POSTERIOR URETHRAL COMPLICATIONS OF THE TREATMENT OF PROSTATE CANCER

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What's known on the subject? and What does the study add?
Urethral strictures, bladder neck and posterior urethral contractures, and urorectal fistulation are three well-recognised complications of the treatment of prostate cancer, whether by surgery or non-surgical treatment. Because these are relatively rare problems the treatment is uncertain. There is a heavy reliance on endoscopic or instrumental management of urethral strictures and of bladder neck and posterior urethral contractures, and there is little discrimination in any of these conditions between those that are the result of surgery and those that are the result of radiotherapy and other treatment methods using external energy sources.

This review aims to clarify current understanding of these three clinical problems and draws attention to the role of reconstructive surgery, particularly when dealing with bladder neck contractures, prostatic urethral stenoses and urorectal fistula. This also shows that the nature of the problem, the recovery time after treatment and the degree of functional recovery is radically different in the surgical as against the non-surgical group, to a degree that the authors believe is not sufficiently stressed when patients are counselled and consented before their primary treatment.

Keywords: complications, surgery, radiotherapy, urethra, prostate, cancer

INTRODUCTION
Urology was established as a specialty in the 19th century, principally to provide specialist treatment for urinary stone disease. In the late 19th century the emphasis drifted to the treatment of BPH and in the late 20th century to carcinoma of the prostate. It could be argued therefore that urology exists largely to treat prostatic disease.
Until late in the 19th century prostatic disease was largely managed by (intermittent) catheterisation as required. There was little, if any, distinction between BPH and prostate cancer. Actually, it was widely believed that all prostatic ‘growth’ was neoplastic until BPH came to be distinguished from cancer at the turn of the 19th to 20th century [1,2].

In 1836, the French surgeon Amussat excised the middle lobe of the prostate with scissors [2] but it was not until McGill of Leeds in England in 1887 developed the procedure, from being a partial piecemeal excision with scissors [3] to an enucleation of the whole of the hyperplastic tissue mass, and urged surgeons to perform this operation as a substitute for the ‘catheter life’ that this started to be considered widely [4]. Indeed, initially, there was considerable resistance. Thompson in London was unhappy with the risks of prostatic surgery [1] and White of Philadelphia advocated castration to shrink the prostate as an alternative [5]. It was the publications of Freyer in 1901 and thereafter [6,7] that really stimulated the development of prostatic surgery, not least because Freyer was such a forceful personality, not to say showman. Various surgeons such as Thompson Walker in the UK [8], Judd in the USA [9] and Harris in Australia [10] improved on Freyer’s somewhat blind transvesical prostatectomy and so developed the safe and reliable form of transvesical prostatectomy that was popular through to the 1940s. Then, in 1945, Millin [11] described the retropubic prostatectomy that became the standard form of prostatectomy until it was superseded by transurethral resection of the prostate in the 1960s and 1970s.

In fact, transurethral surgery has a history almost as long. Early treatments were crude attempts to divide the bladder neck blindly with a modified lithotrite, based on the then current belief that the principal cause of outflow obstruction in prostatic disease was a ‘bar’ at the bladder neck [2]. The ‘galvanocautery incisor’ developed by Bottini in 1877 [2] and the prostatic punch developed by Young in 1909 [12] were significant advances. Young also resurrected the Bottini procedure [13]; but it was Stern in 1926 [14] who developed the first resectoscope (although he called it a ‘resectatherm’) that would be recognised as such today and, since being improved by McCarthy as the Stern-McCarthy instrument [15], has remained the basic pattern for resectoscopes ever since.

An alternative to transvesical or retropubic prostatectomy in the early days of TURP was Young’s perineal prostatectomy, which had the advantage of avoiding an abdominal approach [16]. More importantly, Young developed an alternative form of perineal prostatectomy for the treatment of carcinoma of the prostate [17]. This was the first real attempt to excise and thereby cure a prostate cancer rather than just use an enucleation prostatectomy to ‘disobstruct’ the bladder outflow. For all practical purposes, Young was just about the first person to show any interest in prostate cancer as a specific entity.

