapy (radiotherapy) + brachytherapy, HIFU = high intensity focused ultrasound, IMRT = intensity modulation radiotherapy, LRP = laparoscopic prostatectomy, ORP = open prostatectomy, RARP = robotic-assisted prostatectomy.

8.4.7 Focal therapy

There are growing concerns regarding overdiagnosis and overtreatment of many prostate cancers. Focal, rather than whole gland techniques, are increasingly considered for patients with localized, limited disease as these procedures may be less invasive, are associated with less morbidity and less costly. (130) Such an approach should not replace active surveillance, but should be considered in those who will not accept surveillance or those with focal disease of a grade or volume which justifies treatment. Appropriate candidates include those with either unifocal disease alone or focal disease associated with foci of very low grade/volume disease elsewhere. It is believed that as high as 20% to 30% of men with low-risk disease are appropriate candidates for organ-sparing therapy. (131) Established ablative therapies include cryoablation and HIFU. Tumour destruction is achieved by inducing tissue-targeted temperature extremes. (130) These modalities are further described in the following sections. Other forms include photodynamic therapy (PDT) which employs a photosensitizing drug that accumulates within the prostate. Radiofrequency interstitial tumour ablation (RITA) uses low-level radio-frequency energy to heat, allowing for coagulative necrosis of tissue. Fewer studies exist on PDT and RITA but preliminary results are promising. (132)

Focal therapy relies on identifying the largest tumour focus, or the "index tumour." The index tumour has been shown to contain the highest Gleason sum and is used as a powerful predictor of biochemical failure after prostatectomy. It is critical to define and target the index tumour to achieve effective treatment. (133) Focal therapy traditionally relies on a sufficient number of prostate biopsies to guide the surgeon in performing effective treatment. (116) But there are also concerns that TRUS guided biopsy can account for under-grading or missed tumour and thus magnetic resonance imaging (MRI) has been employed to increase sensitivity of cancer detection. (134)

MRI assists in patient selection, therapy performance, and short- and long-term follow-up of focal ablative therapy. MRI-guided therapy can precisely localize some tumour foci as well as the ability to monitor therapy using MR thermography. (135) The sensitivity and specificity of MRI can be improved by the use of dynamic contrast-enhanced (DCE) MRI, diffusion-weighted imaging (DWI), and magnetic resonance spectroscopic imaging (MRSI) platforms. (133)

It is proposed that using aggressive biopsy schemes in combination with MRI will further refine target localization. (130) While focal therapy may have advantages as a minimally invasive technique with reduced morbidity, randomized-controlled trials are needed to demonstrate long-term oncologic efficacy. In the US, there is greater experience with cryoablation as HIFU is currently not available for clinical use. Focal or "nerve-sparing" cryosurgery was developed out of concerns for preserving potency and reducing morbidity.

Several reports describe success of focal cryosurgery as primary treatment in patients with localized prostate cancer, as short-term oncologic outcomes are at least comparable to whole-gland cryoablation. (136-140) The largest published experience with this "male lumpectomy" was described by Onik *et al.* After a mean follow-up of 4.5 years, 94% of patients were without disease recurrence and 90% were continent. (140)

8.5 Morbidity

Prostate cancer therapy morbidity differs significantly by treatment type. Comparing primary treatment with rate of specific morbidities is complex and inconsistent. (11) Prostate cancer therapy most commonly affects urinary and gastrointestinal systems, as well as sexual function, and typically described as early or late adverse effects (see **Tables 3-6**). The common adverse effects of prostate cancer therapy are often reported with large variability. Assessing morbidity data is confounded by the fact that many adverse effects are known to occur with time even without intervention. For example, gradual physiologic loss of erections occurs over time in surveillance groups. Current prostate cancer therapy morbidity data is further criticized by the fact that what is known is based on single-point estimates of function which lack patient-weighted preferences for early versus late function or decision-regret measures. (11) Prostate cancer therapy morbidity can be assessed by way of serial administration of well-validated instruments during clinical evaluation. For example, sexual function can be comprehensively and accurately assessed by the UCLA Prostate Cancer Index (PCI) or Expanded Prostate Cancer Index Composite (EPIC). (141)

8.5.1 Urinary tract toxicity

Risk of urinary incontinence depends on both primary prostate cancer treatment modality as well as patient pre-treatment comorbidities. Incidence of transient urinary incontinence is highest after radical prostatectomy, occurring in 3-74% of patients, and infrequent in surveillance groups. (11) Urinary incontinence following BT occurs in 0-61% patients and in 0-73% of patients after EBRT. (11) The large variance in incidence for multiple treatment modalities likely reflects differences in defining, reporting, diagnosing and quantifying urinary incontinence. (11) In a longitudinal prospective cohort comparing adverse effect profiles for different primary therapies, overall urinary function and bother outcomes scored significantly higher after brachytherapy or cryotherapy compared to open radical prostatectomy and robotic assisted laparoscopic radical prostatectomy. (142) Wilt *et al.*, conversely found that urinary incontinence was higher in the radical prostatectomy group compared to radiation or hormonal treatment from the PCOS data. (36)

Several comorbidities and other factors predispose patients to urinary incontinence. Sanda *et al.* found that older age at the time of prostatectomy was associated with a higher rate of urinary incontinence. (91) Obesity has also been linked. (143) Men with larger volume prostates have lower levels of continence up to two years after radical prostatectomy in one report. (144)

Irritative and obstructive urinary symptoms are common, but typically transient, after EBRT. (11) Interestingly, both irritative and obstructive urinary symptoms have been shown to improve after prostatectomy. (91,145,146) Hematuria is common after interstitial brachytherapy, occurring in up to 100% of patients within one cohort. (147)

Late urinary tract morbidity, such as urethral stricture disease has been associated with most forms of prostate cancer therapy. The reported incidence of urethral stricture after prostatectomy is variable; an estimated 2.7% to 25.7% of patients who undergo surgery experience this late toxicity and typically present within the first six months after the procedure. (148) A large retrospective cohort compared

stricture rates of open (ORP) versus robotic-assisted radical prostatectomy (RARP). Stricture incidence was 2.6% and 1.4% for ORP and RARP respectively. It was suggested that enhanced magnification and running bladder anastomosis allowed for lower incidence in the robotic-assisted laparoscopic prostatectomy (RALP) group. (149) Radiation therapy modalities, especially when used in combination, are also associated with urethral stricture disease. Elliot *et al.* described an incidence of stricture in 1.8%, 1.7% and 5.2% of patients who underwent BT, EBRT and combined BT and EBRT. (148) In patients who underwent combination HDR BT and EBRT, there was an associated 11% incidence of urethral stricture after six years of follow-up. (150)

8.5.2 Gastrointestinal Toxicity

Gastrointestinal (GI) morbidity is largely associated with radiation therapies. Diarrhea and loose stools occur in up to 25-50% of men after EBRT and can persist for up to three years. (11) Certain GI toxicity, such as rectal bleeding and diarrhea, occur more frequently when BT is combined with EBRT compared to BT monotherapy. (151) The Prostate Cancer Outcomes Study (PCOS) compared men who underwent either radical prostatectomy or EBRT for localized prostate cancer and found that bowel side effects occurred at higher rates in those who received EBRT. (152) Rectal pain is also associated with EBRT and occurs in 12-39% of patients during the first year after treatment. (153,154)

Rectal morbidity occurs in up to 10% of patients and is the most common complication after brachytherapy. Symptoms of late toxicity include rectal bleeding, ulceration, tenesmus and pain and its incidence is dependent on dose. (11)

8.5.3 Sexual function

There has been a major shift in recent years in functional outcomes documentation. Physician reports in sexual health outcomes are now being replaced by documentation of patient perspectives drawn from validated sexual health outcome surveys. (11) Reported risk of erectile dysfunction (ED) is complicated by variability in assessment as well as definition amongst the reported literature. More comprehensive tools are needed. (155) Risk is further confounded by biased treatment recommendations such that younger and more functional men tend to undergo surgery while older and less functional men tend to receive radiotherapy. Use of oral agents to treat erectile dysfunction further complicates the data.

General definitions of potency involve the ability to have erections adequate for vaginal penetration or intercourse without use of medication or other assistance. (156) The National Institutes of Health Consensus on Erectile Dysfunction defines impotence as "the inability to achieve or maintain an erection sufficient for satisfactory sexual performance." (17).

Erectile dysfunction occurs in as high as 60 to 90% of patients one or more years after prostate cancer therapy. (11) Incidence of ED after prostatectomy is reported as high as 88% after five years. (157) Overwhelming evidence has found that nerve-sparing approaches during prostatectomy decrease the risk of post-surgical erectile dysfunction. (91, 158-160) After radiotherapy, the reported incidence ranges from 0-85% one or more years after treatment, but three-dimensional conformal techniques reduce risk. (11) Up to 50% of men who undergo brachytherapy experience erectile dysfunction. (1)

Erectile dysfunction has been observed in active surveillance groups as well, as mentioned previously. (161) Short-term use of adjuvant hormonal therapy combined with either radiotherapy or brachytherapy was associated with poorer sexual health outcomes. (91) Asterling *et al.* prospectively assessed ED in a cohort of patients who underwent cryosurgery as primary treatment for localized prostate cancer. All patients experience some degree of sexual dysfunction after the procedure. After two years, there was a reported 39% recovery rate, suggesting a nerve-sparing approach must be undertaken. (126)

Patient-specific factors also affect outcomes as mentioned previously. Sanda *et al.* found that older age, large prostate size and high pre-treatment PSA negatively impacted sexual function after multiple prostate cancer treatment modalities. (91)

	RARP	ORP	LRP
Anastomotic leakage	3.5	5.2	5.7
UTI	1.6	1.8	2.2
Urinary Retention	1.3	1.5	3.3
Bleeding episode	1.2	6.8	0.8
Urethral stricture	1.0	3.2	1.2
Lymphocele	0.7	1.8	1.5
Hernia	0.6	1.8	2.1
lleus	0.6	1.3	0.1
Rectal injury	0.5	1.1	1.4
DVT	0.5	1.1	0.5
PE	0.5	0.5	0.5
Sepsis	0.3	0.3	0.1
MI	0.2	0.2	0.2

TABLE 3 Surgical Complications (%)

Table modified from "Primary treatments for clinically-localized prostate cancer: a comprehensive lifetime cost-utility analysis," Cooperberg et al. 2011 (226).

TABLE 4 Acute Radiation Toxicity (%)

	IMRT	BT	3D-CRT	EBRT+BT
GI Grade 2	15.6	2.5	33.9	10.3
GI Grade \geq 3	0.1	0.0	2.2	1.1
GU Grade 2	29.8	11.2	35.2	19.5
GU Grade \geq 3	2.3	3.3	3.7	3.5

Table modified from "Primary treatments for clinically-localized prostate cancer: a comprehensive lifetime cost-utility analysis," Cooperberg *et al.* 2011 (226).

TABLE 5 Urinary Toxicity % (ranges)

Urinary Incontinence	RARP	ORP	LRP	IMRT	BT	3D-CRT	EBRT+BT
Incontinence at 12 months	9 (7-11)	11 (8-14)	10 (8-13)				
GI Grade ≥ 2				1.6 (0.8-2.4%)	1.3 (0.6-1.9%)	6.3 (3.1-9.4%)	2.3 (1.13-3.4)
GU Grade \geq 2				2.3 (1.2-3.4)	4.2 (2.1-6.4)	4.1 (2.0-6.1%)	3.4 (1.7-5.1%)

Table modified from "Primary treatments for clinically-localized prostate cancer: a comprehensive lifetime cost-utility analysis," Cooperberg *et al.* 2011 (226).

TABLE 6 Sexual Function

Baseline ED %	All modalities									
Age 50-59 years				26.0						
Age 60-69 years		40.0								
Age 70+				61.0						
New-onset ED (%) (ranges)	RARP	ORP	LRP	IMRT	ВТ	3D-CRT	EBRT+BT			
3 months	66.0 (50-83)	66.0 (50-83)	75.0 (56-94)							
6 months	50.0 (38-63)	63.0 (47-79)	58.0 (44-73)							
12 months	42.0 (32-53)	58.0 (44-73)	53.0 (40-66)	27 (20-34)	57 (43-71)	27 (20-34)	41 (31-51)			
24 months	28.0 (21-35)	49.0 (37-61)	40.0 (30-50)	42 (32-53)	43 (32-54)	42 (32-53)	51 (38-64)			

Table modified from "Primary treatments for clinically-localized prostate cancer: a comprehensive lifetime cost-utility analysis," Cooperberg *et al.* 2011 (226).

8.5.4 Health-related quality of life

Prostate cancer therapy outcomes not only include survival, but also health-related quality of life (HRQOL). Health-related quality of life refers to the impact that the disease and treatment have on a person's physical, emotional and social functioning and well-being. It is emphasized that HRQOL is a patient-centered outcome (11), and can be effectively assessed by validated questionnaires and surveys. (162) Health-related quality of life is divided into cancer-specific and general issues. Prostate cancer specific HRQOL includes domains such as sexual function, urinary incontinence, urinary symptoms, bowel/rectal symptoms and vitality/hormonal score. General domains include issues of well-being common to any medical population (i.e. pain, life satisfaction, etc).

Several multicenter studies have characterized the quality of life after primary treatment for prostate cancer. Data from CaPSURE was drawn from longitudinal surveys of a subgroup of patients who had undergone either brachytherapy or prostatectomy. (163) Prostate cancer treatment was found to have a greater impact on cancer-specific, rather than general HRQOL. Primary prostate cancer treatment type is associated with distinct changes in quality of life domains. (91,163,164) It has been observed that undergoing active versus conservative treatment is associated with greater outcome satisfaction. (165) The Prostate Cancer Outcomes Study (PCOS) used pre-treatment surveys to evaluate the effects of prostatectomy and conventional external radiotherapy. (164) This study conferred that treatment choice, baseline function, and age are the main determinants of changes in disease-specific outcomes. A recent single-centre study compared HRQOL outcomes amongst patients who underwent either ORP or RARP and found the RARP group had greater decisional regret and lower satisfaction. (166)

Preexisting patient comorbidities have been associated with worse HRQOL outcomes. Patient factors such as obesity, large prostate size, high pretreatment PSA or older age are associated with worse patient-reported outcomes. (91) Anast *et al.* found that HRQOL was negatively impacted in obese patients at the time of cancer diagnosis. Interestingly, this study found that for obese men, overall HRQOL recovery was similar to that of normal weight patients. (167) Knight *et al.* found that men with less education experienced worse HRQOL across a wide range of domains and greater urinary and sexual symptoms. (168)

Little data exists on long-term impact of primary treatment for prostate cancer on HRQOL. Huang *et al.* found that primary treatment, age at diagnosis and time from treatment were significant predictors of HRQOL after a four-year follow-up. Changes in quality of life were found to be significantly related to satisfaction with overall outcome among both patients and their partners. (91)

8.6 Comparative and Cost-Effectiveness

As there are differing definitions of recurrence for surgery and radiation, it is a difficult task to compare treatment modalities based on biochemical definition of recurrence. The Institute of Medicine (IOM) has emphasized a need for direct comparison of competing interventions with emphasis on population outcomes. Comparative effectiveness research (CER) is "a strategy that focuses on the practical comparison of two or more health interventions to discern what works best for which patients and populations."(81) The IOM recently included treatment for localized prostate cancer among the top 25 most important topic for comparative effectiveness research. (81) Several cohorts have attempted to describe treatment modality superiority.

Data from CaPSURE (169) compared mortality outcomes for men undergoing open prostatectomy, RT or hormonal therapy. Risk was assessed using Kattan nomogram and CAPRA score. At a mean follow-up of 6.8 years, 17.2% (N=1293) died, 3.0% of whom died of prostate cancer. The hazard ratio for CSM relative to open prostatectomy was 2.2 (95% CI 1.5-3.2) for RT and 3.2 (95% CI 2.2-4.8) for hormonal therapy. Thus, very few men died of prostate cancer, regardless of treatment type. Both risk strategies demonstrated that in only high-risk patients were differences seen in treatment modalities.

A study from Memorial-Sloan Kettering Cancer Center (MSKCC) compared outcomes between open prostatectomy and RT and included low- (N=952) and intermediate-risk (N=1019) patients (170). The most significant variable associated with metastatic progression was risk group, i.e. low/intermediate versus high risk (HR 6.37, 95% CI 3.89 to 10.5). While metastatic recurrence was rare in the low risk group (40% of cohort), absolute differences between treatment types could not be deemed clinically relevant specific to low-risk cohort.

The comparative efficacy of treatment options for prostate cancer remains controversial, but there is no argument that the costs of care vary drastically across modalities. (171,172) One study using 2002-2004 data estimated the total costs over the first five years of treatment to be \$32,135 for watchful waiting, \$35,143 for brachytherapy, \$36,888 for open prostatectomy, \$43,108 for cryotherapy, \$59,455

for external-beam radiation, and \$69,244 for primary androgen deprivation. (172) The data for this study were collected before RARP and IMRT gained popularity, and before Medicare substantially reduced reimbursements for androgen deprivation treatment in 2005.

Another analysis estimated that median hospital direct costs for prostatectomy range from \$4,437 for open surgery to \$5,687 for non-robotic laparoscopic and \$6,752 for RARP. (173) An interesting follow-up found that for obese men, the costs for open and laparoscopic rose substantially but those for RARP did not. (173) These figures do not reflect the purchase price and annual maintenance contract costs for the robot itself; these would add \$2,698 per case assuming 126 cases per year and 7-year amortization. (173) Of course, with higher annual hospital volumes and longer service life this figure would fall—but conversely for hospitals which purchase a robot but use it infrequently— the per-case cost will be very high. Other estimates of gross costs have ranged from \$5,554 to \$10,704 for open surgery and \$7,280 to \$10,047 for robotic-assisted surgery. (174)

Direct treatment costs for conformal radiation and IMRT are estimated to range from 10,900 - 27,357 and 33,837-52,170, respectively. (94) Another analysis calculated total costs over 15 years of 36,808-339,355 for IMRT and 63,511-64,989 for proton-beam therapy. Capital costs for advanced radiation facilities dwarf those of surgical robotic systems: by one recent estimate 23.4M (US31.8M) for a new photon facility and 94.9M (US129.0M) for a new proton facility. (175) It is important to acknowledge important differences in the economic implications of new technologies as they are adopted. In the U.S. the increased costs of laparoscopic and robotic-assisted surgery, in particular, are mostly absorbed by hospitals, whereas IMRT and proton-beam therapy are very highly reimbursed by Medicare and other payers.

The financial considerations may vary greatly across different health care systems. A recent Japanese study, for example, found that open and laparoscopic surgery yielded a net hospital profit, respectively, of $\pm 61,001$ (US3732) and $\pm 75,672$ (US902) per patient. For 3D-CRT, the profit was $\pm 168,727$ (US2024), whereas for brachytherapy, low-dose-rate and high-dose therapy resulted in profit of ± 199 (US2) and loss of $\pm 654,016$ (US87848), respectively. (176)

Formal cost-effectiveness comparisons in prostate cancer are challenging due to both the complexities of defining and measuring oncologic and HRQOL outcomes for prostate cancer, as discussed above, and to weak associations among costs, charges, and collections for prostate cancer care. Moreover, current financial structures in health care delivery offer little to no motivation for providers to pursue cost-effective care. Indeed, payment incentives often reward over-utilization of interventions, or, as is clear from the discussion above, heavily favour one modality over another in the absence of evidence of differences in outcomes.

A recent study, for example, demonstrated that hypofractionating EBRT to 20 treatments over five weeks rather than the typical 40 treatments over eight weeks yielded improved biochemical outcomes and no difference in late toxicity. (177) This protocol, if validated, would improve both outcomes and convenience for patients—but as long as payment is organized on a per-fraction rather than per-patient basis, providers will have a continued incentive to maximize the number of fractions. Likewise, despite outcomes for brachytherapy which appear to be consistently as good as or better than EBRT for low- and intermediate-risk disease, the lower reimbursement for brachytherapy compared to IMRT will continue to drive utilization of the latter. For another example, as noted above, radical perineal prostatectomy might in fact be a more cost-effective approach to prostatectomy than other modalities for some men, yet it is rarely used in practice. (80)

8.7 Summary

Screening with serum PSA followed by systemic trans-rectal ultrasound guided biopsy results in the relative increased detection of men with low- and intermediate-risk prostate cancer. Such patients are candidates for a variety of treatment options, including active surveillance in lieu of immediate treatment for some. Treatment decisions should be driven by cancer risk and patient preference, not by financial incentives or availability of technology. If clinicians aim to improve the quality, effectiveness, and efficiency of prostate cancer care worldwide, we must begin collecting and disclosing patient-reported, risk-adjusted outcomes prospectively, across multiple treatment modalities, facilities, and individual providers.

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Treatment of High-Risk, Clinically Localized, and Locally Advanced Prostate Cancer

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9.1 Introduction

Temporal trends in the incidence of high-risk prostate cancer (PCa) based on the D'Amico risk stratification system have revealed a decline in the proportion of patients with high-risk disease, from 43.9% in 1990–1994 to 29.0% in 2000–2001, and to 24.0% in 2004–2007 in the United States (US). (1) Much of this decline may be attributed to the widespread use of serum prostate-specific antigen (PSA) screening, which has not only resulted in a downward risk migration but also a downward clinical stage migration with most newly diagnosed non-palpable PCa in the US being non-palpable (cT1c) (2). In the current era, the identification of high-risk PCa relies more on clinical variables such as PSA and Gleason score, and less on clinical staging. Various risk assessment schemes incorporating these variables have been developed with hopes of more accurately identifying high-risk PCa, characterizing the likelihood of disease progression and/or mortality, and ultimately facilitating management through better risk stratification.

In this chapter, we will discuss various management considerations including risk assessment, with consideration of tumour- and patient-specific variables, and we will also review current management and treatment outcomes for high-risk clinically localized and locally advanced PCa.

9.2 Defining High-risk and Locally Advanced Prostate Cancer

Selection of the optimal management strategy for men with PCa requires thorough consideration of both tumour and patient-specific factors. Risk stratification based on pre-treatment factors as described by D'Amico allows for estimation of the extent of disease and prediction of the likelihood of disease progression and cancer-specific mortality following definitive local therapy (3, 4). The original 1998 D'Amico risk classification system defined high-risk PCa with the following high-risk features: Gleason score of >8, baseline PSA >20 ng/ml, or clinical stage >T2c. A recent analysis of the outcomes of 3,372 men classified as "high-risk" based on the D'Amico classification system revealed that patients with "high-risk" PCa solely based on cT2c status had significantly lower recurrence rates than cT3 patients, and suggested that a clinical stage T2c is not sufficient to warrant "highrisk" assignment. (1) The American Urological Association (AUA) and the European Association of Urology (EAU) recommend risk assignment according to serum PSA, biopsy Gleason score, and clinical stage, as these characteristics strongly correlate with outcome. (5-8) While most contemporary series utilize a combination of these variables to assign risk (9), there exists no consensus regarding the precise cutoffs that define each category. It is, however, widely accepted that a pre-treatment PSA value >20 ng/ml, biopsy Gleason score of 8-10, or clinical suspicion of extraprostatic extension (>cT2C) based on digital rectal examination (DRE) puts a patient into the "high-risk" category.

Locally advanced PCa, defined as extraprostatic disease on DRE, is classified cT3-T4. According to the National Comprehensive Cancer Network (NCCN), locally advanced PCa includes cancer with a clinical stage of T3b-T4 and is considered "very high-risk" disease. (10) Assessing risk based on numerous clinical characteristics plays an integral role in determining the optimal management strategy in men with high-risk and locally advanced PCa.

9.3 Risk Assessment and Staging

With risk group assignment, PCa may be considered "high-risk" solely on the basis of one adverse prognostic parameter. Additionally, errors in measurement of individual parameters, as evidenced by clinical overstaging and pathologic downgrading, have been reported to occur in as many as 30% and 35% of cases, respectively. (11, 12) With the decision of which treatment to pursue, in part dependent on assessment of individual risk, the "high-risk" classification will undoubtedly have a profound effect on decision analysis and management strategy. Risk stratification schemes have acceptable accuracy in the determination of "low" or "very high-risk" PCa, but often cannot accurately predict the likelihood of disease progression and cancer-specific mortality in patients with "intermediate" or "high-risk" disease. (13)

To more accurately assess risk, nomograms incorporating several pre-treatment prognostic variables that are used in combination have been developed. Examples of such nomograms include the University of California, San Francisco, Cancer of the Prostate Risk Assessment (UCSF-CAPRA) score (14), the Stephenson nomogram (15), and the Kattan nomogram. (16) These externally validated models incorporate age and/or measures of tumour burden (extrapolated from biopsy core characteristics), pre-treatment PSA, clinical stage, and biopsy Gleason grade to predict disease recurrence. (17-19) Biopsy core characteristics, including both the percent of positive cores as well as the percentage of tumour within positive cores, have been shown to be independent predictors of disease recurrence following prostatectomy (20-22), and appear to add incremental value to the predictive ability of the UCSF-CAPRA score and Stephenson nomogram. A recent head-to-head comparison of the UCSF-CAPRA score, Stephenson nomogram, and D'Amico risk stratification scheme in a European cohort demonstrated that the integrative predictive models outperform group risk stratification and better predict PSA recurrence in patients with "high-risk" disease after radical prostatectomy (RP). (23) The use of these nomograms thus appears to improve the accuracy of identifying patients with high-risk PCa when compared with group risk assessment schemes.

Investigations into several additional clinical variables that may add incremental value to the performance of these nomograms are ongoing. Changes in PSA value over time (PSA kinetics) may give insight into variations in the biologic activity or aggressiveness of individual tumours, and may potentially account for variations in disease recurrence in patients who are within the same risk stratum. The value of pre-operative PSA kinetics remains controversial, with some studies showing correlations with outcomes while others do not. (24) A PSA velocity (PSAV) >2 ng/ml/year has been reported to be a significant independent predictor of disease recurrence (25, 26), and PCa-specific death. (27) Pre-prostatectomy PSAV has also been correlated with extraprostatic extension, positive margins, larger tumours, higher Gleason score (25), and with time to metastasis. (28, 29) Several studies have shown promising univariate associations between PSA kinetics and disease recurrence or cancerspecific mortality, while other studies have not confirmed these findings. (15, 30) Therefore, controversy remains regarding the predictive value of pre-treatment PSA kinetics over PSA alone. (31)

Pre-treatment levels of blood-based molecular biomarkers associated with tumour biology, such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), have also shown potential to improve prediction of recurrence following definitive therapy. (32, 33) Recently, a pre-treatment clinical nomogram incorporating plasma levels of transforming growth factor-beta 1 (TGF- β 1) and interleukin-6 soluble receptor (IL-6sR) was shown to enhance the accuracy of prediction of PSA recurrence in an independent, external cohort. (34) Tissue-derived markers provide an additional source of information that may refine risk assessment models. The recent analysis of expression profiles of 31 genes involved in cell cycle progression yielded a gene signature that was predictive of disease recurrence in a screen-detected cohort, and of cancer-specific death in a symptom-detected cohort. (35) The potential of a tissue-based prognostic signature has spurred interest in the development of commercially available tools for biologic assessment of biopsy-derived prostate tissue. (36)

The inaccuracy of clinical staging is evidenced by pathologic up- or down-staging after RP (11, 12, 37) and highlights the potential for misclassification of disease and underperformance of risk stratification schemes. Recent advances in magnetic resonance imaging (MRI) of the prostate have the potential to improve the accuracy of detecting extraprostatic disease (38), identifying Gleason grade (39), and assisting in risk assessment and patient management. A recent model suggested added incremental value of MRI findings to other clinical variables when predicting "high-risk" disease on the basis of presence of extraprostatic disease. (40)

In summary, the challenge in the management of high-risk localized or locally advanced PCa lies, in part, in the difficulty of accurately assessing pre-treatment risk. Although the performance of group risk stratification schemes is acceptable for the extremes, men with high-risk PCa do not share a uniformly poor prognosis. Men in intermediate- and high-risk groups may share similar clinical features, making accurate stratification difficult. The incorporation of numerous additional clinical parameters such as PSA kinetics, biopsy pathologic features, blood- and tissue-based biomarkers, and MRI findings into clinical nomograms may allow for a more accurate identification of "high-risk" disease and ultimately assist with the individualized determination of optimal management strategies.