The treatment of prostate cancer by radiotherapy has almost as long a history as surgical treatment, although initially with only sporadic attempts, generally using radium delivered by specially designed applicators [2]. Young and his colleagues were pioneers in this as well [18,19]. The first significant advance in the local application of radiotherapy, or brachytherapy [BT], as it came to be known, was by Flocks et al. [20] (1951) who injected radioactive gold into the prostate rather than radium. As much as 8000 Gy could be administered in this way with only a very small injected volume. Subsequently, Whitmore et al. [21] described the implantation of $^{103}$Au in 1972, by which time external beam radiotherapy (EBRT), using a linear accelerator had also developed sufficiently to give really quite satisfactory results in selected patients [22]. However, much the most significant development in the treatment of prostate cancer came with the description of his technique of retropubic radical prostatectomy (RRP) by Walsh in 1983 [23–25]. Walsh was not the first to describe RRP, that was Millin in 1947 [26], but he gave it an anatomical basis and showed how the principal adverse consequences of surgery could be avoided or minimised. The more or less simultaneous development and adoption of surgery as a marker for prostate cancer undoubtedly helped to fuel the veritable explosion of interest in the diagnosis and treatment of prostate cancer in the last quarter of the 20th century (and to date) but it was Walsh and his promotion of his technique of RRP that really made the difference [27].

The pioneering efforts of Flocks and Whitmore culminated in the development of modern BT, as technological advances led to computer-based mapping and dosimetry and template-based transperineal delivery.

‘The treatment of prostate cancer by radiotherapy has almost as long a history as surgical treatment’
century, stimulated the development of alternative energy sources for tumour ablation that might avoid the adverse effects of radiotherapy, most notably cryotherapy and high-intensity focussed ultrasound (HIFU). Cryotherapy was really ‘a child of the 60s’ [29,30], but it took several decades, until the early 1990s, to refine the technology sufficiently to make it safe and reliable for use in the prostate. HIFU is a still more recent development, within the last decade, and most of the reports of its clinical usefulness have come in the last 5 years [31–34]. Like cryotherapy there have been reports of its use as a primary treatment of prostate cancer and recent reports for use of HIFU as focal therapy have been particularly encouraging [35], but most patients treated by these two methods have had them as salvage therapy.

In the meantime, open RP has more or less been superseded by laparoscopic RP [36–38] and this too has been superseded by robotic RP [39] for those for whom surgery is appropriate treatment. Thus, today, the patient with organ-confined carcinoma of the prostate may either have a RRP, open in a few cases still, laparoscopic much more commonly, but increasingly supplanted by robotic RP, or alternatively have BT or EBRT, or HIFU or cryotherapy in some units. For those with recurrent disease, it may be possible to salvage them with any of these, either alone, in combination, or sequentially according to the primary treatment and the circumstances.

Given the incidence of prostatic disease and its various treatments it is not surprising that complications occur. With surgery, much the most common are operative bleeding and postoperative incontinence and erectile dysfunction (ED); with radiotherapy, irradiation cystitis, proctitis and enteritis, and ED. We do not propose to discuss any of these issues here, except tangentially. This review is intended to address the less common but more difficult complications of urethral stricture and specifically bulbo-membranous urethral stricture, bladder neck contracture (BNC) and urorectal fistula (URF) that can occur after any of these treatments.

THE NATURE OF THE PROBLEM

The adverse effects of surgery

The adverse effects of surgery are principally caused by sharp or blunt dissection and by diathermy damage in the operative field. There may be trauma to adjacent structures, most obviously to the rectum, bladder base and the adjacent neurovascular structures. There may be technical problems with the suture line of the vesico-urethral anastomosis (VUA) and these may be compounded by operative bleeding, which may continue into the postoperative period, putting tension on the suture line leading to disruption.

The effects of operative trauma are usually self-evident, are usually apparent immediately or in the early postoperative period, and they generally progress to healing with local fibrosis.

The complications of surgery were not widely discussed in the early urological literature apart from operative bleeding and early postoperative voiding difficulty. Indeed, these were the reasons that stimulated Thompson Walker, Judd, Harris and Millin to develop their techniques. There was obvious concern for continence because early case series routinely reported whether the patients were continent, but there was rarely any mention of ED, urethral stricture or BNC. However, there was a steady stream of reports about URF after both simple and perineal RP [40–43], generally attributed to mishap, for whatever reason, when dividing the rectourethralis. More recently, urethral stricture was identified as a problem, initially after TURP. BNC after RP became more widely discussed still more recently, particularly in association with coincidental sphincter weakness incontinence (SWI).

The adverse effects of radiotherapy

Radiotherapy works by damaging DNA and interfering with mitosis, mainly by the generation of free radicals [44]. EBRT is limited in its usefulness by the toxicity to adjacent healthy tissue. Because of the accessibility of the prostate, it is relatively easy to deliver radiotherapy locally with a higher dose and less scatter. Locally delivered radiotherapy, i.e. BT, is potentially more effective and less toxic to surrounding structures and particularly to the rectum,
bladder and urethra. At the tissue level this toxicity is related to the sensitivity of the epithelium to irradiation and to its effects on the microvasculature of the tissue. The epithelium of the rectum is more sensitive than the epithelium of the urinary tract hence irradiation proctitis is a more common phenomenon than irradiation cystitis [45]. In both the bowel and the urinary tract other radiation damage is mediated through the microvascular effects and specifically by progressive obliterator endarteritis, which causes tissue ischaemia or necrosis at its extreme [44,45]. It appears that fibroblast dysfunction rather than simple ‘reactive’ fibrosis is the principal cause of this.

These adverse effects may be immediate, early after treatment, or delayed. Indeed, problems may become manifest many years after the radiotherapy was given. Late morbidity occurs in ≈20% of patients and carries a mortality as high as 11% [46]. Clearly the entire irradiated field may be affected by obliterator endarteritis, ischaemia and fibrosis but anastomoses seem to be particularly affected. There seems to be a relationship of complications to whether radiotherapy is given before surgery or after surgery. Anastomotic complications, at least after resection for rectal cancer, are more common with postoperative radiotherapy than preoperative radiotherapy [47,48], although this is controversial [49]. Most worrying of all is the significant risk of developing rectal cancer 10 years or more after radiotherapy for prostate cancer. The risk may be a 35–70% increase over the normal risk [50]. Suffice it to say that close surveillance of the rectum is prudent after radiation for prostate cancer.

The general complications of radiotherapy were recognised and reported very soon after its introduction as a form of treatment. Barely 2 years after Röntgen discovered X-rays in 1895 [51] and 1 year after Becquerel discovered radioactivity in 1896 [52], the same year that Freund in Vienna and Despeignes in Lyon first used radiotherapy therapeutically [53], and the year before Marie and Pierre Curie discovered radium [54], Walsh of Edinburgh reported the first complication of radiotherapy, the gastrointestinal side effects, in 1897 [55]. Although Young and Flocks described adverse effects of radiotherapy [18–20] it was not really until relatively recently that the toxicity of the combined therapy of BT and EBRT came to be reported [56] and that the ‘devastation’ [57] they sometimes cause was generally appreciated.

Salvage treatment

After EBRT or BT, 20–50% of patients experience PSA failure and a significant number of these will have local recurrence, which is potentially curable by salvage therapy. Salvage RRP is the traditional approach and with some success. The perioperative mortality is low but the morbidity is substantial, averaging ≈40% for urinary incontinence, 2%–4% for BNC, and 5% for rectal injury. Salvage cryotherapy has about the same oncological outcome and morbidity. Urethral sloughing (see below) is a problem in ≈11%, and this of course does not occur after salvage EBRT [58]. Salvage BT also has a similar oncological outcome and a similar incidence of rectal injury but a more serious level of gastro-intestinal and genito-urinary toxicity, although the rate of URF is about the same. On the other hand, the incontinence rate is lower. There is less experience with salvage HIFU but it seems that this too has a low rate of incontinence and rates of BNC and URF that are about the same.