9.4 Patient Individualization

In addition to risk assignment based on tumour-specific variables, determining the optimal management strategy for men with PCa requires careful consideration of patient-specific variables such as patient preference, comorbidities, and life expectancy. As morbidity from definitive local therapy can significantly impact quality of life (41, 42), one can consider deferring aggressive treatment if age, and significant comorbidities, limit both the risk of PCa-specific morbidity and mortality, as well as any expected survival benefit from treatment. Therefore, consideration of an accurate estimate of life expectancy is required to determine the optimal management of men with PCa. The NCCN recommends life expectancy should initially be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration Life Insurance Tables (43), then individually adjusted based on individual comorbidities. (10) This adjustment is essential, as comorbidity has been demonstrated to be a significant competing risk for mortality in men with PCa. A retrospective study examining comorbidities and PCa mortality revealed a PCa-specific mortality rate of 8% in 435 men with high-risk PCa. In the entire cohort, including men across all risk groups, men with Charlson comorbidity scores of 3+ had 8.5x the hazard of death from other causes besides PCa when compared with men having scores of 0. (44) While PCa-specific mortality was generally a rare event in men with significant comorbidities, it is important to realize that for high-risk disease, particularly in men with low-to-moderate comorbidity scores, death from PCa remains a significant contributor to overall mortality. (44, 45) More aggressive treatment for high-risk patients, in the absence of significant comorbidity, seems prudent.

Additionally, the side effects of specific treatments on quality of life must be considered in the decision-making process. The impact of treatment on continence, urinary voiding and storage symptoms, sexual function, and bowel function vary with different treatment modalities both over the short- and long-term. (41, 46) Patients must be made aware of these treatment effects when considering the various treatment modalities available to them.

9.5 Management Options

9.5.1 Radical prostatectomy

Oncologic outcomes vary significantly in men with high-risk clinically localized and locally advanced PCa. Men with organ-confined disease with high-risk features such as Gleason score of 8-10, or PSA >20 ng/ml may be cured by RP alone. On the other hand, men that undergo RP for high-risk disease often require adjuvant therapy to treat locoregional disease. Surgery therefore should be considered in the context of multimodal therapy in an attempt to treat local and suspected regional disease. Variability in treatment outcomes may depend on which clinical variable(s) qualified the patient into the high-risk category. When considering the curative potential of RP, an analysis of outcomes based upon each individual high-risk defining variable is helpful.

9.5.2 High-risk prostate cancer due to Gleason score of 8-10

Pathologic downgrading is common after RP and may indicate that potentially curative resection is being withheld in a subset of high-risk men based on high-grade disease. (47) Examination of the correlation of biopsy Gleason grade with RP Gleason grade at a major academic institution in the US revealed a 35% rate of pathologic downgrading in men with biopsy Gleason score of 8-10. (12) Donohue *et al.* reported a more striking rate of 45% of men with biopsy Gleason score of 8-10 having a Gleason score of \leq 7 in the RP specimen. (48) The 10-year biochemical recurrence-free survival (BRFS) rate in that study was nearly 30% higher in men who were downgraded compared with those whose final Gleason score remained 8-10 (56% vs. 27%). A recent analysis of outcomes of men in the Shared Equal Access Regional Cancer Hospital (SEARCH) Database and a tertiary care medical centre with high-grade (Gleason score, 8-10) disease treated with RP revealed a pathologic downgrading rate of 55% and 34%, respectively. The 10-year BRFS rate in downgraded men was 34% in the SEARCH cohort and 38% in the tertiary care group. (49) Therefore, a significant number of men are pathologically downgraded; these are patients who may benefit the most from a potentially curative resection.

Several studies have demonstrated that men with poorly differentiated tumours at biopsy, regardless of RP specimen Gleason score, can have favourable outcomes after RP monotherapy. The 5- and 10-year BRFS rate in men with biopsy Gleason scores of 8-10 has been reported to range from 40-52% and 27-39%, respectively. (48-50) Outcomes are further improved in organ-confined disease, which has a reported incidence of 26-34% in men with biopsy high-grade disease. (48, 51, 52) In addition, the presence of negative margins in patients with high-grade disease also predicts improved outcomes. (49, 52) The above data suggest that RP alone can achieve cure in some patients with high-grade PCa, particularly those with organ-confined disease, or those who are downgraded.

9.5.3 High-risk prostate cancer due to PSA >20 ng/ml

While a pre-treatment PSA >20 ng/ml has been identified as an independent predictor of recurrence in men with high-risk PCa, (53) several reports have shown that some men who are considered high risk on the basis of pre-treatment PSA can achieve favourable outcomes with RP. Yossepowitch *et al.* reported a 5- and 10-year BRFS rate of 56% and 47%, respectively, in such men treated with RP alone, 33% of whom had organ confined (pT2) PCa. (54) Freedland *et al.* reported a higher likelihood for advanced clinical stage, positive margins, capsular penetration, seminal vesicle invasion, and lymph node involvement in men with PSA >20 ng/ml. In their cohort, 53% of men with PSA values >20 ng/ml were free of biochemical recurrence at 5 years. (55) Similarly, Hull *et al.* reported a 5- and 10-year BRFS rate of 50% and 46%, respectively, in men with pre-treatment PSA levels between 20 and 49.9 ng/ml. Organ confined (pT2) disease was found in 20.6% of those patients. (56) Gontero *et al.* projected a 10-year cancer-specific survival (CSS) rate of 90.9%, 85.4%, and 79.8% in men with PSA levels of 20.1-50, 50.1-100, and >100 ng/ml, respectively, in a cohort of men treated with RP, some of whom received neoadjuvant, adjuvant, or salvage therapy. (57) These studies suggest that a significant proportion of patients with high-risk PCa based on baseline PSA values >20 ng/ml will be organ confined and may benefit from surgery with or without multimodal therapy.

9.5.4 **High-risk prostate cancer due to locally advanced disease** (cT3-T4)

Locally advanced (cT3-T4) PCa is well known to be an adverse clinical feature. (1, 8) However, men with locally advanced disease can have favourable outcomes following RP alone or combined with other therapies. Following RP, the 5- and 10-year BRFS rate ranges from 31-62% and 15-51%, respectively, and the 5 and 10- year CCS rate ranges from 84%-98% and 84%-91%, respectively. (8, 58-61) Adjuvant therapies frequently included androgen deprivation therapy (ADT), radiotherapy (RT), or both at some point after RP, emphasizing the necessity for a multimodal approach. RP monotherapy in men with cT3 disease may be curative, particularly in patients who are downstaged after RP. The clinical overstaging rate ranges from 9-27% (58, 61), highlighting that there is a significant degree of potential risk misclassification in those men with cT3 disease. Consideration of the biopsy Gleason

score may help select patients with cT3 disease who will benefit most from RP. In a study by Gerber *et al.*, men with cT3 disease and poorly differentiated tumours treated with RP had a significantly lower prostate CSS rate than patients with cT3 disease and well or moderately differentiated tumours. (62)

In men with cT4 disease, RP has been described to have a role, although data is sparse. A retrospective analysis of data from the Surveillance Epidemiology and End Results (SEER) database examined 1,093 patients with cT4 PCa, of whom 33% who underwent RP were downstaged to pT3 or lower. Patients who underwent RP alone or in combination with other treatment (n=72) had improved 5-year overall survival (OS) rates compared with men who underwent XRT alone or ADT alone, while survival rates were similar to those men who underwent XRT+ADT (72.6% vs. 71.1%). (63) On multivariate analysis, the benefit of RP was limited to men with known lymph node metastases. Of note, 33% of the patients with cT4 disease who underwent RP were pathologically downstaged to pT3 or lower. These data support the use of RP as monotherapy for select cases of locally advanced PCa, particular for patients with organ-confined disease, though frequently multimodal therapy will be required.

9.5.5 Surgical technique

9.5.5.1 Nerve sparing

No established clinical criteria exist for determining whether to perform a nerve-sparing resection in men with high-risk PCa. The feasibility of a nerve-sparing resection without loss of oncologic control in select patients with high-risk disease has been described (64-66) and relies in part on the accurate determination of local extent of disease. This is particularly relevant for men with high-risk, locally advanced tumours that are amenable to RP, as achievement of adequate oncologic control is more likely to involve wide resection without sparing the neurovascular bundles. Most centres continue to rely on DRE for assessment of extent of disease, which has poor specificity for detection of extraprostatic disease, (67) and may result in an unnecessarily wide excision with loss of potency. The New York University Nerve Sparing Algorithm mandates ipsilateral neurovascular bundle excision in men with a Gleason score of 8-10 if the biopsy specimen reveals >10% tumour volume, or if perineural invasion is present. This algorithm yielded 84% accuracy in making the proper decision regarding preservation or excision of the neurovascular bundles, but it has not been validated on an external dataset. (68) More recently, incorporation of MRI findings into pre-operative staging algorithms has been shown to potentially enhance the ability of detecting extraprostatic disease, (38, 69) and may significantly alter the surgeon's decision to preserve or resect the neurovascular bundle during RP. (70) The use of intra-operative frozen sections, in combination with pre-operative MRI findings, has also been described by some authors to assist with the application of a nerve-sparing approach in select high-risk patients. (71)

9.5.5.2 Robotic-assisted radical prostatectomy

Several contemporary series of robotic-assisted radical prostatectomy (RARP) have demonstrated acceptable oncologic control of high-risk clinically localized, or locally advanced tumours, although long-term follow-up is necessary to validate the oncologic outcomes. (72-75)

9.5.6 Pelvic lymphadenectomy

Current NCCN guidelines recommend that pelvic lymph node dissection (PLND) be performed in patients undergoing RP with a >2% predicted probability of nodal metastasis and in all patients with high-risk disease. (10) Others recommend extended pelvic lymph node dissection (ePLND) in all cases where PLND is to be undertaken, as this leads to significant improvement in the detection of lymph node metastases. (76-78) The prevalence of nodal metastases may be underestimated, as most nomograms are based on a limited PLND. A validated nomogram developed by Briganti et al. can be used to predict lymph node involvement as detected by ePLND. (79) An extended dissection involves removal of all node-bearing tissue between the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis inferiorly, Cooper's ligament distally, and the internal iliac vein proximally. Based on lymphatic mapping studies, some have advocated extending the proximal dissection over the common iliac artery to the level of the ureteric crossing, thus allowing for clearance of approximately 75% of all nodes in the primary lymphatic landing sites. (80) In addition, clearance of nodal tissue along the internal iliac vessels is essential for representative staging, as more than half of all patients with nodal metastasis will harbour disease in this site. (81) Although no consensus exists on the number of nodes required for an adequate dissection, an autopsy study suggested removal of at least 20 nodes is necessary for representative staging. (82)

In addition to improved staging, ePLND may have a potential therapeutic role in PCa. An apparent improvement in disease progression and disease-free survival (DFS) has been demonstrated in a subset of patients with PCa, possibly due to the clearance of micrometastatic disease. (83, 84) A recent analysis of patients with RP from the SEER database revealed that a more extensive lymphadenectomy (>10 nodes removed) was associated with a lower risk of PCa death, even after restricting the analysis to patients with negative lymph nodes. (85)

Extended PLND has been shown to add morbidity, with an increased risk of lymphocele, lymphedema, deep venous thrombosis (DVT), and pulmonary embolism. A large contemporary series found an overall complication rate of 19.8% in men who underwent ePLND compared with 8.2% in men with limited PLND. However, when individual complications were compared, only the rate of lymphocele was significantly higher in patients subjected to ePLND (10.3% vs. 4.6%). (86) The development of a symptomatic lymphocele has been associated with the number of nodes removed; (87) however, other ePLND series have shown more acceptable rates of lymphocele and similar rates of overall complications when compared with limited PLND. (78, 81)

In summary, ePLND appears to result in improved staging and potentially in reduced risk of disease recurrence and improved survival, though at the cost of more complications.

9.6 Neoadjuvant Androgen Deprivation Therapy

A recent Cochrane review and meta-analysis assessed the effectiveness of neoadjuvant androgen deprivation therapy (NADT) in localized and locally advanced PCa. Neoadjuvant androgen deprivation therapy prior to RP did not improve OS or DFS, but did significantly reduce positive margin rates (relative risk [RR], 0.49; 95% confidence interval [CI], 0.42-0.56; p<0.0001), organ confinement (RR, 1.63; 95% CI, 1.37-1.95; p<0.0001) and lymph node invasion (RR, 0.49; 95% CI, 0.42-0.56; p<0.02). (88) These data do not suggest a role for NADT in men with high-risk PCa.

9.6.1 Adjuvant androgen deprivation therapy

The same Cochrane review and meta-analysis examined the role of adjuvant ADT after RP compared with RP alone and showed no significant 5- or 10-year OS advantage to adjuvant therapy. Five and 10-year DSF rates were significantly improved in the adjuvant ADT arms (odds ratio [OR], 3.73; 95% CI, 2.30-6.03, p<0.00001). (89) The Bicalutamide Early Prostate Cancer (EPC) Program demonstrated no improvement in OS in patients with cT3-4, any N; or any T, N+ in the 150 mg/day bicalutamide arm. (90) Dorff et al. reported preliminary results from 481 men with high-risk surgical pathology features following RP randomized to 2 years of adjuvant ADT as part of the SWOG S9221 study. With a median follow-up of 4.4 years, the 5-year biochemical failure-free survival rate was 92.5% and the 5-year OS rate was 95.9%. (91) At the present time, the evidence does not support adjuvant ADT following RP in lymph node-negative patients. The role of adjuvant ADT in men with lymph node-positive disease also remains unresolved. In a prospective randomized trial in the pre-PSA era of 98 men with documented lymph node-positive disease following RP, immediate ADT improved OS and PCa-specific survival when compared with ADT given at the time of symptomatic progression or metastatic disease. (92) However, a retrospective analysis of 731 men that underwent RP (and were found to have positive lymph nodes) in the PSA era, found no difference in OS between men that received ADT within 120 days compared with after 120 days of RP. (93)

9.6.2 Adjuvant versus salvage radiotherapy

While RP is an effective treatment strategy for patients with clinically localized PCa, an estimated 25% of patients will nevertheless experience disease recurrence after surgery. (94) Radiotherapy directed at the prostate bed is the only known treatment capable of eradicating local microscopic residual disease. Adjuvant radiotherapy (ART) is defined as radiation given in the immediate post-operative setting and in the absence of measurable disease (undetectable PSA). In contrast, salvage radiotherapy (SRT) is defined as a treatment given after a demonstrated biochemical recurrence, typically defined in the surgical literature as PSA >0.2 ng/ml after RP. In men with high-risk pathologic features at the time of surgery (positive margins and/or pT3 disease), the risk for biochemical relapse can approach 50%. (7, 95-97) The initial evidence of cancer. There are two principal dilemmas after RP: 1) deciding when and how to provide optimally successful SRT; and 2) in the absence of any measurable disease, whether ART can or should be safely deferred until biochemical failure is

confirmed. This is a particularly relevant challenge given the availability of ultrasensitive PSA assays and the ability to potentially identify recurrence very early. Accordingly, the absolute indications for immediate post-operative RT have come into question. (98)

Adjuvant Radiotherapy

There are three randomized trials, EORTC 22911 (99), ARO 96-02 (100), and SWOG 8794 (101) that have evaluated the role of ART in patients with high-risk PCa. EORTC 22911 randomly assigned 1,005 men with pT3 disease or positive surgical margins after RP to post-operative conventional external beam radiotherapy (EBRT) (60 Gy) or observation. (99) With a median follow-up of 5 years, the BRFS rate in patients receiving ART was 74% versus 53% for the observation arm. ART also provided a benefit for clinical RFS (85% vs. 78%, respectively) and decreased the rate of locoregional failure (5.4% vs. 15.4%, respectively). There was no observed difference in OS, although follow-up was relatively short. Patients with positive surgical margins benefited the most from ART. (102) A similarly designed trial, SWOG 8794, evaluated 425 men with pT3 or positive surgical margins after RP and randomly assigned them to ART (60-64 Gy) or observation. (101, 103) At 12.6 years median follow-up, patients treated with ART had significantly improved metastasis-free survival (MFS) (p=0.016) and OS (p=0.023) compared with the observation arm (median MFS, 14.7 vs. 12.9 years; median OS, 15.2 vs. 13.3 years). Finally, the ARO 9602 trial, which utilized PSA assays with a lower threshold, was designed to determine whether men with pT3 cancer and an undetectable PSA (<0.1 ng/ml) after RP would benefit from three-dimensional conformal ART. (100) At 5 years, ART improved the BRFS rate compared with observation (72% vs. 54%, respectively; p=0.0015). In an unplanned subgroup analysis, positive surgical margins (p=0.00018), tumour stage pT3a/b (p=0.00039), a pre-operative PSA level >10 ng/ml (p=0.0018), and Gleason score of >6 (p=0.029)defined populations with an improved response to ART versus SRT. (100) While not designed to compare toxicities between treatment arms (primarily because the patients in the observation arm subsequently received various treatments including deferred ADT, combination RT and ADT), the randomized ART trials provide comparison of toxicities between RP alone and RP followed by ART. In general, toxicities were increased in patients who received ART, although the absolute rate of events was low. In the European Organization for Research and Treatment of Cancer (EORTC) trial, there was no difference in 5-year severe (grade \geq 3) toxicity between the observation arm and the ART arm (2.6 vs. 4.2 %, not significant [NS]). (99) In the SWOG trial, overall complications were more common in the ART arm (23.8%) when compared with the observation arm (11.9%). (101) Specifically, rectal complications, urethral stricture, and total urinary incontinence were more common in the ART arm (3.3% vs. 0%, 17.8% vs. 9.5%, and 6.5% vs. 2.8%, respectively). Short- and long-term effects of ART were further evaluated in a health-related quality of life (HRQoL) study on patients from the SWOG trial. (104) Patients reported acute worsening of urinary and bowel function, with a resolution of gastrointestinal (GI) symptoms after 2 years. At 5 years, patients with ART continued to have worse urinary function, but global HRQoL was improved compared with patients who did not receive ART. There was no difference in erectile dysfunction (ED) rates between the two arms. The observed rates of adverse effects associated with ART in the ARO trial were also low, with an overall severe toxicity rate of 0.3%. (100) Given the results of these three ART trials and infrequent late toxicity, it has become an acceptable strategy to offer ART after RP for patients with pT3 disease or positive surgical margins.

Lastly, the concept of "adjuvant" must be taken in context of the sensitivity of PSA assays that were used in these three trials. In the EORTC and SWOG trials, 9% and 35% of patients had PSA >0.2 ng/ ml, respectively, at the time of treatment. In the ARO trial, 20% of patients had a PSA >0.05-0.1 ng/ ml, and 59% of patients had a PSA >0.03-0.1 ng/ml.

Salvage Radiotherapy

Numerous retrospective and pooled analysis studies provide outcomes on patients treated with SRT. One large multi-institutional study looked at a cohort of 501 patients with a rising PSA after RP who underwent SRT (median dose, 64.8 Gy). (105) Of the patients, 96% had a PSA level ≥0.2 ng/ml at the time of SRT. On multivariable analysis, independent factors associated with disease progression included pathologic Gleason score of 8-10, pre-SRT PSA level ≥ 2 ng/ml, negative surgical margins, PSA doubling time (PSADT) ≤10 months, and seminal vesicle invasion. The 4-year progression-free survival (PFS) rate for all patients was 45%. Patients with no adverse features had a 4-year PFS rate of 77%. Another large multi-institutional retrospective review of 1,540 patients with a PSA \geq 0.2 ng/ml after RP treated with SRT (median dose, 64.8 Gy) (106) found an overall 6-year PFS rate of 32%. The authors constructed a model using the 6-year BRFS rate as the endpoint and found factors associated with disease progression to include PSA level >0.5 ng/ml prior to SRT, Gleason score of 8-10, PSA doubling time ≤10 months, negative surgical margins, and lymph node metastases. An estimated 48% who received SRT alone when the PSA was ≤0.5 ng/ml were disease free at 6 years compared with 40%, 28%, and 18% of those treated at PSA levels of 0.5-1.0, 1.01-1.5, and >1.5 ng/ml, respectively. These and other studies have identified several favourable prognostic criteria for identifying patients that are likely to benefit from SRT. These include a positive surgical margin, pathologically organ-confined disease, lower PSA level prior to SRT, Gleason score ≤7, longer time interval to failure after RP, and longer PSADT.

While SRT can improve BRFS, its potential benefit on CSS and OS is less conclusive. Trock *et al.* published a retrospective review of 635 men who had a biochemical recurrence after RP. (107) Of the patients, 63% had no further treatment, 25% received SRT (median dose, 66.5 Gy), and 12% received SRT plus ADT. At 10 years, SRT improved PCa-specific survival compared with patients that received no further treatment (86% vs. 62%; p<0.001). SRT only improved PCa-specific survival if given sooner than 2 years after recurrence. The strongest predictor of poor PCa-specific survival was a PSADT <6 months. SRT was also associated with a significant increase in OS. This is in contrast to another large retrospective series from the Mayo Clinic that evaluated 2,657 men who had a biochemical recurrence after RP, of whom 32% received SRT. (108) On multivariate analysis, SRT decreased the risk of local recurrence, distant metastases, and delayed the initiation of ADT but did not, however, significantly decrease mortality compared with patients not receiving SRT (70% vs. 69%, respectively, at 10 years).

SRT is generally well tolerated. Mild-to-moderate acute GI and genitourinary (GU) toxicity is seen in the majority of patients, but the reported incidence of acute severe complications is less than 4%. (109-111) Late complications are seen in approximately 5-20% of patients, but severe late toxicity is rare. (109, 111-114) One series evaluated 308 patients treated with SRT between 1987–2003. (115) Overall, late toxicity occurred in 13% of patients, with grade \geq 3 rectal, urinary, or urethral toxicity seen in only 0.7%. In another multi-institutional study of 959 men who received postoperative RT (81% as SRT and 19% as ART), the 5-year rate of late grade 3 GI and GU side effects was 0.4% and 1%, respectively. (116) The results from randomized ART trials and retrospective SRT studies show that RT can be safely administered in the post-operative setting.

Adjuvant Versus Salvage Radiotherapy?

The current literature on ART and SRT still leaves many unanswered questions, including the optimal dose and timing of treatment. Current American Society for Radiation Oncology (ASTRO) and EORTC consensus guidelines recommend a dose of 64-66 Gy for SRT, with the trials discussed above generally prescribing a dose of 60-66 Gy. (117) However, recent observational studies and a systematic review of the literature found a dose-response relationship, and that doses of 66 Gy to greater than 70 Gy are necessary to sufficiently eradicate disease in the adjuvant and salvage settings. (118-120) A recent meta-analysis of SRT by King (121) found that PSA level prior to SRT and dose were the only two factors that had an independent and significant association with BRFS. This analysis showed an observed 2.5% loss of the BRFS rate for each incremental 0.1 ng/ml PSA at the time of SRT.

Several unanswered questions remain regarding ART and SRT including whether patients might benefit from ADT and/or expanded treatment of the pelvic lymph nodes. In regard to ADT, randomized trials have shown a benefit for ADT combined with EBRT in the primary management of highrisk cancer, but whether ADT offers this same benefit in the adjuvant or salvage setting remains to be determined. A retrospective series analyzed 122 men who underwent SRT after RP, of which 43% received combined treatment with a short-course of ADT. (122) After a median follow-up of 5.9 years, biochemical control was superior in the combination therapy group when compared with RT alone (57% vs. 31%); of note, patients with Gleason score of \geq 8 had an improvement in OS. Two randomized clinical trials currently underway are evaluating the role of ADT in SRT: RTOG 9601 and RTOG 0534. There is no consensus as to whether to include the pelvic lymph nodes for those patients who underwent RP with or without lymphadenectomy.

Three randomized ART trials showed a significant improvement in the BRFS rate with this technique, and one trial showed an OS benefit for pT3 pN0 M0 patients. However, in those trials, a significant proportion of patients had measurable PSA levels at the time of treatment, and they were in essence receiving SRT. In the era of ultrasensitive PSA assays with a threshold of 0.01-0.02 ng/ml, the true definition of adjuvant is in need, as a significant proportion of patients may be reliably determined as not having failed despite having high-risk pathologic features, and those that do fail may potentially be identified at an early time point and in time for successful SRT. Whether there is a downside to waiting until the PSA becomes barely detectable (0.05-0.1 ng/ml) before initiating post-operative RT is not known. Three open randomized trials examining the timing of adjuvant versus salvage RT are currently underway (RADICALS, [123] GETUG-17, [124] and RAVES [125]) to examine these issues.

9.7 **Primary Radiation Therapy**

To date, no randomized studies have compared the efficacy of EBRT with RP in the treatment of localized, high-risk, or locally advanced PCa. The decision to pursue EBRT versus RP is therefore often largely based on the treating physician's clinical experience and bias, as well as patient preference. Retrospective series comparing the two modalities for the treatment high-risk tumours have had widely disparate results, with some studies favouring surgery, others favouring radiation, and some showing equivalence. (126) Drawing meaningful conclusions from the results of these retrospective studies is difficult due to heterogeneity in both the definition of high-risk disease and baseline patient characteristics, as well as the rapid evolution of EBRT dose and delivery techniques. In addition, the combination of EBRT with ADT has further improved the efficacy of RT, particularly in men with high-risk tumours. (127-129)

Delivery Techniques

Three-dimensional conformal radiotherapy (3D-CRT) allows for treatment with higher doses while reducing the risk of acute toxicities. (130, 131) Intensity modulated radiotherapy (IMRT), an optimized form of 3D-CRT, is considered a state-of-the-art, and, per current NCCN guidelines, a required treatment for PCa. (10) An image-guided radiotherapy (IGRT) technique is necessary to accompany the safe delivery of dose escalation by targeting the exact 3D location of the prostate gland during treatment, when the dose delivered to the isocentre is >78 Gy. This most frequently consists of fiducial-based image guidance, although other approaches such as cone-beam computed tomography (CT) can also be used.

Dose Escalation

Several studies have demonstrated superior BRFS of EBRT with dose escalation. After a median follow-up of 51 months, Peeters *et al.* reported a 10% improvement in the clinical or biochemical recurrence rate in men with localized PCa treated with a dose of 78 Gy versus 68 Gy. Most patients with high-risk disease received ADT, although its use was well matched between the two groups. (132) Kuban *et al.* reported a nearly 20% improvement in the clinical or biochemical recurrence rate in men in the 78 Gy arm versus those in the 70 Gy arm. This effect was more pronounced in patients in the high-risk subgroup if PSA levels were >10 ng/ml. Additionally, in the high-risk group, 96% versus 83% of patients were free of distant disease at 8 years in the 78 Gy and 70 Gy arms, respectively (p=0.035). (133) Dearnaley *et al.* reported an 11% increase in the 5-year BRFS rate in men with localized PCa who received a dose of 74 Gy versus 64 Gy. The BRFS rate in men with high-risk disease according to Chism risk criteria was 57% and 43% for the 74 Gy and 64 Gy arms, respectively. (134)

Dose escalation is associated with increased toxicity. Several studies have confirmed that higher radiation doses result in increased grade 2 or greater GU toxicity, most commonly consisting of urinary urgency and frequency, as well as grade 2 or greater GI toxicity involving rectal bleeding and/or proctitis. (133-135) The use of IMRT has significantly reduced toxicity, with a recent study examining high-dose (81 Gy) IMRT reporting an 8-year actuarial likelihood of developing grade 2 or greater rectal bleeding of 1.6%, and grade 2 or greater GU toxicity of 15%. After 8 years, high-dose IMRT resulted in a 49% rate of ED. (136)

Planning Target Volume

Accurate determination of microscopic extraprostatic disease is difficult due to the poor sensitivity of CT, MRI, and positron emission tomography (PET) scanning. The use of prophylactic whole pelvic radiotherapy (WPRT) as a means for improving outcomes in the treatment of undetectable extraprostatic disease with pelvic nodal irradiation has been investigated. To date, no randomized trial has demonstrated a survival benefit to WPRT versus prostate-only RT; however, several recent studies have suggested a benefit, particularly in men with a high risk of nodal involvement. (137, 138) Inadequate treatment doses, lack of conformal techniques and image guidance, lack of uniform usage of ADT, and inadequate sample sizes in some studies may have limited their ability to detect improved clinical outcomes with WPRT. Further confounding factors include the failure of some of these studies to use true WPRT as defined by RTOG 94-13 (superior border L5-S1). (139) Ongoing phase III trials RTOG 05-34 in the salvage RT setting and RTOG 09-24 evaluating primary RT are aimed at clarifying the utility of WPRT, and their results are awaited.

9.7.1 **Primary EBRT combined with androgen deprivation Therapy**

Two randomized trials, EORTC 22863 and RTOG trial 92-02, demonstrated improved outcomes in men with high-risk disease who received long-term ADT combined with RT (140, 141). In EORTC 22863, men with cT1-T2 PCa with World Health Organization (WHO) grade 3, or cT3-T4 disease with any WHO grade were randomized to conventional RT alone, or conventional RT plus ADT for 3 years. After 10 years, men in the RT with ADT arm had a 25% increase in DFS (p<0.0001) and a nearly 20% increase in OS (p=0.004), as well as a 20% improvement in distant MFS (p<0.0001). (140) Subgroup analysis of RTOG trial 92-02 compared RT plus short-term (4 months) or longterm (2 years) ADT initiated 2 months prior to RT in men with cT2c-T4 PCa and Gleason score of 8-10. Long-term ADT administration conferred significant advantages in 10-year OS (45.1% vs. 31.9%; *p*=0.0061), DFS (20.8% vs. 9.4%; p<0.0001), disease-specific survival (DSS) (79.8% vs. 66.9%; p=0.0072), local progression rate (17.8% vs. 27.3%; p=0.0338), distant metastasis rate (25.6% vs. 39.7%; p=0.0019), and biochemical failure rate (56% vs. 73.9%; $p\leq 0.0001$). (141) The TROG 96.01 trial randomized men with non-metastatic, cT2b-T4 PCa to RT alone or RT with ADT for 3 or 6 months started 2 or 5 months before initiation of RT. After a median follow-up of 10.6 years, the greatest effects were seen in the 6-month ADT group, including decreased risk of local progression (adjusted HR, 0.45; 0.30-0.66; *p*=0.0001), distant progression (adjusted HR, 0.49; 0.31-0.76; *p*=0.001), PCa-specific mortality (adjusted HR, 0.49; 0.32-0.74; p=0.0008), and all-cause mortality (adjusted HR, 0.63; 0.48-0.83; *p*=0.0008), compared with RT alone. (142)

The results of EORTC trial 22961 showing that the combination of RT plus 6 months of ADT provided inferior survival when compared with RT plus 3 years of ADT in the treatment of locally advanced PCa also underscores the advantage of longer duration ADT. (129) The evidence therefore clearly demonstrates improved clinical outcomes when RT is combined with long-term (2-3 years) ADT in patients with high-risk PCa.

A consideration of the potential harmful effects of ADT should be made when assessing the potential benefits. In an observational study, Keating *et al.* reported that ADT with a gonadotropin-releasing hormone (GnRH) agonist was associated with an increased risk of incident diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death. (143) However, EORTC trials 22863 and 22961 and RTOG trial 85-31 found no association between ADT and cardiovascular mortality in men with cT3 or lymph node–positive disease. (129, 140, 144)

9.7.2 Interstitial therapy

Men with high-risk PCa are considered poor candidates for brachytherapy alone. (10) D'Amico et al. studied men with high-risk, locally advanced PCa (≥cT3a, Gleason score 8-10, or PSA >20 ng/ ml) treated with brachytherapy alone, brachytherapy with neoadjuvant ADT, EBRT, or both. Brachytherapy alone was suboptimal in regard to PCa-specific mortality after a median follow-up of 5.1 years. The combination of neoadjuvant ADT with EBRT plus brachytherapy was associated with decreased PCa-specific mortality despite the fact that men who received both ADT and EBRT were more likely to have palpable localized or locally advanced disease (p < 0.001), Gleason score of 7-10 (p<0.001), or all three high-risk factors (p<0.001). (145) Fang *et al.* reported outcomes for men with a Gleason score of 8-10 with a PSA \leq 15ng/ml who underwent permanent brachytherapy, with most (91%) receiving EBRT prior to brachytherapy, and some (64.9%) receiving ADT prior to implantation. Ten-year outcome for patients with and without ADT was 92.5% and 95.2%, respectively, for cancerspecific death (p=0.562); 92.6% and 86.5%, respectively, for biochemical progression-free survival (p=0.204); and 66.0% and 75.2%, respectively, for OS (p=0.179). (146) In this non-randomized study, the addition of ADT did not therefore significantly alter outcomes. Demanes et al. reported high BRFS rates in men treated with high-dose rate brachytherapy and EBRT with or without ADT. Subgroup analysis revealed no statistically significant difference in 5-, or 10-year biochemical recurrence free rates in men with high-risk disease who received brachytherapy plus EBRT with (5-year, 81%; 10-year, 70%) or without (5-year, 83%; 10-year, 62%) ADT. (147) The association of brachytherapy after EBRT as a multimodal approach for high-risk, locally advanced PCa is emerging. Further randomized studies are required to elucidate the long-term benefits and side effects.

9.8 Experimental Therapies— Cryotherapy and High-intensity Focused Ultrasound

Most national and international entities consider ablative treatments to be alternative treatment options, which should be classified under investigational status. The American Urological Association (AUA) Best Practice Statement of Cryosurgery for the Treatment of Localized Prostate Cancer reported in 2008 that high-risk patients with a negative metastatic evaluation are candidates for primary cryosurgery but caution that they may require multimodal therapy. (148) The panel also noted that outcomes for clinical stage T3 disease are limited and therefore the role of cryoablation in this disease state is unknown. The AUA Guideline for the Management of Clinically Localized Prostate Cancer, in a 2007 update, noted that although experience with high-intensity focused ultrasound (HIFU) is limited, patients with high-risk localized disease should be offered the opportunity to participate in clinical trials to evaluate forms of treatment. (5) Other guidelines, such as the American College of Radiology (ACR) Appropriateness Criteria for locally advanced high-risk PCa, note that cryotherapy is an experimental option for definitive therapy, stipulating that long-term results are unclear. The NCCN, however, only recommends cryotherapy as an option for salvage treatment in cases of relapse after RT. (10) The EAU identifies cryosurgical ablation and HIFU as alternative treatment options for patients who are not suitable for RP (6); the EAU panel noted ideal candidates should have a PSA <20ng/ml and Gleason score <7. The UK National Institute for Health and Clinical Excellence (NICE) recent guidelines state that HIFU and cryotherapy are only recommended for men with localized PCa in the context of clinical trials. (149) In the US, HIFU is considered as a salvage therapy in clinical protocols, and in Europe and Asia, a number of centres have used HIFU in the primary setting under experimental protocols in low-intermediate risk patients and, in some cases, high-risk patient populations.

9.8.1 **Oncologic outcome—primary whole-gland cryoablation**

One of the largest datasets comes from the Cryo On-Line Data (COLD) registry, containing approximately 1,200 patients treated with cryosurgery. (150) Among a small subset of 31 high-risk patients with 5-year follow-up, Jones et al. reported a BRFS rate of 75.3% (ASTRO criteria) and 62.2% (Phoenix criteria). (150) Long *et al.* reported on a cohort of 385 high-risk patients (≥ 2 of the following: stage \geq T2b, PSA >10 ng/ml, Gleason \geq 7) derived from a multicentre pooled analysis. (154) In a series of 24 high-risk patients with a median of 41 months of follow-up, El Hayek and colleagues reported a PSA failure-free rate of 42.8% at 5 years. (151) Although Guo et al. obtained a BRFS rate at 1, 2, and 3 years of 92.5%, 87.1%, and 73.3%, respectively, following cryoablation for cT3 disease, of concern, 24.4% of patients developed local recurrence or metastasis by 3 years. (152) Preplica et al. reported an 83.3% BRFS rate among 65 intermediate- and high-risk patients (PSA \geq 10 ng/ml, Gleason score \geq 8, or both) treated with cryosurgery at a median follow-up of 35 months according to the ASTRO criteria. (153) Considering only those patients with a Gleason score ≥ 8 , 78.6% of patients achieved a PSA <1.0 ng/ ml at 2 years. Biopsy was only performed in 12% of patients. Finally, in a multicentre study that included 385 intermediate- and high-risk patients (≥2 factors: ≥stage T2b, PSA >10.0 ng/ml, Gleason \geq 7) a 5-year biochemical failure rate of 55% and 64% was reported using the failure definition of PSA >1.0 ng/ml and 0.5 ng/ml, respectively. (154)

9.8.2 **Oncologic outcome—high-intensity focused ultrasound**

Similarly to cryoablation, the definition of treatment success following HIFU has not been standardized, relying on ASTRO, Phoenix, or other definitions. (155) Applying radiation-based PSA criteria to HIFU suffers from discordant PSA kinetics between treatment modalities—radiation-induced cell death and PSA nadir may take 18 months or longer compared with a more rapid PSA decline following ablation. Following HIFU, for example, Poissonnier *et al.* observed that all patients achieved their PSA nadir within 6 months. (156) In addition, PSA bounce does not occur following HIFU. (157)

In a recent multicentre trial, Crouzet *et al.* analyzed outcomes for a large cohort of patients who underwent HIFU with at least 2-year follow-up. (157) Although patients with T3 disease were excluded, 108 patients met the 2003 D'Amico high-risk criteria. All patients underwent biopsy at 6 months regardless of PSA and in the setting of 3 consecutive rises in PSA. According to the Phoenix criteria, the 5- and 7-year BRFS rate was 68% and 62%, respectively. When additional treatments were included into the outcome definition (salvage therapy with RT or androgen deprivation), the 5- and 7-year DFS rate was 57% and 39%, respectively. Although biopsy information was only available in 73.3% of the overall cohort, among high-risk patients, the positive biopsy rate was 28%. Of note, these outcomes include the 35.1% of patients who underwent retreatment. This study is one of the

few with sufficient follow-up of 8 years to report the MFS rate (97%) and the CSS rate (99%). Callea *et al.* performed HIFU in 95 high-risk patients, of which 43.1% had a PSA nadir of <0.5 ng/ml and 36.9% had a positive biopsy following treatment. (158) Ficarra *et al.* evaluated HIFU in a high-risk cohort of patients that included locally advanced disease (cT stage \geq T3a, Gleason \geq 8, or PSA >20 ng/ml). (159) Sextant biopsy positivity at 6 months occurred in 23% of patients. PSA values were not useful in this study due to the use of a luteinizing hormone-releasing hormone gene (LHRH) analog for 3 years peri-operatively.

In summary, evidence from prospective long-term trials is needed before recommending cryoblation or HIFU as primary therapy for patients with high-risk PCa.

9.9 Conservative Management

Conservative management (watchful waiting with delayed ADT) does not appear to be a good option for men with high-risk PCa with a long life expectancy and minimal comorbidities. A retrospective population-based cohort study reviewing long-term outcomes of conservatively treated men with clinically localized PCa revealed a high probability of PCa-specific death in men with highrisk (Gleason grade 8-10) disease, with an observed mortality rate of 121 deaths per 1,000 person years within 10 years of diagnosis. Conversely, in the low-risk group (Gleason grade 2-4), a mortality rate of 6 deaths per 1,000 person years was observed during 20 years of follow-up. (160) An observational study of 223 patients with early stage, initially untreated PCa revealed a PCa-specific mortality rate of 56% among men with poorly differentiated cancer (Grade 3, WHO classification of malignant diseases). (161) In a more recent series, Lu-Yao et al. utilized the SEER cancer registries and reported that men with a median age of 78 years and poorly differentiated tumours who were initially treated with conservative management had a 10-year PCa-specific mortality of 25.6% (95% CI, 23.7%-28.3%). (162) A Scandinavian retrospective analysis of 12,184 men with locally advanced PCa managed with non-curative intent, revealed a PCa-specific mortality rate of 52% and 64% at 8 years for men with Gleason score 7, and 8-10 disease, respectively. (163) A significant risk of disease progression and cancer-specific mortality is seen in men with high-risk PCa, and some form of treatment with curative intent is typically warranted in otherwise healthy men. Watchful waiting should only be considered in asymptomatic men with significant comorbidities conferring an estimated life expectancy of <10 years, in men who have contraindications to local therapy, or in men who are unwilling to accept the side effects of known treatment.

9.10 Primary Androgen Deprivation Therapy

There are now two reported prospective trials comparing primary ADT alone with ADT plus EBRT in men with high-risk, locally advanced disease. Widmark *et al.* included patients with cT1-cT3 N0-X M0 disease showed significant reductions in 10-year BRFS (p<0.001), cancer-specific mortality

(p < 0.001), and overall mortality (p = 0.004) rates for the EBRT plus ADT arm compared with the ADT arm. (164) The long-term ADT administered in both arms was 3 months of combined androgen blockade followed by continuous flutamide monotherapy. The second study, a NCIC/MRC Intergroup study, reported by Warde et al., randomized 1,205 patients with locally advanced or high risk, organ-confined disease, to ADT alone or to ADT plus RT. The ADT consisted of either LHRH agonists or bilateral orchiectomy. At a median follow-up of 6 years, RT combined with ADT improved OS by 8% (HR, 0.77; p=0.033), and PCa-specific survival by 11% (HR, 0.54; p=0.001). Late grade 3 GI and GU toxicities were uncommon events in both arms. Grade 3 diarrhea was reported in 0.7% (ADT arm) and 1.3% (ADT+RT arm), and rectal bleeding in 0.5% (ADT arm) and 0.3% (ADT+RT arm). The grade 3 GU toxicity rate was 2.3% in both treatment arms. (165) In the Bicalutamide EPC Program, after a median follow-up of 7.4 years, men with locally advanced (cT3-cT4, any N; or N +) disease who received 150 mg bicalutamide daily as primary therapy showed no statistically significant improvement in OS compared with those receiving placebo. (90) In a randomized trial comparing immediate versus deferred ADT in men with T0-T4 PCa, a modest but statistically significant increase in OS was demonstrated in the immediate ADT group after a median follow-up of 7.8 years. Death from PCa was the most common cause of death in men in both arms. (166) Primary ADT without local treatment is not recommended for patients who are medically able to undergo local therapy and are willing to accept the side effects of RP and/or EBRT.

9.11 Clinical Trials

The justification of adjuvant radiation therapy is that treatment failure after potentially curative RP is mainly a result of lack of local control. This idea has led to the development of novel multimodal treatment approaches aimed at improving local control. Neoadjuvant or intra-operative RT for highrisk, locally advanced disease is being evaluated as a novel therapeutic approach. (167) The results of phase II clinical trials examining neoadjuvant chemotherapy with or without ADT have found mixed results. Vuky et al. reported preliminary results from a phase II trial in which 31 patients with highrisk disease were treated with docetaxel and gefitinib for 2 months before RP. None of the 31 patients had evidence of complete pathologic response. (168) Short-term neoadjuvant docetaxel and complete androgen blockade in 57 patients with cT1c-T3 disease and PSA >20 ng/ml or Gleason score \geq 7 (4+3) followed by RP found a complete pathologic response rate of 6%, similar to what would be expected from neoadjuvant ADT alone. (169) Prayer-Galetti et al. reported the results of 22 patients with \geq cT3, and/or PSA \geq 15 ng/ml, and/or Gleason score \geq 8 who received ADT until PSA nadir and then a combined regimen of ADT, estramustine, and docetaxel prior to RP. The rate of organ-confined disease was 58% compared with a predicted likelihood of 8% derived from the Kattan nomogram. Of the patients, 85% remained disease free at 5 years. (170) Long-term data regarding neoadjuvant RT or chemotherapy is lacking, and the results of several ongoing trials are eagerly anticipated.

9.12 Summary and Outlook

Numerous challenges remain in optimizing management of high-risk, localized or locally advanced PCa. These include improving our ability to accurately define and stratify risk, improving the imaging modalities to further define the extent of local, regional, and distant disease, and further refining/improving local therapies. Additionally, the optimal timing and delivery techniques of various neoadjuvant and adjuvant therapies require continued investigation (Table 1). Due to the potential lethality of high-risk PCa, aggressive therapy is generally warranted for men that have good WHO performance status and good life expectancy. Frequently, a multimodal approach with some combination of surgery, RT, and ADT is required to maximize oncologic outcomes and mitigate mortality. Ongoing investigations for combining the presently available therapies and novel treatment regimens are ongoing and are of high priority.

TABLE 1 Summary, Principles of Management-High-risk, Locally Advanced PCa

Clinical Stage ≥T3, Biopsy Gleason Score 8-10, or PSA >20 ng/ml

Strategy	Recommendation		
Watchful Waiting	Not Recommended. May be considered for patients unwilling or unfit to undergo potential curative local therapy, or systemic ADT.		
Primary ADT	Not Recommended. Modest survival advantage compared with deferred treatment, but clearly inferior to potential curative therapy. May be considered for patients unwilling or unfit to undergo potential curative therapy.		
Radical Prostatectomy	Recommended. Open or robotic-assisted laparoscopic approach may be considered depending on surgeon experience.		
Pelvic Lymph Node Dissection	Recommended. Extended dissection improves staging and potentially reduces disease recurrence while improving OS.		
Nerve-sparing Resection	Not recommended on the side(s) with extracapsular extension based on digital rectal examination. Further studies are required.		
NADT	Not recommended. Improvements in pathologic outcomes, but no improvement in DFS or OS.		
Adjuvant ADT	Not recommended. Possible improvements in PFS without improvement in OS. Further studies required to determine clinical benefit.		
Adjuvant or Early SRT	Recommended as part of a multimodal therapy. The dose should be at least 66-70 Gy to the prostate bed. Neoadjuvant and concurrent ADT and pelvic lymph node radiation can be considered—clinical trials are ongoing.		
Primary RT	Recommended. Modern delivery techniques including IMRT and (IGRT are required to safely deliver an effective dose (>78 Gy).		
Pelvic Lymph Node Irradiation	Consideration of pelvic lymph node irradiation should be made in patients with a high risk of nodal involvement.		
Neoadjuvant/concurrent/adjuvant ADT Combined with RT	Recommended for a total of 2-3 years		
Interstitial Therapy	High dose rate brachytherapy with EBRT may be considered. Addition of neoadjuvant/ concurrent/adjuvant ADT can be considered although optimal timing and duration and efficacy not yet determined.		
1. Cryosurgery/HIFU	2. As primary therapy should only be considered for patients who refuse RP or EBRT and as an investigational treatment.		



9.13 References

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10

C10

New Therapeutic Targets and Treatments for Metastatic Prostate Cancer

Including Castration-Resistant Prostate Cancer and Prevention of Bone Morbidity in Prostate Cancer Patients

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10.1 The Metastatic Prostate Cancer Clinical Paradigm in the 21st Century

Measurement of prostate-specific antigen (PSA) has profoundly affected virtually all clinical aspects of prostate cancer. A sharp increase in both the incidence of age-adjusted prostate cancer (about 100 percent) and the proportion of patients with early stages of the disease at the time of diagnosis (stage migration) has coincided with the advent of widespread PSA testing (1,2). In a relatively short period of time (only two decades), there has also been a categorical shift in the extent of disease at the time of the initial diagnosis of all stages of prostate cancer. The proportion of patients with clinical evidence of regional and distant metastasis has decreased dramatically. Incorporation of routine serum PSA testing in the management and treatment decisions process has also profoundly influenced the overall clinical landscape of the disease and it is generally felt that conventional staging grouping (TNM staging) does not adequately represent the clinical status of relapsed prostate cancer (3).

In parallel and concomitantly to the stage migration, the proportion of patients offered local modalities of treatment has increased substantially. First, relapses after local treatment usually present with rising PSA levels in the absence of clinical or radiological evidence of local or distant recurrence (M0 disease), whereas only a small proportion of patients treated locally demonstrate early clinical evidence of metastasis (M+ disease).

While precise figures are not available, a significant proportion of patients with M0 disease (biochemically relapsed after local therapy) is initiated on androgen deprivation treatment before metastases are evident (2), and eventually develop subsequent progression without any other clinical evidence of disease (second biochemical progression with serum levels of testosterone in the castrate range (< 50ng/dl)). These patients are categorized as having nonmetastatic, castration-resistant disease and the majority will eventually (over a variable period of time) demonstrate subsequent clinically evident metastasis, at which point they are categorized as having metastatic, castration-resistant disease.

Less than 5% of patients presenting "de novo" with prostate cancer today demonstrate clinical evidence of distant metastasis. These patients are treated with conventional androgen deprivation approaches and when there is evidence of disease progression, they are categorized as having metastatic, castration-resistant prostate cancer. **Figure 1** illustrates the dynamics of this classification, which takes in consideration clinical (including treatment) and biochemical parameters.



10.1.1 Metastatic hormone-naïve prostate cancer

The survival of men with metastatic prostate cancer has changed significantly during the past two decades. The outcome of patients enrolled in clinical trials employing similar regimens of androgen deprivation across the past two decades illustrates and supports this observation. From 1989-1993 the Southwest Oncology Group (SWOG) conducted a trial in 1,387 men with newly diagnosed prostate cancer treated with bilateral orchiectomy with or without the antiandrogen flutamide (SWOG 8894, double blinded-placebo controlled trial) which resulted in no significant differences between arms and the overall median survival in these patients was 33 months (4). From 1995-2009, the SWOG conducted a study in the same patient population (SWOG 9936) which employed a GnRH analogue with bicalutamide either continuously or intermittently. The initial median survival data on patients treated with continuous ADT was 49 months (a comparison between arms has not been performed at this time) (5). The risk of death observed in SWOG 9936 was significantly lower compared to SWOG

8894 (HR 0.77, 95% CI, 0.6-0.8, p< .0001) suggesting a 30% reduction of risk of death (5). Various factors could explain the difference, such as the change in patterns of practice emerging from a wide-spread utilization of the PSA test in the clinic and stage migration, resulting in a lower incidence of unfavourable prognostic factors on SWOG 9936 compared to the older SWOG 8894 (5).

A number of prognostic factors are recognized in patients with metastatic disease, including hemoglobin level, performance status, pain, extent of disease and the presence of significant comorbidities (4,6). The distribution of important prognostic factors among men with metastatic disease enrolled in trials over the past two decades indicates that in the most recent series, the proportion of patients with symptoms, hemoglobin less than 10 gm/dl, limited performance status and extensive metastatic disease is substantially lower than in the older studies. While unintentional patient selection bias cannot be excluded, it is very likely that this is a result of stage migration. The importance of a leadtime effect is further illustrated by the experience in patients who relapse biochemically after local treatment and are subsequently monitored with frequent serial PSA determinations. In this group of patients, the survival figures usually extend beyond the five-year range. Again, this is most likely because of close monitoring and frequent imaging, and early documentation of metastases. Figure 2 illustrates the Johns Hopkins Hospital experience in patients with biochemically relapsed disease after radical prostatectomy, and were subsequently followed by at least yearly PSAs, and scans, and who developed metastatic disease during the follow-up period. The vast majority of patients in this experience have limited metastatic disease, all have normal hemoglobin levels and virtually all are asymptomatic of their disease (7).



10.1.2 Metastatic, castration-resistant prostate cancer

The clinical course of metastatic castration-resistant prostate cancer has also changed considerably, for the same reasons discussed above. Initiation of androgen-deprivation therapy prior to the development of metastasis, and more frequent diagnostic imaging have contributed to earlier detection of metastatic disease in androgen-deprived patients. Furthermore, new treatments have further extended survival in patients progressing after initial hormonal therapy. Although precise figures are not available, the survival of metastatic castration-resistant prostate cancer measured from the first documented metastasis (in the castrate state) until death may now extend well beyond previously reported figures (**Figure 1**). Important recent knowledge gained on the mechanisms of prostate cancer progression in the castrate state of the disease, and better understanding of the biological mechanisms involved in the androgen receptor signalling have provided the rationale for designing some of the most promising targeted treatments for this disease. It is likely that the therapeutic advances resulting from the clinical application of new compounds will further expand the m-CRPC paradigm. Furthermore, the stage migration introduced an excellent opportunity to evaluate the clinical transition from the non-metastatic to the early metastatic state as a clinical model for drug development. This is especially attractive for bone-targeted compounds or other non-conventional cytotoxics, and immune-based approaches that could affect the rate of disease progression. The metastatic castration-resistant state is a "dynamic clinical paradigm"; widely heterogeneous from the clinical points of view. Appropriate definition of the clinical course and careful definition of clinical/laboratory landmarks (new markers, circulating tumour cells, new imaging techniques, etc.) is an absolute necessity to facilitate the development of new promising therapeutic modalities in the m-CRPC state.