On balance then, it appears that salvage RRP and salvage cryotherapy have a higher incidence of incontinence and that BT carries a higher risk of more serious gastro-intestinal and genito-urinary complications; that the fistula risk is the same in all; and that the oncological outcome and the risk of BNC are about the same with all these salvage treatments [58].

Indications for salvage RRP

Given that salvage RRP is a definite option for the management of patients with post-irradiation BNC or URF (see below), it is important to be aware of the potential oncological indications as well as the reconstructive indications for surgery. Thus, a pre-salvage PSA level of <10 ng/mL with a pre-salvage Gleason score of <7, without significant radiotherapy toxicity, in a patient with a life expectancy of >10 years are good prognostic factors, particularly in those who had a PSA level of <10 ng/mL, a Gleason score of <6 and clinical T1c or T2a before their initial treatment. Likewise a pre-treatment PSA velocity of <2 ng/mL/year at the time of initial presentation, and an interval PSA failure of >3 years, in the presence of a negative bone scan and pelvic imaging studies, and a positive re-biopsy, are favourable as well [58].

The adverse effects of cryotherapy

Cryotherapy acts by several processes both during and after the freezing cycle. It causes direct cell damage by formation of intra- and extra-cellular ice crystals, by dehydration and acidosis, and by vascular injury. During the warming phase, cell damage is caused by osmotic cellular swelling and hyperpermeability of the vasculature. If the tissue temperature is reduced to ~ 40 °C for 3 min, coagulative necrosis results, followed by healing and fibrosis [59].

As with HIFU there are several technical factors that need to be addressed to ensure success. As most patients who have been treated with cryotherapy have previously been treated with radiotherapy, the mechanism of the development of complications is difficult to establish for certain, but irradiated tissues are undoubtedly more vulnerable to damage.

The complications of cryotherapy have principally been related to the ability to maintain the normal temperature of the healthy adjacent tissues, particularly of the urethra and rectum, to avoid toxicity, whilst freezing the prostate sufficiently [60]. A particular complication of cryotherapy (or HIFU) in the early period after treatment, is sloughing of the necrotic prostate into the urethra and the voiding difficulty this causes in ≈27% of patients [61]. This is also seen in BT, but less dramatically. Sloughing is also more of a problem in irradiated tissues.

The adverse effects of HIFU

HIFU causes tissue damage by generating heat and by a process known as ‘inertial
If the temperature is raised >56 °C and maintained for at least 1 s, it causes coagulative necrosis. Given that the temperatures achieved during HIFU are usually much greater than this, even short exposures of HIFU are effective. Inertial cavitation is caused by alternating cycles of compression and rarefaction within the tissue, as a result of which bubbles form and collapse and the mechanical stress of this causes cellular necrosis. The necrotic area is ultimately replaced by fibrosis [62].

HIFU is delivered as a sequence of small lesions, each about the size of a grain of long-grain rice [62]. Assuming that the patient is kept absolutely still and that placement of the HIFU lesions is precise, the effect of HIFU is limited to the targeted area and the effect and timing of any adverse effects is immediate or early. However, to date, most HIFU has been delivered as salvage treatment for prostate cancer and so its effects are superimposed on those of radiotherapy.

The complications of HIFU were described in the original reports of its effectiveness and have reduced with its technical development, except when used in conjunction with radiotherapy, especially BT and the combination of BT and EBRT [33,34]. Like cryotherapy, the early period after treatment is principally concerned with maintaining voiding in the presence of sloughing of the necrotic prostate into the urethra. This occurs in ≈36% of patients [31–34].