10.2 Natural History of Progression to Metastasis in Relapsed, Non-metastatic Prostate Cancer

Careful definition of clinical and therapeutic parameters that characterize a patient population prior to the development of m-CRPC is clearly important to further understand the evolving natural history in the new clinical paradigm, selection of potential treatment intervention and definition of endpoints for clinical trials. Baseline characteristics including type of local treatments, pathological features, pattern of progression, extent of disease, and possibly a variety of host factors are most likely of important prognostic significance.

10.3 Non-metastatic (M0), Biochemically Relapsed after Local Treatment (hormone-naïve)

Prostate cancer that has recurred after adequate local treatment, or has progressed after adequate androgen deprivation therapy, exhibits a remarkably variable, and often indolent, natural history. Antonarakis *et al.* (8) recently updated the experience in patients who demonstrate evidence of biochemical recurrence after radical prostatectomy. Between July 1981 and July 2007, a total of 8,801 patients with prostate adenocarcinoma underwent radical prostatectomy at the Johns Hopkins Hospital (Baltimore, Maryland, USA) and then received no adjuvant or salvage therapy unless distant metastases were detected. Of these, 774 men (8.8%) developed biochemical recurrence after a mean (median) follow-up of 8.5 (8) years from the time of surgery (range, 1.0-25.2 years). Biochemical recurrence was defined as a single postoperative prostate specific antigen (PSA) value of at least 0.2 ng/mL. Mean follow-up after prostatectomy was 8.9 years, and after biochemical recurrence was 4.7

years. At the last follow-up, 126 of the 430 patients (29.3%) had developed distant metastases. The median PSA level at the time of the first metastasis was 31.4 ng/mL. Using multivariable regression, three variables emerged as independently predictive of the time to metastasis: PSA doubling time (<3.0 vs 3.0-8.9 vs 9.0-14.9 vs \geq 15.0 months; p < .0001), pathological Gleason score (\leq 7 vs 8-10; p = .005), and time from prostatectomy to PSA recurrence (\leq 3 vs > 3 years; p < .021). Using these three parameters, a table (**Table 1**) was constructed enabling estimation of median metastasis-free survival and five-year probability of metastatic progression after PSA recurrence. These results may provide the framework for the rational selection of patients, treatments, and endpoints for clinical trials involving men with biochemically-relapsed disease and in addition it may provide a rational basis for patient counselling and risk-adapted treatment planning. Similar experience was reported by D'Amico *et al.* (9) in patients treated with radiation therapy as the primary treatment given with curative intent.

TABLE 1 Algorithm for estimating metastasis-free survival using combinations of
pathological Gleason score, time to PSA recurrence, and PSA doubling time.
For each combination of factors (16 possibilities), the median metastasis-free
survival and the five-year probability of metastasis-free survival after PSA
recurrence are provided. 10-year metastasis-free survival probabilities are not
provided due to the small numbers of patients at risk beyond five years in many of
the patient subsets (these data are considered preliminary and require validation).
Adapted from Antonarakis *et al.* (8).

PSADT (months)	< 3			3 - 9				9 - 15				≥ 15										
Gleason score	8 -	10	\leq	7	8 -	10	\leq	7	8 -	10	≤7		≤7		≤7		≤7		8 - 10		≤7	
Time to PSA relapse (years)	≤3	>3	≤3	> 3	≤3	>3	≤3	> 3	≤3	>3	≤3	> 3	≤3	>3	≤3	> 3						
Median metastasis-free survival (years)	1	1	1	1	2	2	4	6	7	6	9	13	10	>11†	15	>14‡						
Metastasis-free rate at 5 years %	12°	0ª	20 ^d	0 ^b	30	19°	43	62	74	67	65	84	81	76	88	93						

10.3.1 Non-metastatic, castration-resistant prostate cancer

A proportion of patients with relapsed prostate cancer managed during the PSA era receive androgen deprivation based prior to the development of metastatic disease. Eventually the majority of these patients demonstrate evidence of advancing disease primarily by subsequent rises of serum PSA levels without any other clinical/radiological evidence of disease. This subset of patients is classified as non-metastatic castration-resistant disease. The clinical course of these patients is extremely variable. Factors that could account for the outcome in the castration-resistant M0 patients include: criteria for initiation of ADT (PSADT, Gleason's score, time from local treatment to evidence of biochemical recurrence), response to the initial hormonal therapy, PSADT at recurrence and PSA level in the castrate state (10,11). It is unclear however, whether PSA dynamics in the hormonenaïve state are similar to the dynamics at the castration-resistant state. Similarly, the most common approach in this group of patients is the use of sequential endocrine maneuvers aimed at androgen receptor signalling pathways, although other approaches, such as bone-targeted interventions are also commonly evaluated in the subset. The effects of treatment (usually multiple interventions are used sequentially) on time to clinical progression has now been evaluated in clinical trials and data on their natural history is likely to be further elucidated from prospective trials.

Nelson and colleagues reported the observations of the placebo arm on a randomized, double-blind, placebo-controlled study to evaluate the effects of atrasentan on time to disease progression in men with progressive castration-resistant prostate cancer and no radiographic evidence of bone metastases (Abbott M00-244) (12). At two years, 46% of subjects had developed bone metastases, and 20% had died. Median bone metastasis-free survival was 25 months. In multivariate analyses, baseline PSA \geq 13.1 ng/mL was associated with shorter overall survival (relative risk [RR], 2.34; 95% confidence interval [CI], 1.71–3.21; *p* < .0001), time to first bone metastasis (RR, 1.98; 95% CI, 1.43-2.74; p < .0001), and bone metastasis-free survival (RR, 1.98; 95% CI, 1.45–2.70; p < .0001). PSA velocity was significantly associated with overall and bone metastasis-free survival. In another placebo controlled trial (prematurely terminated) involving the bisphosphonate zoledronic acid versus placebo, of 201 subjects assigned to the placebo group, one third of the men developed bone metastases after two years, and median bone metastasis-free survival was 30 months (13). Higher baseline PSA and PSA velocity were associated with time to first bone metastasis and survival. Additional information on prior therapy, and response to treatment was not included in the reported results (13, 14). At the present time, there is no consensus on a standard treatment approach for patients with non-metastatic castration-resistant prostate cancer. However most patients are treated with sequential approaches targeting the AR signalling pathways (see below).

10.4 Therapeutic Progress

10.4.1 **Targeting the androgen signalling axis**

The first systemic treatment offered to most men with prostate cancer targets the androgen signalling axis (**Figure 3**), accomplished using androgen deprivation, antiandrogens, or a combination of androgen deprivation and anti-androgens (15,16,17). In the prostate, testosterone, produced by Leydig cells in the testes upon stimulation by luteinizing hormone (LH), is converted to dihydrotestosterone (DHT) by the action of 5 α -reductase (18). DHT, a more potent androgen than testosterone, binds to intracellular androgen receptors to activate the expression of target genes, such as PSA (19,20,21). In the normal prostate epithelium, androgenic hormones principally drive differentiation to a columnar secretory phenotype. However, in prostate cancer cells, the androgen signalling axis contributes to cell growth and survival, as well as to differentiation.

Treatments Targeting the Androgen Axis



As a consequence, most men enjoy an initial benefit to treatment targeting androgen signaling, characterized by a fall in serum PSA and relief of symptoms attributable to prostate cancer. Unfortunately, the ultimate emergence of androgen-independent prostate cancer is common. In most cases, androgen-independent prostate cancers maintain the expression and function of androgen receptors despite therapeutic reduction of serum androgen levels (19-25).

For human prostate cancer cells studied in xenograft models, progression to androgen-independence appears to be associated with increased expression of androgen receptor transcripts and increased abundance of androgen receptors, presumably contributing to an increased sensitivity of the receptors to low levels of androgenic hormones (21-25). Whether this phenomenon occurs commonly in men suffering androgen-independent prostate cancer has not been established. Nonetheless, *AR*, encoding the androgen receptor, is a known target for somatic genome alterations in prostate cancer, especially upon progression of the disease to androgen-independence (24,28-41). *AR* mutations, encoding androgen receptors with altered ligand specificity, can result in agonist activity for anti-androgens, providing one molecular explanation for the "anti-androgen withdrawal" syndrome, in which men with prostate cancer progression, despite treatment with a combination of androgen deprivation and anti-androgens, benefit from discontinuation of the anti-androgen (31-38). Finally, androgen-independent prostate cancer cells containing wild-type androgen levels, as a result of posttranslational modifications of the androgen receptor and/or androgen levels, as a result of posttranslational modifications of the androgen receptor and/or androgen receptor co-activators in response to other growth factor signalling pathways (39-45).

FIGURE 3

10.5 Mechanisms of castrationresistant disease

10.5.1 **Persistent androgen receptor (AR) signalling: AR amplifications, mutations, splice variants**

Activation of the intracellular androgen receptor (AR) by androgens (*e.g.* testosterone and dihydrotestosterone) stimulates cell proliferation while inhibiting apoptosis in prostate cancer cells, resulting in tumour growth and progression (46). In the absence of androgens, AR is bound to heatshock proteins (*e.g.* HSP90) and remains primarily in the cytoplasm. Upon activation by androgens, AR dissociates from the heat-shock proteins and translocates into the nucleus, where it binds (with coactivators and corepressors) to androgen-response elements of DNA to induce transcriptional activation of target genes (47). During progression to castration resistance induced by persistent androgen suppression, AR signalling is maintained through a variety of mechanisms including increased expression of AR (48,49), amplification of the *AR* gene (50), and structural changes in AR caused by genetic mutations (51) or mRNA splice variants (52).

The increased expression, greater stability, and nuclear localization of AR in CRPC are all indicative of an overactive AR, which can be stimulated by minute concentrations of circulating androgens (53). To this end, animal experiments have demonstrated that AR overexpression is necessary and sufficient for growth of many prostate cancer cells in the setting of castrate serum androgen levels (54). Similarly, in patients with CRPC, increased transcription of the AR gene and persistence of the AR protein were found in cancer cells isolated from metastatic tissue samples. In addition to amplification of the wild-type AR gene, increased quantity of AR in CRPC may be caused by greater stabilization and slower turnover of AR (55). Moreover, while wild-type AR is only activated by androgens, the specificity of ligand binding can be broadened by somatic mutations usually occurring in the ligand-binding domain of AR (56). These mutations can lead to decreased specificity and inappropriate activation of the receptor by non-androgens, resulting in a promiscuous AR phenotype that may lead to activation by estrogens, progestins, tyrosine kinases, and other oncogenic signalling molecules. Finally, the castration-resistant state may promote alternative splicing of the AR gene, yielding variant mRNA transcripts lacking the ligand-binding domain, which are constitutively active (57,58). Thus, there are a variety of AR-mediated mechanisms of resistance to androgen deprivation therapy, each of which may be anticipated to require different therapeutic approaches. (Table 2)

TABLE 2 Mechanisms of Castration-resistance in Prostate Cancer.

Persistent androgen receptor (AR) signalling

- Amplification of the AR gene
- Increased expression of the AR protein
- Greater stability and nuclear localization of the AR protein
- Genetic mutations in the AR gene
- Promiscuous activation of the AR protein by non-androgens (e.g. estrogens, progestins, tyrosine kinases)
- Ligand-independent (constitutive) activation of the AR protein
- Active AR mRNA splice variants

Ectopic androgen synthesis

- Androgen synthesis by adrenal glands
- Intratumoural androgen synthesis
- Increased conversion of extra-gonadal androgens to testosterone

Modulation of AR coregulators

- Overexpression of steroid receptor coactivators (e.g. p160, NCOA2)
- Downregulation of steroid receptor corepressors (e.g. β-arrestin 2)
- Facilitation of AR-mediated transcription

Activation of compensatory AR-independent pathways

- Activation of the PI3K/Akt/mTOR pathway
- Activation of the Ras/Raf/MEK/ERK pathway
- Overexpression of anti-apoptotic proteins (e.g. Bcl-2, Bcl-XL, clusterin, survivin)
- Activation of other pathways (e.g. TGF-βR, Wnt/ -catenin, Src kinase, IL-6R)

10.5.2 Ectopic androgen synthesis

Although androgen deprivation therapy (using luteinizing hormone-releasing hormone agonists or antagonists) decreases total serum testosterone levels by approximately 95%, this intervention primarily inhibits gonadal androgen synthesis and does not affect extra-gonadal androgens. It is now established that, in CRPC, there is continuous production of androgens by the adrenal glands as wells as the prostate cancer itself (59,60). Moreover, in the castrate state, intraprostatic concentrations of testosterone and dihydrotestosterone remain sufficient to stimulate AR. The main mechanisms by which CRPC is able to overcome low circulating androgen levels are local conversion of adrenal androgens (*e.g.* androstenedione) to testosterone (61), and *de novo* intratumoural synthesis of androgens through increased expression of steroidogenic enzymes such as cytochrome P450 17 (CYP17) (62). This enzyme is the target of several new drugs for CRPC (63).

10.5.3 **Co-regulators of AR**

Coactivators (and corepressors) function as signalling adjuncts for AR-mediated transcription, facilitating or inhibiting binding and activation of AR to androgen-response elements in promoter and enhancer regions of DNA. Among the most important transcriptional coregulators in prostate cancer is the p160 family of nuclear steroid receptor coactivator (64). Preclinical experiments and studies of human prostate tumours strongly suggest that overexpression of such steroid receptor coactivators is important in the emergence of the castration-resistant phenotype (65,66). In addition, another nuclear receptor coactivator, NCOA2, has recently been reported to function as an oncogene in a subset of prostate cancers (67). Finally, downregulation of AR-related corepressors may also be involved in the development of CRPC (68).

10.5.4 **AR-independent pathways**

Castration resistance may also be caused by the activation of other oncogenic survival pathways through promiscuous activation of AR by non-androgens (*e.g.* estrogens, progestins, antiandrogens, receptor tyrosine kinases), or by alternative mechanisms including activation of compensatory signalling pathways (69). For example, it has been shown that signalling, which is normally AR-dependent, may be triggered in CRPC even at undetectable androgen levels by activation of other receptor tyrosine kinases (*e.g.* IGF-1R, EGF-R, VEGF-R) and their associated signal-transduction pathways (*e.g.* PI3K/Akt/mTOR pathway, Ras/Raf/MEK/ERK pathway) (70). In addition, crosstalk has been observed between the cell-surface tyrosine kinase HER2/neu and/or HER3 and intracellular AR in CRPC, resulting in AR activation by HER2/neu in the absence of androgens (71,72). Activation of other receptors and their pathways (*e.g.* TGF- β R, Wnt/ β -catenin, Src kinase, and IL-6R) has also been implicated in crosstalk with AR (73,74).

Another potential resistance mechanism against castration involves the activation of antiapoptotic pathways associated with survival. In humans and in animal models of advanced prostate cancer, overexpression of the antiapoptotic protein, Bcl-2, has been found to confer resistance to androgen suppression (75). In addition, other antiapoptotic factors related to Bcl-2, such as Bcl-XL and survivin, are also frequently overexpressed in CRPC but not in hormone-responsive disease (76,77).

These biologic features lend themselves to a variety of treatment strategies that have been exploited to develop novel agents. The first to have been shown to confer clinical benefit to patients is to target non-testicular sources of androgen, be they produced by tumour (autocrine) or extra-tumoural sources (paracrine).

The fact the AR is active even through castration therapy makes AR signalling a prime therapeutic target. Indeed, first-generation non-steroidal anti-androgens such as bicalutamide, nilutamide, and flutamide have long been part of the clinical armamentarium, and have been extensively explored in conjunction with castration or as second-line therapy after patients progressed through castration (see section under Combined Androgen Blockade). These relatively low-affinity ligands bind to the C-terminal portion of the AR-ligand binding domain, and function both by passively competing with patients' endogenous AR ligand such as DHT, or by active mechanisms such as recruiting corepressor or inhibiting coactivator binding (However, these agents have the capacity to function as

agonists as well as antagonists, via diverse mechanisms, such as mutations, that render the AR to be promiscuously activated rather than repressed, and by AR overexpression, at which time traditional anti-androgens can induce coactivator recruitment, allow for nuclear translocation, and undergo DNA binding.

10.5.5 **Gonadal androgen deprivation in hormone-naïve disease**

Androgen deprivation therapy for prostate cancer involves reduction of circulating testosterone levels to <50 ng/mL, accomplished via surgical removal of the testis (bilateral orchiectomy), by inhibition of the synthesis and release of pituitary gonadotropins by luteinizing-hormone-releasing hormone (LHRH) analogue suppression of testosterone production, though comparable to that achieved by castration, does not reach its nadir until after 3-4 weeks of treatment. By acting as LHRH agonists, the LHRH analogues first trigger LH release by the pituitary, rarely associated with a symptomatic "flare" of prostate cancer, then after chronic administration, suppress both LH and testosterone production (78,79). Currently, long-acting depot preparations of LHRH analogues (administered monthly, every 3 or 4 months, or yearly) are most commonly used. LHRH antagonists appear to achieve suppression of testosterone production without the brief flare associated accompanying initiation of treatment with LHRH analogues (80,81). However, there are no long-term studies testing the efficacy of LHRH antagonists for prostate cancer, in comparison to bilateral orchiectomy or LHRH analogues, because LHRH antagonists can fairly rapidly lower testosterone levels without a risk for a symptomatic disease flare. Bilateral orchiectomy results in a rapid decline of testosterone to 5-10% of normal values; agents may offer an advantage over LHRH analogues in a clinical setting where such a flare might carry a threat of significant morbidity. Finally, the administration of pharmacological doses of synthetic estrogens, such as diethylstilbestrol (DES), represented the earliest strategy for drug treatment of prostate cancer (81). Accumulated data from several prospective randomized clinical trials for men with metastatic prostate cancer have revealed comparable efficacy of bilateral orchiectomy, DES, and LHRH analogues, regardless of the outcome measure used (82-88)). However, when LHRH analogues were found to have fewer serious treatment complications, such as congestive heart failure and thromboembolic events, than DES, estrogens were virtually abandoned in favour of LHRH analogues for the initial treatment of metastatic prostate cancer. Also, many men find LHRH therapy more acceptable than bilateral orhiectomy.

10.6 Combined Androgen Blockade

As discussed previously, anti-androgens directly interact with the androgen receptor, interfering with its *trans*-activation of target gene transcription. These agents have been used as monotherapy, in an attempt to spare side effects of androgen deprivation, and along with androgen-deprivation therapy, as "complete" androgen blockade. The anti-androgen bicalutamide, given as monotherapy, has been reported to provide a similar survival benefit as bilateral orchiectomy for men with locally advanced, but non-metastatic, prostate cancer (stage T3 and T4). However, it was reported to be inferior to androgen deprivation for men with metastatic disease (89).

Side effects of bicalutamide monotherapy at a 150-mg daily dose include significant gynecomastia, and although libido can be preserved, few men remain fully potent (90). The efficacy of antiandrogens as adjuvant therapy for men with high-risk prostate cancer treated with radical prostatectomy, or as treatment for men with a rising serum PSA after adequate local therapy remains to be established. Weak androgenic hormones such as androstenedione and dehydroepiandrosterone are produced in the adrenal glands. In an attempt to neutralize the effects of adrenal androgens, a combination of bilateral orchiectomy (or LHRH analogues) and a nonsteroidal anti-androgen was promoted as a "complete" and rogen blockade (91,92). Initial reports of the efficacy of this treatment combination prompted the initiation of a large number of clinical trials testing whether "complete" androgen blockade offered an advantage over androgen deprivation alone for men with metastatic prostate cancer. Some 7,987 men with metastatic prostate cancer have been enrolled in 27 prospective randomized clinical trials comparing the efficacy of bilateral orchiectomy (or LHRH analogues) alone, to combinations of bilateral orchiectomy (or LHRH analogues) and anti-androgens (93-95). A review of these trials reveals that 24 of the 27 studies reported no significant differences in survival, and 3 studies showed only modest improvements, which were statistically significant, in favour of "complete" androgen blockade (94). In 1995, the Prostate Cancer Trialists' Collaborative Group (PCTCG) reported the results of a meta-analysis from 22 of the randomized trials comparing "complete" androgen blockade to androgen deprivation alone for 5,710 men with prostate cancer. Their findings showed a 2.1% difference in survival in favour of "complete" and rogen blockade (with a 6.4% reduction in annual risk of death) that was not statistically significant (95) (Figure 4). The Agency for Health Care Policy and Research= (AHCPR; results published at http://www.ahcpr.gov/ clinic/index.html#evidence as AHCPR report No.99-E012) also conducted a meta-analysis of all published "complete" androgen blockade clinical trials, finding no difference in 2-year survival rates (hazard ratio = 0.970 with a 95% confidence interval of 0.866 to 1.087). For the 10 trials that reported 5-year survival data, the meta-analysis revealed a minimal 5-year survival difference in favour of "complete" androgen blockade (hazard ratio = 0.871, 95% CI, 0.805-0.9887).

FIGURE 4

Meta-analysis revealed no survival differences between combined (or "maximal") androgen blockade (androgen suppression + antiandrogen) and androgen deprivation alone (95) (androgen suppression only; see reference 66).

Reprinted from The Lancet, 355(9214), Prostate Cancer Trialists Collaborative Group, Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials, Pages 1491-1498, Copyright (2000), with permission from Elsevier.



10.7 Optimal Timing for Initiating Permanent Androgen Deprivation

Androgen deprivation therapy is the standard treatment for men with metastatic androgen-dependent prostate cancer. However, for men with androgen-dependent prostate cancer evident only as a rising serum PSA, the optimal timing for the initiation of androgen deprivation has not been fully established. There are three randomized trials of "early" versus "late"androgen deprivation therapy with apparently conflicting results. In the first study, Veterans Administration Cooperative Urological Research Group (VACURG) Study 1, men with advanced prostate cancer were randomized to the following groups: immediate treatment with bilateral orchiectomy plus a 5-mg daily dose of DES, bilateral orchiectomy plus a placebo, 5-mg DES per day alone, or placebo alone, with the possibility of a cross-over from the placebo arm at the time of cancer progression (82,87). There was no survival benefit to any treatment arm assignment, suggesting that "early" androgen deprivation therapy was not superior to "late" treatment. In a second study, the Medical Research Council randomized men with prostate cancer (n = 934 men; 434 men with and 500 men without prostate cancer metastasis) to either "early" androgen deprivation or to androgen deprivation offered for symptomatic prostate cancer progression (96).

Using death from prostate cancer as a study endpoint for the men who had overt prostate cancer metastases, no significant difference was detected between the early (65% prostate cancer deaths) versus late treatment groups (69% prostate cancer deaths). In contrast, men with non-metastatic prostate cancer appeared to have fewer prostate cancer deaths (32%) when treated with "early"

androgen deprivation therapy than when not treated "early" (49%). However, 54% of the men in the study who were given immediate androgen deprivation therapy never received any hormonal therapy. In a more recent report, reflecting greater follow-up time, no statistically significant differences were evident for men with prostate cancer treated with early versus delayed androgen deprivation therapy. The Eastern Cooperative Oncology Group (ECOG) carried out a randomized prospective trial of immediate androgen deprivation therapy versus observation in men (n = 98) who underwent radical prostatectomy and were found to have lymph node metastases (97). After a median follow-up of 7.1 years, a significant difference in survival, favouring immediate androgen deprivation therapy, was detected (97).

Unfortunately, there is no clear mechanistic explanation for the different apparent benefits of "early" versus "late" androgen deprivation among the three trials. Currently, many men consider initiating androgen deprivation therapy at the time of prostate cancer recurrence after adequate local therapy, most often evident as a rising serum PSA. Beginning treatment at that time might exploit any added benefit attributable to "early" initiation of androgen deprivation, but will likely increase the chance for the adverse consequences of androgen deprivation, such as bone loss, loss of libido, cognitive decline, and worsening quality-of-life. With a median survival likely greater than 16 years for such men, any adverse treatment-associated consequences are of great concern (12). In contrast, waiting for the appearance of overt prostate cancer metastases before beginning androgen deprivation might miss an "early" androgen deprivation advantage, but permit a longer period of time without treatment-associated symptoms. The PSA doubling time may provide a tool for stratifying men with a rising serum PSA for androgen-deprivation therapy: men with a PSA shorter doubling times require treatment earlier than men with longer PSA doubling times (12).

Over the past several years much emphasis has been placed on toxicities associated with androgendeprivation therapy. The long-term effects of treatment have been noted in recent studies in men with localized disease receiving long-term ADT as part of a combined-modality approach which included ADT for periods longer than six months. Among the most significant morbidity are: bone loss (osteopenia and osteporosis), metabolic syndrome (hyperglycemia and lipid disorder), weight gain, fatigue and sedentary lifestyles, organic heart disease, increased incidence of fatal myocardial infarction, decreased muscle mass, chronic signs of hypogonadism, mood disorders, and possibly progressive cognitive changes. These observations have significantly influenced patients' and physicians' decisions on initiating and choosing ADT as a treatment option.

10.8 Intermittent androgen deprivation

Provocative findings from animal model studies have hinted that intermittent reductions in serum testosterone levels might offer an advantage over continuously maintained androgen deprivation in delaying prostate cancer progression to androgen independence, stimulating a significant body of clinical research on intermittent androgen deprivation therapy (98). In the animal studies, mice carrying 3-gram androgen-dependent cancers were either treated with bilateral orchiectomy (continuous androgen deprivation), or were treated with bilateral orchiectomy and then subjected to tumour harvest after the tumours had regressed at least 30%. The regressed tumours were then

transplanted into intact mice and then treated again with bilateral orchiectomy after the tumours had again grown to 3 grams. This treatment cycle (intermittent androgen deprivation) was continued until the cancer became androgen-independent. Intriguingly, androgen-independent cancer emerged 51 days after initiation of continuous androgen deprivation versus 147 days after initiation of intermittent androgen deprivation. The mechanism for this difference, attributed to a superiority of intermittent androgen deprivation as cancer treatment, has not been fully elucidated. However, other pre-clinical animal model studies have yielded conflicting results. When rats carrying a transplantable androgen-dependent prostate cancer were treated with immediate bilateral orchiectomy, with continuous high- or low-dose DES, or with intermittent high- or low-dose DES, rats treated with continuous androgen deprivation survived 38-50% longer than rats treated with intermittent androgen deprivation (99).

The clinical translation of the intermittent androgen deprivation (IAD) approach is in progress. Few clinical trials have resulted in definitive conclusions regarding the relative efficacy of IAD versus continuous ADT. Issues, such as the most appropriate regimens (monotherapy vs. combined treatment), duration of treatment cycles (duration of treatment vs. endpoints-based), threshold for re-treatment, definition of response versus failure, long-term management plans are all unresolved at this time. Despite all the unanswered questions IAD is frequently offered as a treatment alternative in the clinic. Especially for patients with no evidence of clinical metastasis or in those with minimal metastatic disease (oligometastatic disease) who had complete or near complete responses to treatment, are asymptomatic of their disease, and may be demonstrating intolerance to treatment. Other potential advantages of IAD over continuous ADT include improvement of quality of life (QoL), and attenuation or prevention of complications related to long-term ADT. However, preliminary data suggest a low probability of many short-term ill effects associated with ADT, such as sexual and erectile dysfunction (100-104). Few randomized clinical trials conducted thus far have been adequately designed or sufficiently powered to determine the long-term benefits of IAD in terms of overall disease control (survival and progression-free survival), time to development of androgen independence and the incidence and severity of long-term toxicity associated with ADT (101,102).

A recent report of the NCIC-PR7, which is a randomized clinical trial comparing IAD versus continuous ADT in 1,386 men with nonmetastatic biochemically relapsed prostate cancer after local therapy suggested that the overall survival between the two arms was similar (HR 1.02; 95%CI: 0.86-1.21; p for non-inferiority = 0.009). Preliminary data presented in an abstract form indicate that, at nine years, more patients receiving IAD were likely to die from prostate cancer (122 vs. 97) and less likely to die from other unrelated causes (134 vs. 146) (104).The results of the Southwest Oncology Group Trial 9346 (INT-0162) comparing IAD versus continuous ADT in men with metastatic disease will further define the role of this approach in patients with prostate cancer and until then, IAD in these patients should be considered experimental.

10.9 Novel Androgen Receptor Targeting Agents

Manipulating the androgen receptor axis, as previously reviewed in this chapter, was the first method discovered by which systemic control of the disease could be exerted (105). This section will summarize the known mechanisms by which growth stimulation continues despite serum castrate testosterone levels, and efforts to mitigate those effects via targeted therapy (106).

10.9.1 **BMS-641988**

Novel antiandrogens have been developed to overcome the mixed agonist/antagonist properties of the older (original) nonsteroidal compounds evaluated during the era of combined androgen blockade (flutamide, bicalutamide and nilutamide) (107,108). The first of these agents to be tested was BMS-641988 (109). Despite preclinical evidence that this agent was cytostatic rather than cytotoxic, this drug bound the AR with a 20-fold affinity relative to bicalutamide, and inhibited AR transcription with a 3-7-fold potency in reporter assays relative to bicalutamide (109). It was active in animal models with both mutant AR and overexpressed wild-type AR. However, clinically, the drug did not appear to be as active as the preclinical data might suggest. In a dose-escalation study involving 61 patients with castration-resistant metastatic disease, only 16% of patients enjoyed a >30% decline in PSA. All responders were chemotherapy-naïve; no patients previously treated with chemotherapy had a significant PSA decline. Furthermore, patients did appear to demonstrate an anti-androgen withdrawal response after BMS-641988 was discontinued, suggesting that the drug still retained some partial agonistic properties. These data suggested that the drug was a less potent AR antagonist than anticipated, with greater agonist activity than hoped. Combined with the emergence of seizure activity as a component of the toxicity profile, the drug was abandoned.

10.9.2 **MDV3100**

MDV3100, however, emerged as a successor to BMS-641988 in the effort to develop a novel antiandrogen with pure AR antagonism and a favourable toxicity profile. MDV3100 is an oral agent that appears to bind to the AR with five to eight times the affinity of bicalutamide and two to three times the affinity of DHT, as measured through a competitive displacement assay using F-18 fluorinated DHT. The anti-tumour effects of MDV3100 appear to be mediated by inhibiting AR nuclear translocation, DNA binding, and coactivator peptide recruitment. In contrast to bicalutamide, MDV3100 expresses no agonistic properties and does not recruit coactivator proteins (110).

In a human prostate cancer cell line that overexpresses AR, termed VCaP, MDV3100 functioned to suppress growth and to induce apoptosis, even when bicalutamide did not. Similarly, *in vivo* tumour suppression was evident in castration-resistant AR-overexpressing LNCaP/AR xenograft models, revealing tumour reduction. Mice treated with MDV3100 had prolonged time to tumour progression relative to bicalutamide as well.

MDV3100 was tested in men with castration-resistant metastatic prostate cancer in a phase I/II clinical trial conducted under the auspices of the Department of Defense/Prostate Cancer Foundation Prostate Cancer Clinical Trials Consortium (PCCTC). (8) Patients were treated at doses that ranged from 30 to 600 mg per day. A total of 140 patients were treated. The drug was found to be absorbed rapidly, between 30 minutes and four hours, and to have an approximate half-life of one week, with a steady state achieved after one month of treatment. Replicating the preclinical data seen with the competitive displacement of FDHT, 22 patients underwent PET scanning using the same F-18 radiolabeled DHT, showing that in humans, the drug targets the AR and displaces FDHT (111).

Most notable, however, were the PSA declines observed at all doses, both in patients who had prior chemotherapy exposure and those who were chemotherapy naïve. Fifty seven percent (95% CI, 44-69%) of patients who were chemotherapy naïve enjoyed a 50% PSA decline, as did 36% (95% CI, 25-48%) of patients who had previously exposed to chemotherapy. The proportion of responders increased by dose up to 150 mg per day; dose escalations above that level appeared to result in no improvement in response proportion. Median time to PSA progression was durable enough not to have been reached for all patients combined at the time of publication, nor was it reached for chemotherapy naïve patients; it was 27 weeks for patients who had chemotherapy exposure. Median time to radiographic progression was 47 weeks (95% CI 34-not reached) in all patients, not reached for patients who were chemotherapy naïve, and 29 weeks (95% CI, 24-59) in patients with previous chemotherapy treatment. The dose-limiting toxicity, like BMS-641988, was seizures, suggesting that this is a class effect, and was observed at the 360 and 600 mg doses. Otherwise, the drug was well tolerated; the dose in the phase III trials is 160 mg/day (112).

MDV3100 is now in the final phases of phase III testing. Two phase III clinical trials have been initiated. The first (the "Affirm" study) randomized 1,170 patients with metastatic CRPC on a 2:1 basis to either MDV3100 or a placebo. These patients had to have progressed despite one or two prior docetaxel-containing regimens. The primary endpoint was overall survival, looking for a 25% improvement in the treatment arm, with secondary endpoints of time to progression, radio-graphic progression-free survival, and post-treatment PSA and circulating tumour cell alterations. This study is fully accrued, and is awaiting enough events to occur in order to assess the primary endpoint. The second, named the "Prevail" study, will randomize 1,680 patients with metastatic CRPC who are chemotherapy and ketoconazole naïve on a 1:1 basis to either MDV or placebo. The co-primary endpoints are overall survival and radiographic progression-free survival. The protocol is still accruing.

10.9.3 **ARN-509**

While MDV3100 completes its final registration-level studies, newer anti-androgens with even greater antagonistic actions are undergoing development. ARN-509 is a small molecule that lacks partial agonist activity, also reduces nuclear translocation, and impairs AR binding to DNA. Pre-clinically, it appears to be more potent than MDV3100. It is presently undergoing phase I/II clinical trials (112).

The anti-androgens therefore represent a drug class that, although old, has seen a renewed vitality owing to an enhanced understanding of AR biology and the mechanisms underlying bicalutamide resistance, as well as the design of drugs to leverage that biology and overcome those resistance

mechanisms. As a class, they appear to have significant activity even in patients who are not only castration resistant, but taxane resistant as well (113). Furthermore they are oral agents, well tolerated, and unlike abiraterone, appear not to require the concomitant use of steroids, a significant consideration in this population. Definitive trials to demonstrate clinical benefit in a variety of contexts are ongoing, the results of which are anticipated to be available in 2012 (114).

Several enzymes involved in androgen synthesis are highly upregulated in CRPC compared to those with androgen sensitive prostate cancer (3). The pivotal enzymes in androgen synthesis are cyto-chrome P450 17- α -hydroxylase and C17,20-lyase (CYP17), and are critical for synthesis of androgens in adrenal glands, testis and prostate tumours (115-119).

10.9.4 **Abiraterone acetate**

Abiraterone acetate, a pregnenolone analogue, is an orally administered small molecule inhibitor of the androgen biosynthesis enzyme CYP17 (17- α -hydroxylase and C17,20-lyase), and is more potent and selective than ketoconazole. Several phase II trials have been conducted of abiraterone with and without prednisone, with PSA-RR of 51-85% and durable radiologic responses seen in both chemotherapy naïve and docetaxel pretreated CRPC patients (115,116).

In a randomized double-blind phase III trial, 1,195 patients with metastatic CRPC who had received prior docetaxel, or up to two lines of chemotherapy were randomized in a 2:1 fashion to receive 5 mg of prednisone twice daily with either 1000 mg of abiraterone acetate (797 patients) orally or placebo (398 patients) (120). After a median follow-up of 12.8 months, an interim analysis was performed and the study was unblinded. Overall survival (OS), the primary end point, was significantly longer in the abiraterone acetate-prednisone group than in the placebo-prednisone group (median 14.8 months vs. 10.9 months) p<0.001), as well as significant improvements in PFS (5.6 months versus 3.6 months, and RR (38% versus 10%). Abiraterone has been approved by the FDA (American) and EMA (European) agencies for this indication. Adverse effects were minimal and were associated primarily with secondary mineralocorticoid excess, including fluid retention (30.5%) and hypokalemia (17.1%), but greater than or equal to grade 3 hypokalemia (17.1%) or hypertension (1.3%) were infrequent. A phase III trial of abiraterone acetate versus placebo (both plus prednisone) in men with CRPC who have not received prior chemotherapy has completed accrual (clinicaltrials.gov/ct2/show/ NCT00887198), with the results pending.

10.9.5 **TAK-700**

TAK-700, (Millennium Pharmaceuticals, Cambridge, MA, USA), is a selective 17,20 lyase inhibitor that down regulates androgenic steroid production *in vitro* and *in vivo* (117). Updated results of a phase I/II trial of TAK-700 in metastatic CRPC were reported at the ASCO 2011 annual meeting (121,122,123). Ninety-six chemo-naïve patients with metastatic CRPC were treated in the four following TAK-700 dose cohorts: 300 mg twice daily (n=23), 400 mg twice daily with prednisone (n=24), 600 mg twice daily with prednisone (n=26), or 600 mg daily without prednisone (n=24). The most common grade 3-4 side effects were fatigue (9%) and diarrhea (3%). At 12 weeks, PSA response rates (\geq 50% decrease) were 63%, 52%, 41%, and 62%, respectively, in the four above mentioned dose cohorts with a concomitant decline in the serum androgens and mean circulating tumour cell

numbers. In addition, there was a decrease in the median dehydroepiandrosterone sulfate (DHEA-S), testosterone levels, and mean circulating tumour cell numbers, in all groups. Of 43 patients with RECIST-evaluable disease at the time of report, six had a partial response, 23 had stable disease, and nine had disease progression. Currently, TAK-700 is being evaluated in separate phase III trials of men with progressive CRPC, who are either chemotherapy-naïve or had progressive disease after or while being treated with a docetaxel-based regimen. TOK-001, formerly known as VN/124-1, inhibits prostate cancer growth by multiple mechanisms. In addition to inhibiting CYP17, it directly antagonizes the AR receptor and also down regulates AR protein expression (123). A phase I/II trial of TOK-001 has been initiated in chemo-naïve patients with CRPC.

10.10 Taxane-based Chemotherapy

In the late 1990s, early clinical studies of docetaxel reported promising activity in patients with metastatic CRPC which resulted in the conduct of two randomized phase III studies; TAX 327 and study SWOG 99-16. TAX 327 (the pivotal study for FDA approval of docetaxel for prostate cancer) included three study arms: docetaxel 75 mg/m² every 3 weeks plus prednisone (10 mg daily), weekly docetaxel 30 mg/m² (5 of 6 weeks) plus prednisone, versus mitoxantrone 12 mg/m² every 3 weeks plus prednisone (124,123). A total of 1,006 patients were randomized. The docetaxel every-3-weeks regimen resulted in significantly superior survival and higher PSA and pain response rates compared with mitoxantrone. The survival was 18.9 versus 16.5 months, the reduction in the HR of death was 0.76 (0.62-0.92). The weekly docetaxel regimen showed a trend towards survival benefit compared with mitoxantrone, but this did not reach statistical significance. A significantly greater proportion of patients who were treated with the docetaxel every-3-weeks regimen experienced a reduction in pain (35% vs 22%; p=0.01), greater than or equal to a 50% reduction in PSA (45% vs 32%, p<0.001), and an improvement in QoL (22% vs 13%, p=0.009) compared with patients who received mitoxantrone. Grade 3/4 toxicity was infrequent, other than neutropenia (32%), but the incidence of febrile neutropenia during the entire course of chemotherapy, was at most, 3%. The second study, SWOG 99-16 evaluated the combination of docetaxel plus estramustine against mitoxantrone plus prednisone (124). The median overall survival was superior in the group receiving the docetaxel regimen (17.5 vs. 15.6 months, HR 0.80 [0.67-0.97]). The patient characteristics were quite similar to those of the TAX 327 study, as were the survival outcomes. The incorporation of estramustine in the docetaxel regimen, however, was characterized by increased gastrointestinal and cardiovascular toxicity (mostly thromboembolic complications) (125-128).

Multivariate analysis, identified several independent prognostic factors for survival, such as the presence or absence of pain, performance status, the number of metastatic sites (3 or more), presence of liver metastases, baseline hemoglobin and alkaline phosphatase, and type of progressions at baseline (measurable soft tissue disease or bone scan progression versus PSA only, or non-measurable disease progression), PSA at baseline and PSADT. (129-131).

10.10.1 **Docetaxel retreatment**

Patients with mCRPC "progressing" after a docetaxel-based chemotherapy should be divided in two groups: those not responding or progressing during, or shortly after, chemotherapy (docetaxel-refractory cases) and those who benefited from treatment and who demonstrate evidence of disease progression some time after treatment is interrupted. Patients who have not progressed during treatment are considered as having potentially docetaxel-sensitive disease. While these two groups are not clearly defined, this simple distinction provides a rationale for docetaxel retreatment for the group of patients on the latter group before moving to second-line chemotherapy options (*ie*, cabazitaxel) (134-135). Preliminary published experience of intermittent chemotherapy showed that this approach is feasible and has potential advantages in terms of extending disease control without increased toxicity (134-139).

10.10.2 Cabazitaxel

Cabazitaxel is a second generation taxane that exhibited cytotoxic activity in a broad range of cell lines and tumour models and greater potency than docetaxel in multidrug-resistant tumour cells (11). An additional characteristic of cabazitaxel is its ability to penetrate the blood-brain barrier *in vivo*, which is limited with other taxanes (133).

A phase I trial determined that cabazitaxel had linear pharmacokinetics similar to docetaxel and highlighted the favourable tolerability profile of cabazitaxel compared with docetaxel. The principal dose-limiting toxicity of cabazitaxel was neutropenia; other observed side-effects, including nausea, vomiting, diarrhea, neurotoxicity, and fatigue, were generally mild to moderate (133). Twelve of the 24 patients evaluable for clinical response had stable disease for more than four months, and there were two partial responses in two patients with prostate cancer; both had a reduction in measurable disease and reduced significantly PSA levels.

The phase III TROPIC trial was a randomized, open-label, multicentre, multinational trial, conducted to assess whether cabazitaxel plus prednisone improved overall survival compared with mitoxantrone plus prednisone in men with mCRPC that had progressed either during or after docetaxel treatment (133). Patients aged 18 years and over with mCRPC progression despite docetaxel treatment were treated with prednisone 10 mg/day and randomized to receive either intravenous cabazitaxel 25 mg/m² over 1 hour, or mitoxantrone 12 mg/m² over 15–30 minutes every three weeks for 10 cycles.

A total of 755 patients were randomized to receive cabazitaxel (n=378) or mitoxantrone (n=377). The median follow-up for both treatment groups was 12.8 months. The treatment groups in TROPIC were well balanced with regard to demographics and baseline disease characteristics. All patients demonstrated evidence of disease progression to initial docetaxel treatement. Approximately 70% of patients had progressed within three months of completing docetaxel treatment; indeed, almost one-third of patients had progressed while they were receiving docetaxel.

The study met the primary endpoint, with significantly improved median overall survival in patients receiving cabazitaxel (15.1 months; 95% CI: 14.1–16.3 months; p < 0.0001) compared with those who received mitoxantrone (12.7 months; 95% CI: 11.6–13.7 months) (**Table 3**) **Figure 5** shows updated

survival figures) (14). The HR for death was 0.70 (95% CI: 0.59–0.83; p < 0.0001). Cabazitaxel doubled median PFS compared with mitoxantrone (cabazitaxel 2.8 months vs mitoxantrone 1.4 months; p<0.0001). TTP was also significantly improved (p<0.0001) in those patients who received cabazitaxel. Cabazitaxel treatment significantly improved overall objective response (RECIST) more than two-fold compared with mitoxantrone (p<0.001). The *PSA* response (> 50%) rate was significantly higher in the cabazitaxel group compared with the mitoxantrone group and patients receiving cabazitaxel also had a significantly longer median time to PSA progression (**Table 3**) (133).

Patients in the cabazitaxel or mitoxantrone groups received a median of 6 and 4 cycles of treatment, respectively. The most common AEs experienced by patients were hematologic. There was a greater incidence of hematologic AEs with grade \geq 3 severity in patients who received cabazitaxel. For example, 81.7% and 7.5% of patients in the cabazitaxel group experienced grade \geq 3 neutropenia and febrile neutropenia, respectively, compared with 58% and 1.3% of patients in the mitoxantrone group.

Cabazitaxel treatment also increased the incidence of non-hematologic AEs, including diarrhea [46.6% vs 10.5% for mitoxantrone; grade \geq 3 diarrhea (6.2% vs 0.3%)] and asthenia [20.5% vs 4.6% for mitoxantrone; grade \geq 3 asthenia (12.4% vs 2.4%)].

A total of 18 patients (4.9%) who were treated with cabazitaxel died from causes other than disease progression within 30 days of receiving their last dose of cabazitaxel. This compares with three drug-related patient deaths (0.9%) in the mitoxantrone group. The most common cause of death in patients who were treated with cabazitaxel was neutropenia and its clinical consequences, such as septicemia. However, no further deaths due to neutropenic complications occurred in the cabazitaxel group following the Independent Data Monitoring Committee communication to the TROPIC investigators about the need to strictly adhere to the study protocol regarding dose delays and modifications and managing neutropenia with granulocyte colony-stimulating factor (G-CSF) according to American Society for Clinical Oncology guidelines (140).

Based on the results of the TROPIC trial, cabazitaxel was approved by the US FDA in June 2010, and by the EMEA in 2011 for use in combination with prednisone for the treatment of mCRPC previously treated with a docetaxel-containing regimen.



TABLE 3 Summary of Efficacy Results in the TROPIC Trial

Endpoint	Mitoxantrone (N=377)	Cabazitaxel (N=378)	HR (95% CI)	<i>p</i> -value
Median OS (months)	12.7	15.1	0.70 (0.59–0.83)	<0.0001
Median PFS (months)	1.4	2.8	0.74 (0.64–0.86)	<0.0001
Tumour response rate (%)	4.4	14.4	—	0.0005
PSA response rate (%)	17.8	39.2	—	0.0002
Pain response rate (%)	7.7	9.2	_	0.63

CI = confidence interval; HR = Hazard ratio; OS = overall survival; PFS = progression-free survival; PSA = prostate specific antigen; TTP = time to tumour progression.

10.10.3 **Docetaxel-based combination therapy**

Docetaxel has been combined with platinum-based compounds with encouraging preliminary results. In a phase II study, patients with castration-resistant prostate cancer (CRPC) progressing after docetaxel achieved treatment responses with carboplatin plus docetaxel, and responses were more likely in those who had previously responded to docetaxel (128). GVAX, a vaccine composed of prostate cancer cell lines modified to secrete granulocyte macrophage colony-stimulating factor (GM-CSF), underwent a phase III trial in combination with docetaxel in patients with symptomatic

metastatic CRPC. This trial, known as VITAL-2, was interrupted early due to an unexpected higher death rate in the GVAX arm. Another trial (VITAL-1), compared GVAX with docetaxel in patients with asymptomatic CRPC and found no OS difference (141).

DN-101 (calcitriol) is a high-dose formulation of calcitriol, an activated vitamin D analog that has antiproliferative effects against prostate cancer cells *in vitro*. The combination of docetaxel plus calcitriol was evaluated in a randomized phase II trial that suggested an improvement in OS, with a significant improvement in \geq 50% PSA reduction compared to docetaxel monotherapy, but final results of a phase III trial (ASCENT-2) in 953 men with progressive CRPC found a significantly shorter OS for the combination of docetaxel plus calcitriol compared to docetaxel plus prednisone (median 17.8 vs. 20.2 months) (135). The reasons for the shorter survival were unclear but could relate to the use of weekly schedule of docetaxel in the control arm which was not as effective as the every 3-week schedule in the pivotal TAX-327 study. Other agents developed in combination with docetaxel or as single agents are reviewed in the next section.

In conclusion, while docetaxel remains the gold standard first-line chemotherapy for mCRPC, it is clear, however, that our knowledge of the biologic mechanisms involved in the progression of meta-static castration-resistant prostate cancer has reached a level at which the discovery of more effective targeted approaches will probably further improve outcomes.

10.10.4 New tumour-specific targeted approaches

While we now have several therapies that have been shown to extend survival in patients with castration-resistant prostate cancer (docetaxel, cabazitaxel, sipuleucel-T, abiraterone acetate, and radium-223), none of these approaches are curative, and annual mortality rates from prostate cancer remain unacceptably high. For this reason, the discovery of novel treatment strategies for this patient population remains a critical endeavour and the identification of alternative therapeutic targets has never been more actively pursued. In addition to the other strategies previously summarized in this chapter, our accelerated understanding of other biologic and cellular processes driving prostate cancer progression and metastasis has fueled the preclinical and clinical exploration of a myriad of molecular targets comprising alternative oncogenic pathways (**Figure 6**). Such cellular processes reflect the basic hallmarks of cancer and include: angiogenesis and tumour microenvironment interactions, cell growth and proliferation, apoptosis, cell nutrition, DNA repair, and epigenetic regulation (142). This section will review several novel therapies currently in clinical development that may enter the therapeutic arsenal in the next five years. Such therapies include angiogenesis inhibitors, mTOR (mammalian target of rapamycin) pathway inhibitors, apoptosis-inducing drugs, IGF (insulin-like growth factor) pathway antagonists, epigenetic therapies, and PARP (poly-ADP ribose polymerase) inhibitors.

In CRPC, androgen receptor (AR)-dependent signalling almost always persists, but with a substantial heterogeneity in the intensity of this signalling (143). To this end, prostate cancers with lower AR activity or those exposed to prolonged periods of androgen suppression may demonstrate up-regulation of other oncogenic pathways, including Src kinase, clusterin, epithelial-mesenchymal transition (EMT) pathways, PI3 kinase, c-MET, and others. Numerous other drugs inhibiting alternative pathways that have crosstalk with AR-dependent pathways have been evaluated in clinical trials. Here, we will focus on selected promising agents currently being investigated in phase II and III studies (**Figure 6**).

FIGURE 6

Novel Pathways and Targets in Metastatic CRPC.



Abbreviations: CRPC, castration-resistant prostate cancer; AR, androgen receptor; A, androgen; HSP, heat shock protein; VEGF-R, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; IGF-1R, insulin-like growth factor receptor-1; HDAC, histone deacetylase; DNMT, DNA methyltransferase; PARP, poly (ADP-ribose) polymerase; CoAct, transcriptional coactivators.

Apoptosis

Clusterin, a stress-induced anti-apoptotic chaperone protein expressed in various cancers including prostate cancer (3), has received renewed attention due to the development of an antisense inhibitor to this protein. Importantly, expression of clusterin in prostate tumours increases after treatment with androgen ablation or chemotherapy (144,145), conferring a more resistant phenotype. Custirsen is a novel intravenously-administered antisense oligonucleotide moiety that inhibits clusterin at the mRNA level (**Figure 6**), increasing sensitivity to androgen deprivation as well as chemotherapy in prostate cancer cell lines and xenograft models (146-148).

In a randomized phase II study of docetaxel with or without custirsen in 82 patients with metastatic CRPC, PSA responses (58% vs. 54%) as well as progression-free survival (7.3 vs. 6.1 months) were similar in both arms. However, overall survival trended in favour of the combination arm (23.8 vs. 16.9 months, p=0.06), although survival was not the primary endpoint of this study and confidence intervals around these estimates were wide and potentially confounded by subsequent therapies(149).

Adverse events associated with custirsen included fatigue (>80%), fever (30-50%), rigours (40-60%), diarrhea (40-60%) and rash (20-40%). Another phase II study of second-line chemotherapy (docetaxel retreatment or mitoxantrone) plus custirsen in patients with docetaxel-pretreated CRPC has recently been published. In that trial, overall survival in the docetaxel-custirsen and mitoxantrone-custirsen arms was 15.8 versus 11.5 months respectively, while time to pain progression was 10.0 versus 5.2 months respectively (150). Finally, a registrational placebo-controlled phase III study of docetaxel retreatment with or without custirsen for the second-line management of men with docetaxel-refractory disease has been launched (**Table 4**). Pain improvement has been chosen as the primary endpoint in this trial. In addition, a first-line randomized phase III study of docetaxel with or without custirsen in men with chemotherapy-naïve CRPC is also underway; the primary endpoint of that trial is overall survival (**Table 4**).

Another class of drugs mediating their effect via the apoptotic pathway are the survivin antagonists. Survivin, one of the most cancer-specific proteins identified, has been shown to inhibit apoptosis as well as to enhance cell proliferation and promote tumour angiogenesis in multiple tumour types including prostate cancer (151). Because of its marked upregulation in malignant tissues but not in normal cells, and the observation that its suppression leads to inhibition of tumour growth, survivin has attracted attention as a promising target for anticancer therapies. Two agents in this class are currently in clinical development. The first is LY-2181308 (an antisense oligonucleotide that binds to survivin mRNA)(152), and the second is YM-155 (a small molecule survivin inhibitor)(153). Several phase II studies investigating these two drugs in men with metastatic CRPC are now underway or have recently completed accrual (**Table 4**).

Src kinase signalling

Src is a non-receptor tyrosine kinase signal transduction protein that is important in tumour cell proliferation, migration, angiogenesis, survival, and transition to the castration-resistant state (154). Src also controls normal and abnormal osteoclastic activity, and has been implicated in development and progression of bone metastases (155). Dasatinib is an oral inhibitor of multiple oncogenic kinases including Src. In experimental models, dasatinib suppressed proliferation of prostate cancer cell lines (156) and inhibited adhesion, migration, and invasion (157). In addition, dasatinib reduced tumour growth and lymph node involvement in a prostate cancer mouse xenograft model (158). A phase II study of single-agent dasatinib in men with metastatic CRPC did not show significant PSA responses, but 19% of patients were free of disease progression at six months. Additionally, more than half of subjects had more than or equal to a 40% decline in urinary N-telopeptide levels (a marker of bone resorption), and 60% showed reductions in bone alkaline phosphatase (159). In a separate phase I/II study combining dasatinib with docetaxel in a similar patient population, PSA responses were observed in 57% of participants, objective radiographic responses were seen in 60% of men, and 30% of patients with bone metastases showed amelioration in bone scans (160). A large placebocontrolled randomized phase III study evaluating this combination in 1,500 men with metastatic chemotherapy-naïve CRPC has completed accrual (Table 4), and will examine overall survival as its primary endpoint. Adverse effects of dasatinib include diarrhea (62%), nausea (47%), fatigue (45%), and fluid retention (21%). Newer Src kinase inhibitors such as saracatinib (161) are in earlier stages of clinical development in patients with metastatic CRPC (Table 4).