URETHRAL STRICTURE

Urethral strictures are common during the same period of life as prostatic disease occurs. The incidence rises rapidly after the age of 50 years [63]. A coincidental stricture is therefore to be expected in patients with prostatic disease from time to time. Patients with prostatic disease are prone, additionally, to particular types of stricture disease in specific locations. Instrumentation of the urethra may cause a stricture at the external meatus, fossa navicularis, penoscrotal junction and in the region of the urethral sphincter ('sphincter strictures') because these are the narrowest parts of the urethra. Catheterisation tends to cause trauma at the peno-scrotal junction, where the urethra is curved, causing what Blandy [64] describes as a pressure sore of the urethra and a stricture as a result (Fig. 1), often long. Catheter strictures may occur with all types of treatment because a period of catheterisation is common to all of them and the most common site is the bulbo-membranous urethra.

Meatal strictures, catheter strictures and other types of anterior urethral strictures, are all addressed elsewhere [63]. This review will address the problems of bulbo-membranous urethral strictures, BNCs and prostatic urethral stenosis.

Discussion of urethral strictures as a complication of the treatment of prostate cancer is confused by three issues. The first is terminological. The consensus view is that the term 'stricture' should refer to a constriction of the lumen of the anterior urethra [65], or 'spongiose urethra' to be more anatomically correct [63]. Similar constrictions proximal to the perineal membrane should, by the same consensus, be referred to as contractures or stenoses [65]. These stenoses or contractures might be at the level of the bladder neck, or the prostatic urethra, or the membranous urethra (where some people still use the term 'sphincter stricture', as we have used it above). For the purposes of consistency in this review we will refer to bladder neck contractures (BNCs), prostatic urethral stenoses and bulbo-membranous urethral strictures.

‘Urethral strictures are common during the same period of life as prostatic disease occurs’
The second confounding issue is the exact site of the contracture/stenosis/stricture. Several reports include both (anterior) urethral strictures and (posterior) stenoses, which may be BNCs after RP, or stenoses of the bladder neck and/or prostatic urethra after radiotherapy or bulbo-membranous urethra strictures after either, and lump them all together under the heading of ‘urethral strictures’ [66–69]. This is not usually the fault of the authors but of the way the data they have analysed was collected.

The anatomy after all forms of treatment is in any case distorted. Urologists rely on identification of the bladder neck, the verumontanum and the urethral sphincter mechanism to identify specifically which parts of the urinary tract are affected by stenosis or stricture and the absence of any of these as a result of surgery, or the impossibility of defining them by imaging or endoscopy makes exact description difficult.

After a RRP, either a surgically reconstructed or a ‘preserved’ bladder neck is sutured to the remains of the membranous urethra. However ‘flat’ the bladder neck appears to the surgeon after the VUA at the time of surgery, it commonly appears funnelled on postoperative imaging and this makes it difficult to determine the exact site of the VUA (Fig. 2). This funnelling appears to us to be because the vesico-urethral anastomosis comes to lie within the levator sling when seen on MRI (personal unpublished observation). The funnelled area may be part of a BNC (Fig. 3a–c), regardless of whether or not the more distal bulbo-membranous urethra is involved as well, particularly in patients who have had salvage radiotherapy.

Distortion after cryotherapy or HIFU is most obviously seen when there is sloughing of the urethra distorting and disguising the anatomy (Fig. 4) (less so after BT). Subsequent healing with fibrosis can cause the prostate to shrivel up and be very difficult to identify surgically when explored retropubically. The anatomy is least disturbed after EBRT.

The third confounding issue is that any review of strictures or stenoses refers only to those that are either symptomatic or are encountered incidentally, and most commonly when a catheter is passed before orthopaedic or cardiac surgery, or prior to artificial urinary sphincter (AUS).
implantation, in patients with a previous history of treatment for prostate cancer. There is no series that describes routine endoscopic or radiological follow-up of patients after RP to detect the true incidence.