Angiogenesis

Tumour angiogenesis is thought to play an important role in prostate cancer maintenance and progression, and elevated plasma levels of vascular endothelial growth factor (VEGF) have been correlated with advanced clinical stage and decreased survival (162). Additionally, antibodies to VEGF slow tumour proliferation in prostate cancer xenograft models, especially when combined with chemotherapy (163). However, despite strong preclinical rationale, a phase III randomized study in men with chemotherapy-untreated CRPC (CALGB 90401) failed to show a survival advantage with the anti-VEGF antibody, bevacizumab, when combined with docetaxel compared to docetaxel used alone (22.6 vs. 21.5 months). However, significant improvements were seen with respect to PSA responses (70% vs. 58%), and radiographic responses (53% vs. 42%), as well as progression-free survival (9.9 vs. 7.5 months) (164). These results do not necessarily indicate that bevacizumab may never have a role in the treatment of CRPC. Future development of this and other anti-angiogenic agents may rely on combinations with other classes of angiogenesis inhibitors or other chemotherapeutic drugs whose toxicities do not overlap, and will require careful patient selection for those men most likely to benefit from this class of agents. Finally, a similar agent, aflibercept (VEGF trap), has competed phase III enrolment in combination with docetaxel and overall survival results are awaited (Table 4).

An alternative approach has focused on tyrosine kinase inhibitors (TKIs), agents that block angiogenic transmembrane receptors such as the VEGF receptor (VEGFR) (Figure 6). In phase II studies involving men with metastatic CRPC, oral sorafenib was shown to prevent radiological progression and even caused regression of bone metastases in some patients (<10%), without inducing significant PSA responses (165,166). Similarly, oral sunitinib produced some partial radiographic responses (~10%) with minimal effect on PSA levels in men with both chemotherapy-naïve and docetaxelpretreated CRPC (167,168). In addition, a single-arm study of docetaxel plus sunitinib demonstrated tolerability and a reasonable degree of clinical activity in the front-line setting (39% objective response rate), with over 90% of men surviving one year (169). However, a definitive randomized phase III study comparing single-agent sunitinib versus placebo in 800 patients with docetaxel-refractory disease was found not to confer an overall survival improvement (170). This result suggests that single-agent anti-VEGFR or PDGFR-based therapies may be insufficient to produce clinical benefit. However, exploring the activity of these VEGF TKIs in combination with established cytotoxic and immune-modulatory or hormonal therapies remains of some interest, given the theoretical potential for synergy when combining these agents. Adverse events related to the use of these TKIs include fatigue (30-50%), nausea (20-40%), hypertension (15-25%), diarrhea (30-50%), hand-foot syndrome (20-30%), rash (25-40%), and congestive heart failure (rare).

Another target that has received recent attention is the MET protein, a transmembrane receptor whose only known ligand is the hepatocyte growth factor (HGF). Aberrant activation or overexpression of MET is a common event in prostate cancer (especially in castration-resistant bone metastases), and is associated with proliferation, invasion, and angiogenesis (171,172). Moreover, androgen suppression has been shown to induce increased MET expression (173). Cabozantinib (XL184) is an oral potent inhibitor of MET and VEGF-R2 that has demonstrated robust anti-angiogenic, anti-proliferative, and anti-invasive activity in preclinical systems (174). Results from a phase II study in men with metastatic CRPC who had received up to one prior chemotherapy revealed objective responses in about 10% of patients with measurable soft tissue disease (with 74% of men showing
some degree of tumour regression), and improvements in bone scans in a remarkable 76% of men with osseous metastases, which was often accompanied by pain improvements (67% of patients) (175). Toxicities associated with this agent include fatigue (67%), diarrhea (55%), anorexia (51%), emesis (44%), and hypertension (22%). While the 12-week success rates, particularly in the bone, are strikingly high (including some complete resolutions of skeletal abnormalities as visualized on bone scan), the lack of robust PSA responses and especially the uncertainty over the durability of these results as measured by progression-free survival, will require confirmatory controlled trials to assess the overall clinical benefit of this agent as well as the appropriate dose for long-term use. As the prostate cancer landscape is changing rapidly, the evaluation of cabozantinib in the post-cabazitaxel and/ or post-abiraterone setting would be one such approach to the rapid evaluation of clinical benefit of this novel dual MET/VEGF-R2 inhibitor. Further investigation of this agent's activity in the bone using novel imaging techniques (18F-PET) or pharmacodynamic studies is also being considered to further understand how this agent is controlling osseous metastatic disease.

A final angiogenesis-inhibiting agent that has received renewed attention is the oral quinoline derivative tasquinimod (**Table 4**). Although the anti-angiogenic properties of this agent have been amply demonstrated in several *in vitro* and *in vivo* prostate cancer models (176) the exact mechanism of action of this drug remains elusive and appears to be unrelated to VEGF receptor inhibition. However, one proposed action of tasquinimod involves inhibition of S100A9, a calcium-binding protein involved in cell cycle progression and differentiation, as well as recruitment of tumour-infiltrating myeloidderived suppressor cells (177). Encouragingly, a randomized double-blind placebo-controlled phase II study involving 200 patients with chemotherapy-naïve metastatic CRPC met its primary endpoint and demonstrated that patients receiving oral tasquinimod had a median progression-free survival of 7.6 months versus 3.2 months in those receiving placebo (p= 0.001) (178). Adverse events with this agent included gastrointestinal disorders (40%), fatigue (23%), musculoskeletal pain (12%), and asymptomatic elevations of pancreatic enzymes and inflammatory markers. Rare but serious toxicities were heart failure (1%), myocardial infarction (1%), stroke (1%), and deep vein thrombosis (4%). A multicentre randomized phase III trial of tasquinimod versus placebo in patients with chemotherapy-untreated metastatic CRPC is now accruing.

PI3K/Akt/mTOR pathway

Given the high prevalence of PTEN loss and PI3 kinase pathway activation in metastatic prostate cancer, the development of agents that target components of this key oncogenic survival pathway has focused initially on men with metastatic CRPC (179). One critical component has been the TORC1 pathway, a key gatekeeper protein that regulates extracellular and nutrient-based signalling with the metabolic programs and energy outputs of many cells including malignant prostate cancer cells (180). Although mammalian target of rapamycin (mTOR or TORC1) inhibitors may have modest single-agent activity in advanced CRPC (181), the combination of these drugs with docetaxel is attractive in theory, given their ability to reverse or delay chemotherapy resistance in prostate cancer cell lines (182,183). In addition, these agents may induce apoptosis when combined with chemotherapy in patients who have activation of the Akt pathway as a result of PTEN mutation/loss or other genetic alteration (184). Limitations of the use of single-agent TORC1 inhibitors have included feedback upregulation of upstream survival signals (such as PI3 kinase and growth factor receptor levels) as well as the lack of induction of apoptosis or prolonged cytostasis due to parallel activation of alternate oncogenic pathways (185-187).

Several mTOR inhibitors have entered human clinical testing in combination with other agents (**Figure 6**). One of these, everolimus, is currently being evaluated in combination with docetaxel for the first-line treatment of metastatic CRPC (188), and is also being used in combination with carboplatin for the treatment of docetaxel-refractory disease (**Table 4**). In addition, temsirolimus and everolimus are being tested in combination with anti-androgen therapy in men with chemotherapynaïve CRPC (based on preclinical studies showing synergistic activity of anti-androgens with mTOR inhibitors) (189,190), and also as maintenance therapy after responding to docetaxel treatment (191). A third mTOR inhibitor, ridaforolimus, is also being investigated in the phase II setting as mono-therapy in men with taxane-refractory CRPC (**Table 4**). Toxicities of mTOR agents include maculo-papular rash (20-40%), hypertriglyceridemia (40-70%), hyperglycemia (30-60%), allergic reactions (3-5%), pedal edema (15-30%), mucositis (40-60%), pneumonitis (5-10%), and thrombocytopenia (20-40%).

An alternative strategy focuses on directly inhibiting proximal mediators of the mTOR pathway, such as phosphoinositide 3-kinase (PI3K) or Akt (**Figure 6**), that are frequently activated in advanced prostate cancer (192,193) or related with recurrent disease following prostatectomy (194). Following from encouraging preclinical data (195,196) there are now a number of agents with activity against the PI3K/Akt pathway that are currently being tested in men with CRPC (197,198). The development of strategies to identify pre-treatment biomarkers (*i.e.* from tumour specimens, specialized imaging, or circulating tumour cells) that may predict which men are likely to benefit from PI3K/Akt inhibitors will be essential in the rational development of these agents.

IGF-1R pathway

Insulin-like growth factor 1 receptor (IGF-1R) and its ligands may play a key role in prostate carcinogenesis through mechanisms that involve mitogenesis, anti-apoptosis, and cellular transformation (**Figure 6**). Moreover, IGF-1R is often overexpressed in prostate tumours and can mediate cell proliferation and resistance to androgen ablation (199,200). Therapeutic monoclonal antibodies that bind to the extracellular domain of IGF-1R can potently inhibit the function of this receptor. In prostate cancer cell lines and in xenograft models, such antibodies have been shown to inhibit growth of both androgen-dependent and -independent tumours (201,102).

Cixutumumab is an intravenous fully human IgG1 monoclonal antibody that specifically targets IGF-1R, inhibiting ligand binding and IGF signalling (203). In a phase II study of cixutumumab in men with metastatic CRPC, 29% of patients demonstrated stable disease for 6 months, while a similar percentage experienced PSA responses (204). Toxicities with this agent included fatigue (20-30%), hyperglycemia (15-25%), thrombocytopenia (10-20%), hyperkalemia (5-10%), and muscle spasms (10-20%). A phase II study combining cixutumumab with mitoxantrone compared to ramucirumab (an anti-VEGFR2 monoclonal antibody) with mitoxantrone in men with docetaxel-refractory metastatic CRPC has completed accrual (**Table 4**).

Figitumumab is a second fully human anti-IGF-1R IgG2 monoclonal antibody that has entered clinical testing (205). In a phase Ib study of intravenous figitumumab given in combination with docetaxel to men with metastatic CRPC, 22% of patients had objective tumour responses and 67% had disease stabilization lasting \geq 6 months (206). In addition, 90% of patients with measurable CTC levels at baseline achieved \geq 30% reductions in CTC counts after treatment. Toxicities of this

combination regimen were leucopenia (including neutropenia) (20%), fatigue (50%), diarrhea (25%), and hyperglycemia (10%). A randomized phase II study of figitumumab combined with docetaxel in men with chemotherapy-naïve (arm A) and docetaxel-refractory (arm B) CRPC has completed enrollment (**Table 4**).

Epigenetic therapies

Histone deacetylases (HDACs) are regulators of histone acetylation status which is critical for androgen receptor-mediated transcriptional activation of genes governing cell survival, proliferation, differentiation, and apoptosis (207) (**Figure 6**). Vorinostat is an oral HDAC inhibitor that has demonstrated anti-tumour activity in prostate cancer cell lines as well as in animal models (208). However, a phase II study of vorinostat monotherapy in men with docetaxel-refractory CRPC did not show significant PSA or radiological responses, and was associated with a high frequency of adverse events including fatigue (80%), emesis (75%), diarrhea (35%), and weight loss (25%) (209). A second HDAC inhibitor, panobinostat (used both as an oral and intravenous agent), has completed phase I testing in combination with docetaxel (210,211). The IV formulation has been chosen for future development. Side effects of panobinostat include nausea (75%), diarrhea (50%), thrombocytopenia (50%), and fatigue (38%). A phase II trial of single-agent IV panobinostat in docetaxel-refractory disease is currently ongoing (**Table 4**).

DNA methylation of key tumour suppressor genes represents another epigenetic mechanism by which prostate cancer may progresses to a castration-resistant state (212). The hypomethylating agent, azacitidine (**Figure 6**), is a subcutaneously (S/C) administered drug that exerts its antineoplastic effects by inhibiting DNA methyltransferases (DNMTs) in promoter regions of genes, leading to reversal of gene silencing (213). In preclinical prostate cancer models, azacitidine reverses resistance to androgen ablation and chemotherapy (214), making this agent attractive for clinical trial development. To this end, a phase II study of azacitidine in men with chemotherapy-naïve CRPC induced lengthening of PSA doubling times in 56% of patients and resulted in a median progression-free survival time of 12.4 weeks (215). Toxicities of azacitidine included fatigue (41%) and neutropenia (18%). Another phase II study evaluating the combination of docetaxel and azacitidine in men with docetaxel-pretreated CRPC is underway (**Table 4**).

PARP inhibition

Poly (ADP-ribose) polymerases (PARPs) are a family of enzymes that mend single-strand DNA breaks through the repair of base excisions (**Figure 6**). PARP inhibition leads to accumulation of single-strand DNA breaks which, if left unchecked, lead to double-strand DNA breaks at replication forks (216). These double-strand breaks are repaired by homologous recombination, mediated in part by the tumour suppressor proteins, BRCA1 and BRCA2. Preclinical studies have shown that *BRCA1/2* mutation combined with PARP inhibition creates a "synthetic lethality" for such cells (217). This results in exquisite sensitivity of *BRCA1/2*-mutant cells to PARP inhibitors. Another group of tumours that show increased sensitivity to PARP inhibition are those that harbor PTEN loss, a frequent phenomenon in CRPC. To this end, PTEN-null tumours exhibit genomic instability due to downregulation of Rad51 and impaired homologous recombination, or due to defects in cell-cycle checkpoints (218).

Olaparib was the first PARP inhibitor to reach human clinical testing (**Figure 6**). In a phase I study of oral olaparib in patients with *BRCA1/2*-mutated tumours, this agent produced notable responses in several subjects including a >50% PSA drop with resolution of bone metastases in a man with BRCA2-related CRPC (219). Toxicities of olaparib include gastrointestinal disturbance (40%), fatigue/somnolence (30%), lymphopenia (5%), and thrombocytopenia (5%). A larger phase II study of olaparib in patients with advanced *BRCA1/2*-mutated cancers is ongoing (**Table 4**). However, the key to the success of PARP inhibitors in CRPC patients will be the identification of biomarkers of sensitivity to these agents outside of the traditional germline *BRCA1/2* mutations, including PTEN loss or somatic or alternative genetic or epigenetic alterations in DNA repair enzymes.

Another important property of PARP inhibitors is their ability to enhance the activity of DNA-damaging cytotoxic agents (*e.g.* alkylators, platinum compounds, and topoisomerase inhibitors) (220). To this end, addition of the PARP inhibitor, veliparib (ABT-888), to temozolomide potentiates the antineoplastic effects of the alkylating agent in several cancer cell lines and animal xenograft models (220). This provided the rationale for conducting a single-arm phase II study examining the combination of oral veliparib and oral temozolomide in men with metastatic CRPC who have progressed after one to two prior chemotherapies (**Table 4**). Adverse events with veliparib are minimal, and no dose-limiting toxicities were reported in phase I trials. Finally, a randomized phase II cooperative group trial of carboplatin and paclitaxel with or without veliparib in the second-line treatment of metastatic CRPC is being planned.

TABLE 4 Selected ongoing phase II and III clinical trials of novel targeted therapies for men with metastatic CRPC.

Target/Pathway	Agent	Phase	Treatment Arm(s)	Primary Endpoint	Clinical Trial Identifier
VEGF-R Sorafe (angiogenesis)	Sorafenib	ll	Single-arm trial: sorafenib 400 mg orally twice daily [post-docetaxel]	Time to disease progression	NCT00414388
		II	Single-arm trial: sorafenib 400 mg orally twice daily plus docetaxel 75 mg/m² IV every 3 weeks [pre-docetaxel]	≥50% PSA ↓	NCT00589420
	Ramucirumab	II	Randomized trial: cixutumumab (see below) 6 mg/kg IV every 1 week plus mitoxantrone 12 mg/m ² IV every 3 weeks <i>vs.</i> ramucirumab 6 mg/kg IV every 1 week plus mitoxantrone 12 mg/m ² IV every 3 weeks [post-docetaxel]	Progression- free survival	NCT00683475
VEGF-Trap (angiogenesis)	Aflibercept		Randomized trial: aflibercept 6 mg/kg IV plus docetaxel 75 mg/m ² IV every 3 weeks <i>vs.</i> placebo IV plus docetaxel 75 mg/m ² IV every 3 weeks [pre-docetaxel]	Overall survival	NCT00519285

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mTOR (angiogenesis)	lemsırolimus	II	Single-arm trial: temsirolimus 25 mg IV every 1 week, plus anti-androgen upon progression [post-docetaxel]	Change in circulating tumour cell counts over time	NC100887640
	Everolimus	II	Single-arm trial: everolimus 10 mg orally daily plus docetaxel 75 mg/m² IV every 3 weeks [pre-docetaxel]	Objective response rate	NCT00459186
		II	Single-arm trial: everolimus 5 mg orally daily plus carboplatin AUC=5 IV every 3 weeks [post-docetaxel]	Time to disease progression	NCT01051570
	Ridaforolimus	II	Single-arm trial: ridaforolimus 50 mg IV every 1 week [post-docetaxel]	Objective response rate	NCT00110188
S100A9 (angiogenesis)	Tasquinimod		Randomized trial: tasquinimod 1 mg orally daily <i>vs.</i> placebo daily [pre-docetaxel]	Progression- free survival	NCT01234311
Clusterin (apoptosis)	Custirsen	III	Randomized trial: custirsen 640 mg IV every 1 week plus docetaxel 75 mg/m ² IV every 3 weeks vs.docetaxel 75 mg/m ² IV every 3 weeks [pre-docetaxel]	Overall survival	NCT01188187
		III	Randomized trial: custirsen 640 mg IV every 1 week plus docetaxel 75 mg/m ² IV every 3 weeks <i>vs.</i> placebo IV every 1 week plus docetaxel 75 mg/m ² IV every 3 weeks [post-docetaxel]	Improvement in pain	NCT01083615
Survivin (apoptosis)	YM-155	II	Single-arm trial: YM-155 5 mg/m² IV daily over 7 daysplus docetaxel 75 mg/m² IV every 3 weeks [pre-docetaxel]	Objective response rate	NCT00514267
	LY2181308	II	Randomized trial: LY2181308 750 mg IV every 1 week plus docetaxel 75 mg/m ² IV every 3 weeks vs.docetaxel 75 mg/m ² IV every 3 weeks [pre-docetaxel]	Progression- free survival	NCT00642018
IGF-1R (cell nutrition)	Cixutumumab	II	Randomized trial: cixutumumab 6 mg/kg IV every 1 week plus mitoxantrone 12 mg/m ² IV every 3 weeks <i>vs.</i> ramucirumab (see above) 6 mg/kg IV every 1 week plus mitoxantrone 12 mg/m ² IV every 3 weeks [post-docetaxel]	Progression- free survival	NCT00683475
		II	Single-arm trial: cixutumumab 6 mg/kg IV every 1 week plus temsirolimus 25 mg IV every 1 week	Time to disease progression	NCT01026623
	Figitumumab	II	Single-arm study: figitumumab 20 mg/kg IV every 3 weeks plus docetaxel 75 mg/m²	Objective response rate	NCT00313781

IV every 3 weeks [pre- and post-docetaxel]

TABLE 4 Selected ongoing phase II and III clinical trials of novel targeted therapies for men with metastatic CRPC. Cont'd

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Src kinase (bone regulation)	Dasatinib	111	Randomized trial: dasatinib 100 mg orally daily plus docetaxel 75 mg/m² IV every 3 weeks <i>vs.</i> placebo orally daily plus docetaxel 75 mg/m² IV every 3 weeks [pre-docetaxel]	Overall survival	NCT00744497
	Saracatinib	II	Randomized trial: saracatinib 175 mg orally daily <i>vs.</i> zoledronate 4 mg IV every 4 weeks [pre- or post-docetaxel]	Change in bone resorption parameters	NCT00558272
HDAC (epigenetics)	Panobinostat	II	Single-arm trial: panobinostat 15 mg/m² IV on days 1 and 8 of a 21-day cycle [post-docetaxel]	Progression- free survival	NCT00667862
DNMT (epigenetics)	Azacitidine	II	Single-arm trial: azacitidine 150 mg/m ² IV on days 1-5 of a 21-day cycle plus docetaxel 75 mg/m ² IV every 3 weeks [post-docetaxel]	Objective response rate	NCT00503984
PARP (DNA repair)	Olaparib	II	Single-arm trial: olaparib 400 mg orally twice daily [pre- or post-docetaxel]	Objective response rate	NCT01078662
	Veliparib	II	Single-arm trial: veliparib 40 mg orally twice daily on days 1-7 of a 28-day cycle plus temozolomide 150 mg/m² orally on days 1-5 of a 28-day cycle [post-docetaxel]	≥30% PSA $↓$	NCT01085422

TABLE 4 Selected ongoing phase II and III clinical trials of novel targeted therapies for men with metastatic CRPC. Cont'd

10.11 Bone-targeted Approaches

The field of bone health in metastatic prostate cancer has rapidly expanded over the last decade and has led to the emergence of a multitude of bone-targeting approaches showing activity in this patient population. The bisphosphonate, zoledronic acid, has been shown to delay the occurrence of skeletal-related events and has become a standard of care in mCRPC. More recently, denosumab, a RANK ligand inhibitor, has been proven to be active for the same indication, and has recently been approved for metastatic prostate cancer. Bone-seeking radiopharmaceuticals have largely been used for palliation purposes but new developments and ongoing work may lead to their increased use in the future.

10.11.1 Symptoms and complications related to bone metastases

Pain

A significant proportion of patients presenting with metastatic prostate cancer do not have pain (221). If treated early before the occurrence of such pain, the outcome of preventative measures may be more significant (222). Active targeted treatments to prevent bone complications, in the form of skeletal-related events (SREs), should be considered in this group of patients. A sub-analysis of a randomized clinical trial assessing zoledronic acid (ZA) for the prevention of bone complications in metastatic patients showed that treatment effect was greater in patients who began treatment prior to

the appearance of pain. (2) Eventually most patients with bone metastases will end up experiencing pain. The development of pain in metastatic prostate cancer patients seems to be an independent predictor of cancer-specific survival (223,224).

Skeletal-related events

Skeletal-related events (SREs) are a frequent, if not, inevitable consequence of metastatic disease, and constitutes the endpoint of almost every study assessing the activity of bone-targeted agents. They include: 1) pathological bone fractures, 2) the need for surgery or palliative radiotherapy to bone due to fracture or pain, and 3) spinal cord compression. SREs represent a significant cost in terms of quality of life, financial expenditure, and reduced survival (225,226,227).

Bone metabolism

Bone is not a static organ and is continuously in a dynamic state of turnover. Bone remodelling is due to the interaction of two types of cells: the osteoclast, which contributes to bone resorption, and the osteoblast, which contributes to bone deposition (228). There is a crosstalk between these two cell lines, which is mediated, among others, by the receptor activator of nuclear factor kappa- β (NFKB) ligand (RANKL).

Initially identified in 1998, this mediator was characterized in the context of the discovery of an endogenous decoy molecule, osteoprotegerin (OPG). (229,230) OPG, a member of the super family of tumour necrosis factor receptors, is a regulator of the activity of RANKL: it binds this ligand, preventing it from interacting with its receptor on osteoclasts, therefore reducing bone decay.

10.11.2 Rationale for bone-targeted approaches in mCRPC

In 1889, Paget described the notion of malignant tumours' propensity to metastasize to specific organ sites (231). In the case of prostate cancer, this happens to be bone. In recent years, the demonstration of molecular events associated with the prostate cancer cells' progression in the bone matrix would confirm the long-standing theory (232,233).

It has been demonstrated that circulating prostate cancer cells influence the dynamics governing the interaction of osteoblasts and osteoclasts through the secretion of a number of cytokines. These include PTHrP, BMP, TGF β , IGF, FGF, VEGF, and Wnt among others. The osteoblast is activated by this stimulus and increases its bone matrix biosynthesis, as well as the synthesis and secretion of RANKL, which in turn, will bind its receptor on the osteoclastic cells. This event will not only increase bone resorption, but will also drive the secretion of mediators, such as PDGF, BMP, TGF β , IGF and FGF (233) to which the neoplastic cells themselves are sensitive. A vicious cycle sets in whereby tumour cells secrete mediators, and receive a favourable feedback specific to bone. Furthermore, this vicious cycle is compounded by evidence that OPG is reduced in prostate cancer, at least according to *in vitro* studies, thus enhancing RANKL availability and favouring increased bone turnover (234). Bone turnover in the neoplastic setting results in resorption of healthy bone and deposition of sclerotic bone which is radiographically denser but strucurally weaker than the former (235).

One of the premises of bone targeting in neoplastic disease is therefore to break the cycle of cancerbone interaction and render the bone microenvironment unfavourable to its implantation and proliferation. Two classes of agents achieve this purpose through different molecular mechanism, and have found their application in the clinical setting. These include bisphosphonates and RANK ligand inhibitors.

Bisphosphonates have been in clinical use for more than a hundred years (236). They are the most frequently used class of bone-targeted therapy and are available in oral (PO) and intravenous (IV) formulations.

The chemical structure of bisphosphonates is very similar to inorganic pyrophosphate, with two phosphate groups attached to a central carbon moiety (237). This explains the ease with which they bind calcium in the bone matrix. Adding nitrous compounds to the carbone moiety side chain increases their potency by several hundred-folds, reaching a peak with compounds such a zoledronic acid (238). Bisphosphonates are internalized in osteoclasts by endocytosis, and the molecular mechanism of action of the nitrogen containing compounds consists of an inhibition of the mevalonate pathway (through farnesyl diphosphate synthase inhibition), thus impeding prenylation of small GTPases such as Ras, Rho and Rac, which will be deleterious to cellular morphology and activity (238,239,240). Indeed it has been shown that bisphosphonates inhibit osteoclast differentiation, reduce osteoclast function and induce apoptosis (241-243).

Although PO formulations of bisphophonates are available (*e.g.* etidronate, clodronate, alendronate, risedronate), none have shown significant activity in metastatic prostate cancer. Additionally, most have the inconvenient side effect of digestive symptoms that affect compliance to treatment. Zoledronic acid (ZA) is presently a standard of care in the treatment of metastatic prostate cancer. It is administered intravenously monthly for the indication of SRE prevention in patients with metastatic castration-resistant disease.

In the setting of a randomized controlled trial evaluating ZA against placebo, this molecule was the first bisphosphonate to show activity in reducing SREs in metastatic, castration-resistant prostate cancer (secondary prevention) (244). A total of 643 patients were randomized in this study to receive either ZA or placebo every three weeks for a total of two years. The result was a 22% reduction in SREs in the ZA (4 mg) group compared to placebo (38% vs. 49%, p=0.028), which compares favourably to analogous trials conducted in metastatic breast cancer. Furthermore, time to first SRE was increased by 5 months (488 vs. 321 days; p=0.009). The mean annual incidence of skeletal complications in the ZA group was reduced when compared to placebo (0.77 vs. 1.47 events per year, p= 0.005). There was an overall risk reduction in SREs over time of 36% in the ZA group (244,245). ZA consistently diminished bone-related pain with statistically significant differences at 3, 9, 21 and 24 months throughout the trial (p≤0.05) (245).

ZA has also been studied in non-metastatic prostate cancer and has been shown to prevent cancer treatment-induced bone loss (CTIBL) in patients undergoing androgen deprivation therapy (ADT) (246). Furthermore, ZA (4 mg IV every 3 months for 12 months) also increased bone mineral density (BMD) with respect to baseline, and this was most evident in the lumbar spine. These results held true whether ZA was administered every 3 months or yearly (246,247).

Zoledronic acid is well tolerated and presents a safe toxicity profile with proper monitoring. The most frequent adverse events are an acute phase reaction, consisting of myalgias and flu-like symptoms after the infusion, and renal insufficiency. Serum creatinine monitoring is recommended and dose adjustments as per product monograph should be strictly adhered to. Although hypocalcemia is not a major concern, judicious surveillance of this electrolyte is wise, with proper calcium replacement as needed. Finally, osteonecrosis of the jaw (ONJ) is a serious, albeit rare complication of ZA treatment and will be discussed later in this text.

According to preclinical studies as well as exploratory analysis of available randomized trials, zoledronate may possess a certain anti-tumoural effect going beyond SRE reduction. Not only does ZA disrupt the vicious cycle of bone-tumour interaction as previously discussed (247-249), but it may also have a direct action on cancer cells, whereby it induces apoptosis or acts with cytotoxic chemotherapy synergistically (250-256).

Denosumab is a fully human monoclonal antibody with a specific high affinity to RANKL. Similar to endogenous OPG, by binding RANKL, denosumab reduces its availability to interact with RANK on the osteoclast, thereby inhibiting activation of these cells, and consequently reducing bone turnover (257,258). Phase III studies have shown that denosumab is effective in three different clinical settings: 1) prevention of bone loss and fractures in patients with hormone-sensitive, non-metastatic prostate cancer on ADT, 2) reduction of SREs in patients with castration-resistant metastatic prostate cancer, and 3) the prevention of metastases in castration-resistant non-metastatic prostate cancer.

Denosumab has been recently assessed to evaluate whether it could increase time to metastases occurence in a population of metastases-free, castration-resistant prostate cancer patients. The trial, which was randomized and placebo controlled, included 1,432 patients with increasing PSA (PSA \geq 8 ng/dL before randomization or a PSA doubling time \leq 10 months), and no radiographic evidence of bone metastases. It was shown that bone metastasis-free survival as well as time to bone metastasis were increased in the denosumab arm (120 mg SC every 4 weeks) compared to placebo by 4.2 months (HR 0.85 and 0.84 with *p*=0.028 and 0.032, respectively). Also, time to symptomatic bone metastasis was increased, with a HR of 0.67 (*p*=0.01). No difference was seen in overall survival (OS) between the denosumab and placebo groups (HR=1.01; *p*=0.91) (259). However, OS was not a primary or secondary endpoint of the study (257).

In a randomized multicentric phase III clinical trial, denosumab (120 mg SC every 4 weeks) was tested against the standard of care, zoledronic acid (4 mg IV every 4 weeks), for the prevention of SREs in mCRPC patients. A total of 1,901 subjects were randomized, and the primary objective for non-inferiority testing against zoledronic acid was time to first on study SRE. In case of non-inferiority, secondary objectives to be tested included, superiority for time to first SRE (single event), as well as time to first and subsequent on study SREs (multiple events). Final analysis revealed that there was an 18% risk reduction with respect to time to first SRE in the denosumab arm compared to the zoledronic acid arm (superiority p=0.008). Analysis for the secondary objective of multiple SREs revealed the same rate of risk reduction. Denosumab did not, however, show any advantage for overall survival or progression when compared to zoledronic acid. The adverse events were also similar in both groups. Of note, however, is that patients receiving denosumab presented more hypocalcemia and muscle spasms, whereas the zoledronic acid group had more pyrexia and flu-like symptoms (260).

10.11.3 Osteonecrosis of the jaw (ONJ)

ONJ presents classically with exposed bone in the oral region with a predilection to the mandible (261). Healing may take several weeks and, although conservative treatment is recommended, surgical intervention may be necessary. ONJ was initially thought to be mainly a complication of IV bisphosphonate therapy (262). However, there have been a few reports of it occurring in the setting of oral BP (263). Furthermore, ONJ has been shown to be associated to denosumab when the drug was given on a monthly basis, implying that the disorder is not an exclusive class effect of bisphosphonates, but is more likely related to inhibition of osteoclast activity (264). Risk factors in patients on bone-targeted therapy include poor dental hygiene, pre-existing oral pathology, use of poorly fitted dentures, and oral surgery while ongoing treatment with BPs or denosumab. This being said, ONJ remains fortunately a relatively rare event (1-2%) as seen in the phase III study of denosumab versus zoledronic acid. Prevention of ONJ during bone-targeted therapy entails keeping appropriate dental hygiene, periodic dental check-up, and avoidance of invasive dental procedures (264-266).

10.11.4 Bone-seeking radiopharmaceuticals

The rationale for using radiopharmaceuticals directed against bone metastases is to provide pain relief with minimal side effects. Indeed, metastases being often multifocal in PCa patients, it is often impossible to cover all disease using external beam radiotherapy (which attacks normal and pathological bone) without risking significant morbidity. Radiopharmaceuticals that have been used clinically in prostate cancer include ³²P, ⁸⁹Sr, ¹⁸⁸Re, ¹⁵³Sm, and ²²³Ra (267-277). Of these, only strontium-89 and samarium-153 have been approved by the FDA for the treatment of palliating pain resulting from multiple osseous blastic metastases.

Most of the radionuclides that have been used up to now have included beta-emitting particles. Such is the case with ¹⁵³Sm and ⁸⁹Sr. These produce relatively low energy radiation, but have the inconvenience of having a low radiobiological effectiveness, with track lengths in tissues of up to a few millimeters (271). Conversely, alpha-emitting bone-seekers, such as ²²³Ra, provide a dense ionizing radiation, known as high-LET (linear energy transfer), with a low range of less than 100 mm. This allows more focused radiation delivery and theoretically should spare bone marrow in the process (278).

Strontium (⁸⁹Sr) localizes mainly in areas of osteoblastic activity. It is administered intravenously and concentrates in bone precisely in proportion to osteoblastic activity. Approximately 20% of the compound is retained in the subject after 90 days despite the fact that its biologic half-life is about four to five days (270). Pain is usually relieved within 1-3 weeks, albeit, a painful flare may occur two to three days after administration, and relief lasts approximately 6 months (270-274). No survival benefit has been noted using this agent (272).

Samarium (¹⁵³Sm) is complexed with a phosphate compound (ethylenediaminetetramethylene phosphonic acid), which accumulates in the skeleton proportionately to osteoblastic activity (271). Approximately 75% of patients receiving this therapy experience pain relief. (55) Although no statistically improved survival was noted, a trend towards that endpoint was observed in at least one study (275).

A randomized, multicentre, placebo-controlled phase II study has been published assessing the value of radium (²²³Ra), an alpha-emitting bone-seeker, in the setting of metastatic CRPC (278). A total of 64 patients were randomized to receive four IV injections of ²²³Ra (50 kBq/kg, n=33) or placebo (n=31) (279). Radium was well tolerated and hematological adverse events were not statistically different between the two treatment arms of the study. There was a reduction in bone alkaline phosphatase (a marker of bone turnover) in the radium-treated group (-65.6% vs. +9.3% for placebo; *p*<0.0001). More importantly, time to PSA progression was significantly longer in the active treatment (26 weeks vs. 8 weeks for placebo, *p*=0.048). Unfortunately, no difference was noted in time to first SRE, or in median overall survival, albeit, there was a trend for the latter endpoint in favour of the active treatment (65.3 weeks vs. 46.4 weeks for placebo; *p*=0.066). A recently completed phase III study randomized patients with mCRPC on a 2:1 basis to either radium-223 or placebo. Overall survival was the primary endpoint. Median survival was 14 months for the treated patients as opposed to 11.2 months for those who received a placebo, conferring an approximate 30% improvement in OS (HR 0.699; *p*=0.0022). If approved by FDA, this will be the first bone-targeted agent to demonstrate a survival advantage.

Myelosuppression constitutes the major side effect of this therapeutic modality. In the case of samarium, this side effect is more related to uptake than to administered dose, such that myelosuppression is greatest in patients with extensive metastatic burden (280-282). Marrow suppression takes place approximately two to four weeks after administration (273). To avoid this side effect, it is recommended that treatment be witheld in patients who have received chemo- or radiotherapy within six weeks. This being said, it is rare to have grade 4 toxicity and the new alpha-emitting agents promise less myelosuppression than the older radiopharmaceuticals.

10.11.5 Bone markers in targeted therapies

The availability of multiple bone-targeting agents presents an opportunity for sequential use or even combination therapy. However, for such a use to be clinically practical, it is important to be able to define what is considered a treatment success and failure in order to identify a trigger point for switching treatment. The answer to this may come from biomarkers of bone turnover. Available and well-characterized markers include N-telopeptide (NTx) and C-telopeptide (CTx) of type I collagen quantifying bone degradation, and serum bone-specific alkaline phosphatase (ALCP) for bone deposition (283). Combining these markers provides a more accurate snapshot of the ongoing bone remodelling in prostate cancer patients (284).

The aforementioned markers may have prognostic value. Patients with elevated markers of resorption and/or formation were found to be at higher risk of SREs and reduced survival compared to patients with normal levels (285,286). Response to therapy may also be predictive of outcome. In a retrospective analysis on data from the randomized trial of ZA in CRPC patients, it was shown that subjects with elevated baseline NTx levels who normalized their NTx levels had a 59% reduced risk of death compared to those with a persistently elevated NTx (286-288). This result was reproduced in other studies; showing a better OS when patients on ZA had lower markers compared to baseline after three months of treatment. Taken together, these findings may allow clinicians to identify highrisk patients earlier and eventually, to define treatment failure as a failure to normalize bone markers. In theory, persistently elevated markers in a patient after initiation of a bone-targeted therapy may warrant changing the bone-targeted agent or adding a new agent (*i.e.*, chemotherapy). Further confirmatory studies are indicated however, before bone markers gain widespread clinical applicability.

10.12 Immunotherapy

10.12.1 Active Cellular Immunotherapy for Prostate Cancer (Sipuleucel-T)

In 2010, the US FDA approved Sipuleucel T (Provenge®, Dendreon, Seattle, WA, USA) for the treatment of men with asymptomatic or minimally symptomatic, mCRPC. This approval marked the first specific active immunotherapy ("vaccine") approved to treat any type of solid tumour. Supporting data came from a series of three phase III trials, all with a similar design, and all enrolling the same basic patient population. The first of these trials (D9901) was reported in 2006 (289). A total of 127 patients were enrolled and randomized on a 2:1 basis to receive treatment with Sipuleucel T, or with placebo. In this initial trial, the primary endpoint (time to progression [TTP]), was not statistically significantly different between the two treatment groups. However, a pre-planned analysis showed an improvement in overall survival in the treatment group (25.9 vs. 21.4 months; HR=1.70; p=0.01). A second phase III trial, D9902B was later reported (290). This trial also showed a trend towards increased survival, but that result was not statistically significant. In both trials, treatment was welltolerated, with side effects predominantly limited to a flu-like syndrome, including fever, chills and fatigue. Pivotal data supporting regulatory approval came from a 512 patient trial (IMPACT, D9902B). Although the basic design of IMPACT was similar to D9901 and D9902B, the primary endpoint of this third, larger trial was overall survival. That endpoint was met, with a survival of 25.8 months in the treatment group and 21.7 months in the placebo group (HR 0.77; p=0.02) (291). These survival data should be interpreted in light of the fact that patients on the placebo group could cross over to active treatment upon progression, by enrolling in a secondary, salvage protocol. Approximately 50% of the patients in the placebo group eventually received active treatment, potentially diluting or otherwise confounding the survival results.

Although about 15% of the patients in the IMPACT trial received prior treatment with docetaxel, it is expected that, in clinical practice in the US, most patients treated with Sipulecuel-T will be chemotherapy naïve. Currently, multiple agents are in development for men with mCRPC; one of these, the novel hormonal therapy, abiraterone acetate (discussed previously) (292), has recently been approved for men who have progressed on or after standard chemotherapy. This agent inhibits androgen synthesis by blocking cytochrome P450 C17 (CYP17) a critical enzyme for testosterone synthesis. Thus, the drug blocks androgen synthesis by the testes, the adrenal gland, and presumably intratumourally. A phase III trial evaluating a potential survival benefit of this agent in pre-chemotherapy patients (COU-AA-302, NCT00887198) has completed enrollment, and final results are pending. If these data are positive, men with early mCRPC would have a second treatment option, but physicians who wish to prescribe Sipuleculel-T will need to choose whether to administer this treatment before or after abiraterone acetate. Immunologically, this sequencing decision is complicated by the practice of administering prednisone, or another corticosteroid along with abiraterone acetate to suppress compensatory increases in adrenocorticotropic hormone (ACTH) and resultant symptoms. Indeed, the post-chemotherapy FDA approval of this agent specifies its usage along with prednisone. Answering this question definitively would require a large-scale, randomized phase III trial, most likely with a survival endpoint. To our knowledge such a trial has not been planned to date. In this context, it must also be determined whether abiraterone acetate administration absolutely requires pre-emptive corticosteroid treatment. While men who progress on or after docetaxel are often maintained on prednisone for palliative benefit, pre-chemotherapy use of abiraterone could involve extended periods of time, and the side-effects associated with long-term administration of prednisone to these asymptomatic patients could prove far less acceptable. Indeed, it has recently been argued that, in the majority of patients, co-administration of prednisone with abiraterone is not clinically required (293). Outside of the US, these considerations are of less relevance at the current time, as Sipuleucel-T is not yet widely available on a global scale.

10.12.2 Immune Checkpoint Blockade in Prostate Cancer (Anti-CTLA-4, Ipilimumab)

Activated CD4 and CD8 T cells are critical in the immune response to various pathogens and to tumour antigens. Activation of these T cells is a complex cellular process, involving both nonspecific, as well as specific signals. The specific signal (Signal 1) comes in the form of a peptide presented in the context of a particular MHC molecule; each T cell expresses a single T cell receptor, specific for a particular peptide. Recognition of peptide (+ MHC) alone is not sufficient for T cell activation, instead, at least one or more additional signals must be relayed to the T cell for it to become fully functional. This second signal (Signal 2) usually comes in the form of an interaction between "co-stimulatory" molecules on the surface of antigen-presenting cells, and a receptor on the T cell known as CD28. Under certain conditions, T cells upregulate CTLA-4, which binds to co-stimulatory molecules with greater affinity than does CD28. Engagement of CTLA-4 on T cells prevents their further activation and proliferation, that is, CTLA-4 effectively hijacks the co-stimulatory signal and converts it to an inhibitory one. Ipilimumab (Yervoy™, Bristol-Myers Squibb, Princeton, NJ, USA) is a monoclonal antibody that binds to CTLA-4 with high affinity, effectively blocking this inhibitory signal, allowing T cell activation to proceed. Ontologically, CTLA-4 most likely did not evolve to prevent the immune system from responding to tumours. Instead, CTLA-4 serves to restrain a normal anti-pathogen immune response and to prevent self-reactivity. Data supporting this role came from multiple studies in mice in which CTLA-4 was genetically knocked out (*i.e.*, inactivated). The studies demonstrated that the knockout mice succumb to multi-organ lymphoproliferative autoimmunity by approximately three to four weeks of age (294,295). Thus, the immune-related adverse events noted in clinical trials of ipilimumab are not completely unexpected, but instead reflect a somewhat predictable consequence of blocking this key immunological checkpoint. In fact, in some studies, the induction of immune-related adverse events (IRAEs) appeared to correlate with clinical benefit from ipilimumab treatment (296,297).

Commercial development of ipilimumab has focused largely on melanoma, and the US FDA approval for this indication was recently granted. Ipilimumab has also been evaluated in several hundred patients with prostate cancer, in a series of several phase I and phase II trials. Only a few of these datasets have been published in peer-reviewed journals. The first phase I trial of ipilimumab in men with prostate cancer tested the safety of a single 3 mg/kg dose in men with mCRPC (298). A total of

14 patients were enrolled and treated, and PSA "response", defined as a >50% decrease in baseline PSA, was documented in 2 out of the 14 patients. A single dose of ipilimumab was well tolerated, with a single grade 3 IRAE observed. The study most relevant to ongoing phase III trials, MDX-021, was an open-label, dose escalation study of ipilimumab administered four times at three-week intervals to men with mCRPC. The dose of ipilimumab was escalated from 3 mg/kg to 10 mg/kg. The agent was administered along with a single dose of 8 Gray (Gy) of radiotherapy to a bone lesion, in an effort to deliver tumour antigens from dying cells to the immune system in a pro-inflammatory manner. An abstract presented in 2008 documents a rate of PSA decline of approximately 20%, and a side-effect profile not appreciably different than those observed in prior trials of ipilimumab in patients with metastatic melanoma (299).

Two large phase III trials of ipilimumab have been initiated for patients with mCRPC. The first of these, (CA184043, identifier NCT00861614) was initiated in 2009. This blinded, phase III trial will enroll approximately 800 men with prostate cancer who have been previously treated with docetaxel chemotherapy; these men will be randomized (1:1) to radiotherapy + ipilimumab or to radiotherapy + placebo, with a primary endpoint of overall survival. The treatment scheme includes a dose of 8 Gy of radiation to between one and five metastatic bone lesions, with radiotherapy given one or two days prior to ipilimumab (or placebo) administration. The treatment regimen includes four doses of the agent at 10 mg/kg at three-week intervals, followed by maintenance dosing every three months in patients who do not meet formal stopping criteria. The estimated completion date is 2013. A second phase III trial of ipilimumab was subsequently initiated in an earlier patient population. This blinded, randomized phase III trial (CA184095, NCT01057810) will enroll men with asymptomatic mCRPC who have not received prior docetaxel chemotherapy. The treatment regimen is identical to that of CA184043, with the exception of radiotherapy to metastatic bone lesions not being included. In addition, randomization will be in a 2:1 manner. Planned enrollment is approximately 600 patients, and is expected to conclude in 2015. Taken together, these two randomized phase III trials could potentially be pivotal in extending regulatory approval for ipilimumab to prostate cancer, but integration into that future treatment landscape could prove complex.

10.12.3 **ProstVac VF – A Poxvirus Based "Vaccine"** for Prostate Cancer

A major advance in public health was the eradication of smallpox, achieved through a large-scale vaccination program in which over one billion individuals worldwide were immunized using a vaccinia-based vaccine. To utilize this technology to treat cancer, recombinant viruses can be generated using DNA engineering to incorporate tumour-associated proteins into the viral backbone. In an initial work performed at the National Cancer Institute (NCI), a prostate cancer vaccine was generated by the incorporation of PSA into the vaccinia backbone. This choice was based primarily on its relatively exclusive expression in the prostate gland and in prostate cancer. This selection has a functional basis as well, PSA has enzymatic activity, and may play a role in tumour progression and the development of metastases (300). Early clinical trials were relatively straightforward, recombinant PSA was inserted into the vaccine backbone, and administered on a monthly schedule to men with mCRPC along with subcutaneous GM-CSF as an adjuvant at the vaccine site. In the first such trial, 42 patients were treated, vaccine was generally well tolerated, and several evaluable patients were demonstrated to have increased T cell reactivity to PSA, suggestive of *in vivo* immunogenicity

in humans (301). A series of subsequent optimization steps (and trials) refined the platform significantly (302), and led the current iteration of the vaccine, which is about to enter a phase III randomized study (see below). The first optimization step involved modification of the PSA peptide itself; a point mutation in the PSA epitope that binds to the most common Class I MHC (HLA-A2) was identified on the basis of its ability to stabilize MHC molecules on the cell surface, and incorporated into future vaccine iterations (303). A more profound modification to the platform came through the incorporation of a heterologous prime/boost vaccine strategy. This was important because repetitive vaccination with recombinant vaccinia-based vectors is attenuated by an immune response to the many highly immunogenic viral proteins that make up the backbone (i.e. it is difficult to boost the immune response to a recombinant antigen expressed in vaccinia backbone vector by repetitive administration) (304). Potential poxviral backbones useful for boosting vaccinia include fowlpox vectors; although fowlpox viruses infect mammalian antigen presenting cells, viral coat proteins are not expressed - leading to only a minimal antibody response. Recombinant fowlpox vectors expressing PSA were generated, and a phase II trial was performed to determine the optimal sequencing of Vaccinia-PSA and Folwpox-PSA immunization. This study, administered by the ECOG, showed that the preferred sequence was a recombinant vaccinia-PSA (rV-PSA) prime, followed by a series of recombinant fowlpox-PSA (rF-PSA) boosts (17). Data supporting this sequence were both immunological and clinical, with the rV-PSA -> rF-PSA sequence showing a delay in PSA progression as compared to either vaccine used alone (306). A final modification to the recombinant vaccinia platform was based on preclinical data showing that incorporation of immunologically active molecules into the rV and rF backbones could greatly increase immunogenicity. In important preclinical studies, the NCI group showed that the addition of three immune-stimulatory molecules (B7-1, ICAM-3 and LFA-1) to a rV-PSA vector increased immunogenicity in a synergistic manner (307). This modification, known as TRICOM, was incorporated into later iterations of the platform, including an ECOG study in men with biochemically recurrent prostate cancer (308).

The most important study of ProstVac to date was a randomized phase II study in men with asymptomatic mCRPC, a similar population to that enrolled in the Sipuleucel-T phase III trials (309). In this study, 125 men were randomized 2:1 to either rV-PSA (TRICOM) followed by three monthly boosts with rF-PSA (TRICOM), given with local GM-CSF as an adjuvant, or to an empty fowlpox vector (placebo). The primary endpoint of this trial, time to progression, was not met but an analyses of overall survival showed an apparent benefit in the treatment group (OS 25.1 vs. 16.6 months; HR=0.56; p=0.0061). These results are interesting in that they closely mirror the outcome of a similar patient population treated with Sipuleucel-T; indeed both datasets show an increased survival benefit without apparent differences in radiographic progression. These data also provide additional support to the notion that immunotherapy for prostate cancer may provide clinical benefit, especially in men with an earlier stage of metastatic disease. Based on these data, an industry-sponsored (Bavarian Nordic Immunotherapy, Mountain View, CA, USA), randomized phase III trial of ProstVac VF has been announced. This trial will enroll men with a favourable predicted outcome, and will include three arms: placebo, ProstVac VF + GM-CSF, and ProstVac VF alone. This global trial will be fairly large, with a planned enrollment of 1200 patients.

10.13 Summary and Future Directions

This chapter summarizes some of the most recent advances in the systemic treatment of prostate cancer. Treatment options have expanded significantly. The number of newly approved compounds has grown rapidly since the initial approval of docetaxel in 2004 based on a significant survival benefit for patients with metastatic castration-resistant disease. It is clear that improved understanding of mechanisms involved in the growth and metastasis of prostate cancer, from the "bench to the bedside", has reached a level where additional tangible improvements are likely to occur in the near future. The natural history of this disease appears quite different from only two decades ago. Contemporary definition of clinical states of the disease, in a way that describes more accurately the current clinical scenario of prostate cancer outlines more precisely all the different paradigms. It also facilitates considerations for therapeutic interventions. For example, the distinction between biochemically relapsed and clinically relapsed disease, hormone naïve (and potentially sensitive) and castration-resistant disease, as well as hormone-refractory disease describe new clinical paradigms with unique clinical significance that require a review of what was previuosly considered "standard" therapeutic approaches. The knowledge about the biology of the androgen receptor has modified the notion and previous definition of hormone-refractory disease, and consequently, served as the basis for developing new compounds which were recently approved in the US and in Europe for standard clinical use. Additional androgen receptor targeting compounds are in the advanced stages of clinical development and will likely become important additions to our clinical armamentarium.

In the section of new targeted agents, new compounds in active development for this disease are outlined. While currently there are more drugs available for the treatment of metastatic CRPC than ever before, we are still left with several challenges and unanswered questions. First, we must determine how newly approved and experimental therapies should ideally be sequenced in individual patients with CRPC. Second, we will need to develop logical strategies to optimally combine new and old therapies in a rational manner, and to understand mechanisms developed by tumour cells to overcome the cytotoxic or antiproliferative effects of some of our most active treatments. Is our current level of understanding of negative feedback loops and alternative pathways of activation to overcome resistance to monotherapy sufficient for selection of optimal combinations? For instance, should mTOR inhibitors always be combined with IGF pathway inhibitors, or should PARP inhibitors only be used together with DNA-damaging chemotherapies? Additionally, can PTEN loss predict benefit from PI3K or PARP inhibitors? Ultimately, only prospective trials incorporating biomarkerdriven hypotheses will be able to address these key clinical questions. Moreover, we must select our patients more carefully based on clinical or molecular characteristics, in order to identify the subset most likely to benefit from a particular therapy. Thus, the collection of tumour specimens or correlative samples may be essential in identifying and validating novel targets in carefully designed studies.

Finally, it is imperative that we design specific trials with the goal of quickly, yet reliably identifying agents that do not hold promise, while enabling those that do to move swiftly to registrational studies. Some suggestions for improved clinical trial design are listed below, and reflect the collective opinions and experience of the authors:

- Early-phase prostate cancer-specific trials should be conducted that are guided by disease-based pathways, with early integration of potential predictive biomarkers.
- 2. More informative phase II studies (*e.g.* randomized phase II trials instead of single-arm phase II studies with historical comparisons) should be performed prior to embarking on phase III trials.
- **3.** The combination of agents simply because of feasibility should be avoided (*i.e.* trials testing an approved agent with or without an experimental drug should be discouraged), unless there is substantial scientific/mechanistic rationale based on demonstrated preclinical/clinical data.
- Clinically relevant endpoints should be utilized in phase II trials (*i.e.* not just PSA parameters), while also setting a high bar for go/no-go decisions to transition from phase II to phase III studies.

- Phase III studies should be designed to compare an experimental agent against an established active therapy, rather than against a placebo.
- 6. New efforts should focus on identification of alternative surrogate biomarkers of clinical benefit (*e.g.* change in circulating tumour cell counts at 12 weeks after initiation of therapy), potentially shortening the duration of pivotal phase III trials and permitting an earlier signal of efficacy.
- Trials should be designed with prospectively defined predictive biomarkers (*i.e.* biomarker-stratified studies); these trials would have the ability to investigate clinical outcomes to an experimental agent in patients both with and without a given biological marker.