**Bulbo-membranous urethral strictures after RP**

As far as we are aware this has never been specifically studied, although it has been mentioned in some reports [67,68]. The incidence is therefore difficult to establish because few authors have tried to distinguish them from BNCs when it is possible to do so, and it is often not possible to do so because they merge indistinguishably with BNC in many patients, as discussed above. The incidence appears to be lower after laparoscopic RRP than after open RPP [70]. Most post-surgical urethral strictures are generally apparent within 3 months of surgery, whereas urethral strictures (and prostatic urethral stenosis and BNC) after radiotherapy show a steady increase for up to 2–3 years after primary treatment [68]. Hormonal treatment is associated with an increased rate of stricture in at least one report [71], bearing in mind, of course, that in men of this age the natural incidence of urethral strictures increases year by year and so even watchful waiting would be, and is reported to be, associated with an annual increase of urethral strictures [68].

The diagnosis is normally made based on symptoms initially and then by flow rate studies, endoscopy and imaging in the usual way [63]. Exact delineation of the anatomy may be difficult for the reasons referred to above but the critical questions are whether or not the sphincter mechanism is involved and the length of the strictured segment.

Sphincter strictures are due primarily to instrumentation or catheterisation [63,72–74]. These are best treated with dilatation, in an attempt to preserve sphincter function [74]. In the absence of a complication, e.g. a false passage, this is often effective. The alternative is end-to-end urethroplasty, which almost invariably leaves the patient with urinary incontinence and requires either a bladder neck reconstruction [74] or, more reliably, an AUS to complete the reconstruction.

Sub-sphincteric urethral strictures in the proximal bulbar urethra are also common and sphincter strictures may spread downwards into the proximal bulbar urethra making surgery more difficult.

Clearly the challenge for isolated bulbar urethral strictures is to avoid damage to the sphincter mechanism. For short strictures anastomotic urethroplasty is theoretically appropriate [63] and has been described [68], but a non-transecting approach would be best, in our view, to avoid having two anastomoses within a centimetre or two of each other, risking ischaemia of the segment of urethra between them. This might be a non-transecting anastomotic repair [75,76] or a traditional patch repair [63]. For longer urethral strictures, and for peno-bulbar urethral strictures, mainly due to catheterisation, a dorsal patch buccal mucosal graft urethroplasty gives reliable results but, other forms of patch repair, may be appropriate [63,68].

**Bulbo-membranous urethral strictures after radiotherapy**

Again, the incidence is difficult to determine, for the same reasons as in non-irradiated patients, but it certainly seems that bulbo-membranous urethral strictures are significantly more common and more difficult to treat after radiotherapy. After EBRT alone or BT alone, the incidence is lower than after the combination of the two [68]. After BT alone, the incidence is reported to be 0–12%, usually 4–5%, and is highly correlated with the dose administered below the apex of the prostate [66]. Consequently, in theory at least, the incidence can be reduced by careful planning and the judicial use of supplementary EBRT [66].

Bulbo-membranous urethral strictures amount to 90% or more of reported strictures. We expect this is due to under reporting of more distal strictures, although it is reasonable to suppose that more distal strictures are more likely to be catheter-related than radiotherapy-related. They also tend to be longer and more frequently obliterate than in non-irradiated patients after RRP and to recur more frequently and more rapidly after dilatation or urethrotomy.
anterior urethral strictures in any other non-irradiated patients with similar experience; nor indeed is it usually the case, although this is not our experience; and so is genuinely an anastomotic component of the anastomosis after a RRP (Fig. 3A) [73] (which is within the urethral proximal to the sphincter-active urethra [81].

In general, at its mildest, it occurs when the urethral catheter is removed. It is helpful to know the dose and type of radiotherapy the patient has had. After EBRT alone, average stricture length seems to be ∼2 cm (Fig. 5). Compared with strictures in BT patients, EBRT strictures are not commonly obliterative; they are less complicated to treat; and they may theoretically be amenable to anastomotic urethroplasty because they are short enough. We have performed anastomotic repair of short strictures in selected patients with very short strictures as have others [79] but generally we prefer a patch repair with a flap, as this seems safer.