Although the future of targeted therapies for advanced prostate cancer looks bright, we must continue to combine good science with innovative drug development strategies to successfully chart this course. Continued advances in our understanding of prostate cancer genomics and proteomics will likely further expand our armamentarium of treatment options for patients with CRPC moving forward.

The bone is a major site of morbidity not only from the metastatic point of view but also as a complication for long-term androgen deprivation. Knowledge about the possible link between the effects of androgen suppression and metastasis has further supported the rationale for studying the effects of bone-targeted approaches beyond simply addressing the morbidity of androgen suppression in the bone. The intent is to achieve better overall control of prostate cancer by targeting biological steps involved in the microenvironment of the metastatic process of prostate cancer.

Finally, targeting the immune system in prostate cancer makes a great deal of sense for several reasons. Prostate cancer is characterized by paradigms that exhibit relatively long periods of clinical progression consistent with the expected effects of immune therapies. These therapies are more likely directed towards delaying progression rather than inducing the more classical clinical effects associated with other modalities of treatment, such as androgen deprivation and cytotoxic chemotherapy (such as PSA declines, symptomatic improvements and delay of clinical progression). The recent approval of Sipuleucel-T is certainly a significant event for immunotherapy and certainly prostate cancer as well. The basis for approval of the cell-based immunotherapy is specifically discussed in the section above.



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Committee



Patient's Perspectives in Prostate Diseases

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11.1 Introduction

To ensure that we developed a comprehensive report on the patient's perspective in prostate disease, the committee was structured to include representatives from as many countries as possible. We concentrated heavily on the pertinent websites for much of the information and tried as best we could to contact representatives from these organizations to ensure that our descriptions of their respective activities were accurate, and as up to date as possible.

The Committee would like to acknowledge the vision of the ICUD in welcoming patient representatives to their deliberations. It is also reassuring that patient organizations are given an opportunity to interact with the international urological community in advancing the patient-physician partnership.

This report is an update of a similar chapter in the ICUD 2006 Prostate Cancer book titled "Patient's Perspectives in Prostate Diseases. (1) Despite its title, as before, the chapter will concentrate exclusively on patient perspective issues related to prostate cancer and therefore will have only passing relevance to other prostate diseases.

Over the last decade an appreciation of the importance of the patient's perspective has greatly deepened and expanded. Consequently, the recourses and organizations available to patients have increased exponentially. This chapter can only describe a small portion of the activity now occurring in this area. The committee apologizes to those relevant organizations and activities that are not included in this report. For example, we were not able to gain sufficient data to include in this report about evolving organizations in many Asian countries.

An initial topic for this report could be: who is the patient of concern and why is his perspective important? In this context, a patient is a man who could or does have prostate cancer. By extension, it also includes the friends or relatives of such a man. In times past, a patient was just what the Latin root of the word implied; namely, someone who had to have patience and endure his misery. For many reasons, this prospect has been drastically altered. Now, modern medicine can often resolve that misery. In addition, the relationship between the physician and the patient has changed. Formally this relationship was unidirectional; that is, from physician pronouncement to patient acceptance. Now, mostly to the advantage of both parties, the relationship is bidirectional and more of a dialogue.

The reasons for this "watershed" in the physician-patient relationship are many and included the following:

- 1. A greater emphasis on the rights of a patient and a greater appreciation of medic ethics including the principle of beneficence, autonomy and individual treatment.
- **2.** Common access to the advantages of the communication/ information revolution.
- **3**. Competitive and conflicting claims within organized health care.
- 4. The increasing presence and influence of complementary and alternative medicine strategies.
- **5.** An increase in medicine's legitimate alternatives for treatments for many of prostate cancer's challenges.
- 6. The increasing recognition that "for the busy physician, the details of diagnosis and treatments are familiar territory. For the frightened patient, it's uncharted territory and a potential minefield". (1)

11.2 Patient Concerns

There are a plethora of questions and concerns that can confront a man (and his friends and/or family) who could or does have prostate cancer. A list of such questions would include the following:

- 1. What is the prostate gland; where is it; and what does it do?
- 2. What is PSA and why is it important?
- 3. What is prostate cancer and how is it related to other cancers? How common is it? What causes it? How does it start? Why is it sometimes called an old man's disease and its development inevitable with age? Why is it also sometimes described as heterogeneous and often a chronic cancer? What is metastasis and how does prostate cancer metastasize? How do people die when they have prostate cancer?
- 4. How does one detect prostate cancer? Related to this, what is screening and why is it now so controversial? Will someone explain the pros and cons of prostate cancer diagnosis and will my medical coverage pay for a prostate cancer "check-up" if I decide to have one?
- **5.** What are staging and grading and why are they important? Specifically what is the Gleason score, what is a CT scan, and what is

- a bone scan? What is my stage and grade, and what does that mean regarding my prostate cancer survival?
- 6. What are the possible therapies for my cancer and their advantages and disadvantages? Specifically, what is a radical prostatectomy, lymphadenectomy and robotic surgery? What is radiation therapy and, more specifically, what is brachytherapy, external beam therapy, IMRT, and proton therapy? What is hormone therapy and why is it useful in prostate cancer? Finally, if hormone therapy stops working, what are other possible effective therapies?
- 7. What is a clinical trial and why should I be interested in participating?
- How will I know if I am cured? If I am not cured, what can be done; how long will I live; what will I experience; and how can I cope?

Increasingly, the answers to these questions are revealed to the patient not only by his physician, but also from the activities of prostate cancer support groups and coalitions.
11.3 Prostate Cancer Support Groups and Coalitions

Support groups for cancer survivors and their families are not a new entity, but their proliferation and influence over the last two decades, especially in prostate cancer, has been tremendous. There are many reasons for this phenomenon and among them are the following:

- The change in attitude between both the physician and patient that emphasizes patient rights and the need for information and dialogue. On the other hand, physicians are now often more pressed for time, and responsibility for the patient has increasingly shifted from the individual physician to a "team approach". (2)
- 2. The dissemination of the information technology capabilities.
- The fact that prostate cancer is common and its clinical course heterogeneous, and even in the advanced case often relatively lengthy. Thus, there are a lot of patients around at any one time.
- 4. The hugely successful activities of the breast cancer support groups have galvanized men to learn from them and duplicate their efforts.
- **5**. Men have gradually become more willing to reveal and discuss their prostate cancer and their accompanying concerns.

Because of the great proliferation of prostate cancer support groups, this chapter cannot do justice to all of those that exist. Also for reasons previously mentioned, only a few Asian groups are included.

11.3.1 **Europe**

Europa Uomo

The primary European patient support group is *Europa Uomo*, the European Prostate Coalition. It is an international and non-profit association as a confederation of national, autonomous patient groups from most countries of the European Union.

Launched in 2004 and patterned after the successful European breast cancer group called Europa Donna, it is now represented in 23 countries with each country having one voting member. These countries include Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Lithuania, Norway, Poland, Portugal, Romania, Slovak Republic, Spain, Sweden, Switzerland, the Netherlands and the United Kingdom.

Europa Uomo represents and supports patient groups for prostate diseases in general (about 50 million men in Europe), and prostate cancer in particular (about 3 million men). The aims include: increasing awareness of prostate diseases; supporting individualized management based on optimal medical treatment and personalized patient care; as well as promoting patients' advocacy focused on quality of life based on solidarity and mutual respect. Its rapid expansion is due in part to the close collaboration with the professional organizations, most particularly the European Association of Urology and the European School of Oncology. The goals of these latter organizations include: providing information and education on evidence-based management; recognizing the need to

inform and educate men on holistic patient care; and joining in advocacy with other patient support groups. These goals for Europa Uoma were originally presented in a 10-point manifesto at its conception focusing on quality of life for the patients and their families, the need for appropriate early detection of cancer, the promotion of multi-professional quality care and appropriate medical infrastructure, and last, but not the least, the advancement of prostate cancer research.

The launch of the European Partnership Action Against Cancer (EPAAC) in 2009 by the European Union gave a huge boost to patient advocacy as this program focused on the patient first and involvement of patient advocates in all aspects of prevention, screening and treatment of cancer. (3)

Subsequently, Europa Uomo launched a call-out on prostate diseases in Antwerp on the occasion of the European prostate day:

- Governments to be aware of prostate diseases
- Governments to support research into biomarkers
- Awareness of the risk factors of prostate cancer
- Tailored treatment of the individual patient through appropriate use of PSA testing
- Partnership-building to reduce burden of disease, identify common actions, and overcome inequalities in medical treatment and holistic care.

This call for partnership building was immediately followed by a partnership drive, including most professional associations in Europe as ECCO, ESMO, ESTRO (also nursing and pharmacists associations) as well as advocacy groups such as ECPC, Europa Donna and research groups. The expectations from this EPAAC program include a consensus on the patient first and then his cancer, patient rights and obligations, patch the fragmentation of medical treatment, optimize national cancer plans and promote shared risks (triple win) in medical innovations. The base of this professional and public approval is probably related to its mantra. Disease management and organization is based on two entities: optimal medical treatment (exclusive for health professionals) and holistic patient care (shared but with the permanent inclusion of patient advocates).

An accurate picture of the identity and activity of Europa Uomo can best be appreciated by a perusal of their excellent website. (4) There, one will get a glimpse of their extensive activities. These include staging joint symposiums for patients at scientific congresses, providing periodic news about the organizations activities, and medical news updates related to prostate cancer. There is also a section providing extensive, easily accessible links to most of the other patient support organizations (*e.g.* US TOO) and to prostate cancer information sites (*e.g.* prostatecancerinfolink.net). Finally, the Europa Uomo website contains a search engine with linkages to many other websites that contain prostate cancer information and search facilities.

11.3.2 North American Support Groups and Coalitions*Us TOO*

The organization was founded in 1990 in the US by five men who had been treated for prostate cancer. Its official name is "Us TOO International Prostate Cancer Education & Support Network". It is a grassroots organization formed over 20 years ago and has grown into an education and support network of 325 support-group chapters worldwide. Its goal, like many support groups, is to provide men and their families with free information, materials and peer-to-peer support so they can make informed choices on detection, treatment options and coping with ongoing survivorship. Its key mission is often summarized in the three words: support, education and advocacy.

As with Europa Uomo, a great deal of what Us TOO is about and its activities can be obtained through its website. (5) Briefly, its core activity is to support and unify regular support group meetings in its over 300 chapters. The goal of these meetings is of course to provide emotional and communal support, but also to provide unbiased information from experts in areas related to prostate cancer, including treatment options, pain control, nutrition, mental health, and coping strategies. There are also newsletters, which provide the latest news of interest to patients and concerned others, such as modern treatment strategies and emerging new ideas and therapies. The organization also provides general and special updated educational resources though a variety of venues. They also have online "discussion communities" dedicated to supporting and educating prostate cancer patients. Similarly, they have what they call their "circles of love" which provide emotional resources such as books, brochures, web-based resources and even inspirational music for companions and families struggling to support their loved ones. Finally, they devote considerable effort to advocacy; that is, participating in a variety of efforts to increase funding for early detection, diagnosis, treatment and research. Since the organization is primarily a volunteer group, there are significant efforts towards fundraising for their organization and volunteer recruitment.

The Prostate Cancer Foundation (PCF) (6)

This organization was started in 1993 by the financier, Michael Milken, after he developed prostate cancer. It is not primarily a patient support group but is focused on advocating for and supporting research in prostate cancer. Their support is centered on discovering new strategies for diagnosis and cure. Uniquely, they have developed a red-tape cutting process for identifying and channeling resources to the world's top scientific minds and developing mechanisms for encouraging communication and collaborations among the scientists to speed up breakthroughs.

Without a doubt, their efforts in funding and communication, particularly in the US have hugely galvanized and expanded the quality and quantity of prostate cancer research. A large part of their efforts have also been to champion for increased government funding and private support. Accordingly, PCF has helped build a global research enterprise of nearly \$10 billion. Through the generous contributions of its donors, they have funded more than 1,500 programs at nearly 200 research centres in 12 countries. Accompanying the fundraising efforts is a significant enterprise to better educate patients and their families, especially as it relates to new research developments. Some of the most cutting-edge information about prostate cancer can be found on their website. Finally, each year, they conduct a three-day meeting of top prostate cancer researchers, PCF research grant

awardees, top researchers from other related disciplines, and scientific representatives from biotech companies involved in prostate cancer research. It is undoubtedly one of the best prostate cancer research meetings in the world.

The Prostate Cancer Research Institute (PCRI)

Two medical oncologists founded the organization in 1996. Their stated purpose was to develop "an organization providing insightful clinical research in combination with high-level educational activities directed at both the patient and physician..." (7) Its efforts are primarily educational and some would say that they take significant positions with regard to certain therapies (*e.g.* hormone therapy for more than advanced disease and a preference for radiation therapy over surgery). Nonetheless, their efforts at patient education are very extensive as is evident from their website. (7) For example, they have a phone-in helpline where patients can receive individualized advice from knowledgeable laymen who are prostate cancer survivors or partners of same. They also have extensive printouts to help patients make therapy decisions. There is of course a regular newsletter containing news about the PCRI and new developments in prostate cancer treatment. Most prominently, they conduct a large yearly conference that brings together patients, caregivers, physicians and institutional supporters for interactive sessions and lectures.

ZERO–The Project to end Prostate Cancer

This organization is a patient advocacy group based in Washington, DC. ZERO is committed not only to reducing prostate cancer or alleviating the pain from the disease, but to ending it. ZERO envisions a future where all men who have been diagnosed with prostate cancer will be cured or are able to manage their illness with a good quality of life, with the support they need to minimize physical and emotional suffering, and to cope effectively throughout their cancer journeys. To accomplish ZERO's goal, the organization works to increase research funds from the federal government to find new treatments for prostate cancer. Through the Great Prostate Cancer Challenge, a premier men's health event series, ZERO raises awareness and funds local grants to end prostate cancer. ZERO also conducts free testing through the Drive Against Prostate Cancer, a nationwide mobile testing program for prostate cancer. ZERO's website (8) is a great resource for all affected by prostate cancer, providing education to patients, families, and those at risk.

The Prostate Net®

Virgil Simons, an African-American prostate cancer survivor, founded this organization in 1996. As such, the core objective of The Prostate Net's mission is to develop and maintain an interactive matrix of educational tools and services that will:

- 1. Educate consumers most at-risk from a diagnosis of prostate cancer;
- 2. Inform the community on other diseases and conditions of negative impact;
- **3.** Motivate consumers to make informed choices as to healthcare and lifestyle management;
- 4. Lay the foundation for ongoing health care information dissemination and interaction between the community and medical centres;
- **5**. Create an interactive network to maximize broad scale, mass communications of actionable health messages.

A somewhat unique activity of this group is to bring prostate cancer education directly to key areas of social interaction in the black and other minority communities: churches, service agencies, motorcycle dealerships, and barbershops. Indeed, they have a "Barbershop Initiative®", begun in 2004, that has placed computers with streaming information about prostate cancer in select barbershops. This organization has also created federally funded educational and research programs in high-risk communities and developed public education and screening programs that have impacted more than 30,000 men to date. Their "Gentlemen Check Your Engines" and "I'll Go If You Go" programs are specifically targeted to reach women and men to help increase male participation in their health responsibility. Public awareness about prostate cancer is a major focus of the organization and their website (9) provides a variety of tools and guidance to facilitate the implementation of these initiatives at the local and international levels. The Prostate Net currently services individuals and agencies with information and intervention activities in more than 50 countries.

Prostate Conditions Education Council

(PCEC, formally the Prostate Cancer Education Council)

Dr. Crawford, an internationally distinguished urology clinician and researcher, founded this organization in 1989. This was the year that prostate cancer became the most common cancer in American males and the second leading cause of death. Men were not educated about prostate cancer and most cases that were diagnosed were advanced and not curable. The initial goals of the PCEC were to raise awareness and promote early detection. Their stated purpose as seen on their website is as follows: "Our mission is to save lives through awareness and the education of men, the women in their lives, as well as the medical community about the prevalence of prostate cancer, the importance of early detection, available treatment options and other men's health issues; to conduct nation wide [sic] screenings for men; and perform research that will help the detection and treatment of prostate cancer and other men's health issues." (10) They are best known for raising awareness (e.g. sponsored "walks") and conducting nationwide prostate cancer screening activities. Prostate Cancer Awareness Week remains the largest screening event for any cancer in the world. There have been numerous findings that have been generated from this screening program. Some of these findings are as follows: establishing an age of 35 to begin screening; establishing that if an initial PSA is less than 1 ng/ml, then the screening interval can be extended to every five years; that there are age-specific values for PSA; and establishing the value for PCA3. Other findings are listed on their website. (10) The website also has a rather extensive information section containing "the basics" of all phases of prostate cancer.

Prostate Cancer International

This enterprise was founded relatively recently by Mike Scott and is primarily focused on providing informational and interactive resources on the internet with an international emphasis. (11) Their programs include developing a prostate cancer community awareness council which is to serve as a grassroots initiative focused on prostate cancer awareness and advocacy. Also, they developed a "let's talk about prostate cancer" video series that can help people to "meet" opinion-makers across the prostate cancer community from respected clinicians, to patient activists and support group leaders. Finally and principally, they constructed five interconnected informational prostate cancer websites for the global community that are as follows:

- A Prostate Cancer InfoLink a classic website with extensive, highly structured content together with a daily news blog, and a mentoring service through which people can ask questions about prostate cancer
- A Prostate Cancer InfoLink Social Network a website where anyone (e.g. patients, family members, and health professionals) interested in, or affected by prostate cancer can "gather" to share information and knowledge
- **3.** Prostate Cancer Africa a website providing core informational resources about prostate cancer for every nation in Africa
- 4. Prostate Cancer Caribbean a website providing core informational resources about prostate cancer for every island nation in the Caribbean
- El Cáncer de Próstata en Latinoamérica

 a website providing core informational resources about prostate cancer for every nation in Central and South America

The National Alliance of State Prostate Cancer Coalitions (NASPCC)

This is a relatively new organization. It is a group of state prostate cancer coalitions in the US. Its website describes it as "an umbrella organization meant to encompass participation by all states – through their state prostate cancer coalitions, state prostate cancer task forces or state prostate cancer foundations." (12) These organizations are to be distinguished from individual local support groups although very often these groups are the initiators and participants of the state coalitions. Initially, representatives from prostate cancer coalitions in 25 states and other interested individuals came together to explore the formation of such a participatory alliance. Subsequently, this number has increased. Their vision is to eventually enlist organizations from all 50 states into their "alliance".

Though still mostly in the development stage, this group envisions sponsoring educational forums and serving as a clearinghouse for programs and best practices that have worked in various states by and through their prostate cancer coalitions. It is hoped that all of the participating state prostate cancer coalitions will derive great benefit from networking in a formal meeting once a year. Further, they hope that such a "coming together" of the prostate cancer community that is represented by all of the states that participate in NASPCC will represent a huge critical mass and this "strength in numbers" will help make prostate cancer more of a national health care priority.

Prostate Health Education Network (PHEN)

Tom Ferrington founded PHEN. He is an African-American prostate cancer survivor. Accordingly this group is specifically focused on increasing the prostate health education and awareness among African-American men. As fully described on their website (13), the group has several rather unique activities:

- 1. They host an annual meeting called The African American Prostate Cancer Disparity Summit on Capitol Hill in Washington, DC. The summit brings together congressional, government, medical and research leaders along with survivors to assess the status, review progress and outline new strategies for eliminating the prostate cancer racial disparity.
- 2. They sponsor a "national radio awareness campaign" which broadcasts prostate health awareness messages by various leaders such as elected officials and church leaders.
- 3. They have developed "working partnerships" with leading cancer and medical centres, and other organizations. These partnerships provide prostate cancer screenings, educational outreach, and support groups.

PHEN developed a prostate cancer survivor network. As such, they mobilize survivors within the PHEN-focus cities and states to provide volunteer "on the ground" outreach, advocacy and support services within their communities. They also have an e-newsletter to provide online education and awareness services. Finally they stage a "Rally Against Prostate Cancer" event which combines the internet and television broadcasts to highlight what they label as the "African-American prostate cancer crisis".

PAACT, INC. (Patient Advocates for Advanced Cancer Treatments, Inc.)

This organization was started by Lloyd Ney in 1984 and thus, was one of the earliest support group communication vehicles in the US. The group publishes a quarterly newsletter that contains timely articles on the latest developments in the treatments for prostate cancer and other health issues related to the disease. They started many PAACT support groups in the nation and were active in political lobbying for prostate cancer issues via email, phone, or fax. Like many support group websites, the PAACT site (14) contains an educational section that succinctly explains most of the issues confronting a patient.

Other prostate cancer-focused organizations in the US that should be mentioned, if only in passing, are: The Men's Health Network, (15) and Male Care. (16)

The Prostate Cancer Foundation of Canada (PCC)

Ron Evason, a prostate cancer survivor, founded this organization in 1994. Its initial primary mission was to increase funding for prostate cancer research. Over the years, the organization fused with other like-minded groups and is now called "Prostate Cancer Canada". With its new name and identity, the Foundation broadened its mission to "the elimination of the disease through research, education support and awareness". (17)

A branch of the PCC is The Prostate Cancer Canada Network (PCCN). This entity is comprised of over 70 independent prostate cancer support groups from coast to coast across Canada. These groups provide services at the grass-roots level, through monthly peer meetings, special educational events, outreach programs and presentations to service clubs, community health fairs, etc. As is the intention of most support groups around the world, the Canadian groups' emphasis is on members and leaders to freely share their own stories rather than give specific medical information. Medical experts who are invited to the meetings facilitate much of the inevitable discussions about treatment options and advances. Partners and family members are welcome at general meetings but some groups choose to hold separate meetings for their partners to encourage opportunities for sharing personal feelings, reactions and experiences, to deal with burnout and other related issues as they cope with this disease.

Many Canadian groups hold separate meetings for those men dealing with advanced prostate cancer. These "Warriors" usually meet on the same night as the regular meetings, but in a separate room before joining the main meeting. An affiliated group in Calgary (www.pccncalgary.org) maintains an extensive video library of meeting presentations. For eight years, PCCN group leaders have met annually in conference to exchange ideas and improve their services to their communities.

Prostate Cancer Foundation of Australia (PCFA)

This is the "umbrella" national network of support groups in each state and territory of Australia, consisting of men and women who have a passion for assisting others who encounter prostate cancer. This network is made up of over 120 groups who meet locally to provide one-to-one support, giving a vision of life and hope after treatment. The stated goals of this foundation involve: promoting and funding world-leading, innovative, research into prostate cancer; implementing awareness campaigns and education programs for the Australian community, health professionals, and government; and supporting men and their families affected by prostate cancer through evidence-based information and resources, support groups and Prostate Cancer Specialist Nurses. Resources include newsletters, educational pamphlets for both local and advanced disease and a variety of educational videos. Their website (18) is comprehensive and easy to access.

11.3.3 Singapore

Prostate Cancer Befrienders

Apparently in all of Southeast Asia, the advent of prostate cancer patient support groups came about in 2001, when the first prostate cancer support group was set up at the Singapore General Hospital by Dr. Christopher Cheng. It began as an extension of the urology department's effort to provide counseling and support to men after undergoing radical prostatectomy for prostate cancer. Funded by the Department of Urology, the initial group of 12 volunteer prostate cancer survivors and activists would befriend men with a new prostate cancer diagnosis and share insights on treatment and recovery. This small advocacy group was coordinated with the help of urologic oncology nurses and supported by urologists involved in their treatment and care.

Patient advocacy is still in its relative infancy in Singapore and Southeast Asia and there is considerable opportunity for expansion and maturation of a full-fledged and self-funded volunteer prostate cancer support group to advance the care of prostate cancer survivors and cancer research.

11.4 **Published Educational Materials**

The factors that stimulated prostate cancer patient support groups and coalitions were also in part responsible for a deluge of materials including many books to help inform patients about their prostate cancer. A listing and/or discussion of these materials need not occupy space in this chapter. Almost all these materials are referenced in many of the websites listed.

11.5 The Future and Concluding Remarks

Public awareness and education about prostate cancer has dramatically expanded in the last two decades. This phenomenon occurred for many reasons, many of which were listed in this chapter. Most of this expansion is due to the energy, dedication and vision of prostate cancer survivors. These men, individually, and collectively through their respective organizations, have also become powerful advocates for accelerating research support for prostate cancer from government, industry and private organizations and individuals.

Yet there is much to be done. This can be recognized by comparison with the activity and success of the breast cancer patient groups. Also, prostate cancer is the most common solid cancer among humans causing much patient concern and stress and it is still a major cancer killer of men. One obvious need is for more coordination between groups around the world. Another is to increase advocacy for more government-sponsored research. Another need is to increase awareness of, and participation in clinical trials. Indeed, a theme that should reverberate more among all prostate cancer coalitions and support groups must be the importance, if not obligation, of all prostate cancer survivors to support and where appropriate, consider participation in clinical trials.

Another area for improvement is information discrimination. The web is very good at delivering information; some would say too well! But it remains a significant burden for the patient to decipher and discriminate. While the physician can help in that regard, it often is not sufficient. Perhaps it would be helpful to increase the exposure of the potential or actual prostate cancer patient to the prostate cancer clinical care pathways now actively in continual revision by many professional organizations (*e.g.* NCCN (19), ASCO (20), EAU (21), AUA (22), Prostate Cancer Canada (23)). Of course in most cases these documents, developed now for the practicing physician, would need to be simplified for optimal patient utilization. In that context a very important issue is to more clearly and effectively explain the expanding controversies surrounding PSA-based screening.

While patient empowerment is important, it is also important to develop and disseminate better methods whereby men can develop a trusting relationship with their treating physician(s). It should not be just the responsibility of the physician to make this happen. Finally it would seem that further efforts to empower the patient should also entail allowing ready access by the patient to his own medical records. Efforts to accomplish this goal are underway in several countries but the issue is

complicated and many of the associated problems require further work. This access should not only entail what is transferred, but also how and when. For example, it would be advantageous if the patient would control when and how he receives information, such as the results of a prostate biopsy or a PSA determination, rather than keeping that control in the hands of physicians and/or their surrogates. Much anxiety is generated waiting for that clinic appointment, phone call or email.

There are of course many other areas in which prostate cancer survivors and/or their advocacy groups can ease the burden of this cancer on its victims and their families. Indeed a listing would be much too lengthy here and would constantly be changing as the patient advocacy enterprise in prostate cancer continues to grow, as it surely will. In conclusion, what needs to be emphasized is that we need to continually improve our understanding of the patient's perspective toward his prostate cancer and implement appropriate advances in management that emanate from that understanding. As has been demonstrated from what has already been done, this activity can generate vast improvements in patients' well-being. What may be less obvious is that it can also improve the ability of physicians to care for these patients and probably improve outcomes.

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