By contrast, after the combination of BT and EBRT, the average stricture length is 4 cm and nearly half are obliterative. A short stricture is rare (Fig. 6) and when it happens an anastomotic repair is rarely successful (in our experience), and a flap repair is more likely to be appropriate and successful in those with non-obliterative strictures who are not controlled by interval urethral dilatation. Even so, recovery is slow and the recurrence rate is significant, and so we find that those with obliterative strictures, are often best treated with suprapubic catheterisation, if tolerated, or, because suprapubic catheters are often poorly tolerated in the post-radiotherapy patient, because of uncontrolled bladder spasms and pain, by supra-vesical urinary diversion.

Exact delineation of the anatomy may be difficult for the reasons referred to above but the critical questions, as in the non-irradiated patient, are whether or not the sphincter mechanism is involved and the length of the strictured segment. There must also be an assessment of whether or not there is evidence of any other significant intestinal or urological complications. Particularly important is whether patients have a reduced bladder capacity due to irradiation, as this has a bearing on voiding symptoms after urethral reconstruction.

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**BLADDER NECK CONTRACTURE**

**BNC after RP**

This was first reported substantively in 1987 [81]. In general, at its mildest, it occurs proximal to the sphincter-active urethra (Fig. 3A) [73] (which is within the urethral component of the anastomosis after a RRP) and so is genuinely an anastomotic contracture. BNC after RRP occurs in 0.4–32% of patients [81–95]. The range is wide but most retrospective reviews from individual institutions reported by physicians quote a 5–10% incidence or lower [84–86], whereas administrative or registry reviews report an incidence of 20–30% [87,88]. It is less common after open perineal RP than after open RP [89]. It is also reported to be less common after laparoscopic RP [90] than after open RP. It appears to be related to technique and particularly to the method of bladder neck reconstruction and the accuracy of epithelial apposition. It also tends to occur more commonly in patients with a large prostate, who therefore have a greater gap to bridge after RP, suggesting that tension at the anastomosis may be a cause. A previous TURP is another preoperative risk factor. Postoperative bleeding and haematoma formation can also put tension on the anastomosis and increase the risk of disruption and BNC as a consequence. Other postoperative risk factors include extravasation of urine in the early postoperative period and acute retention when the urethral catheter is removed. It is more common in the obese, in diabetics, in patients with vascular disease and in smokers [92,93].

There is a well-recognised association with SWI [94]. There is a less well-recognised associated with URF (see below).

There seems little doubt that most mild contractures can be treated with urethral dilatation [89,93–98]. A single dilatation or urethrotomy is successful in 25–73% of patients [92]. In some instances, this is coupled with self-catheterisation to maintain the effect. For more fibrotic contractures, more aggressive intervention is necessary with a rapid progression in most series through bladder neck incision [99,100] and bladder neck resection [73,101]. Some authors have tried combining bladder neck incision with injection of the site of the incision with triamcinolone [102] or mitomycin [103] with apparently good results, but not apparently good enough for others to race to emulate their experience.

There is undoubtedly a group of patients who can be managed endoscopically but inevitably there are some in whom this fails. Indeed, 27% are reported to be refractory to three or more attempts at endoscopic...
Several authors have reported success with urethrotomy or bladder neck incision combined, when necessary, with implantation of a Urolume stent, coupled, when indicated, with implantation of an AUS to restore continence [94,104–106]. Extraordinarily high success rates have been quoted. The success rate of a stent in this situation seems to be substantially higher than the use of the Urolume in any other situation [107,108], suggesting a somewhat optimistic approach to reporting results. Longer term follow-up has dampened the enthusiasm of some of those earlier reports [109] and a more realistic view appears to be that this approach should be considered in those who wish to avoid major reconstructive surgery, or who are unfit for it, provided they are prepared to accept repeated endoscopic intervention to deal with complications related to the stent [101,110].

Generally, to have undergone a RRP in the first place, these are relatively ‘fit and healthy’ individuals and so should, in our view, be considered for revision of their VUA. This has been described abdomino-perineally and transperineally [98,111–114]. In all, 24 patients have been reported in these five reports with generally satisfactory results. Although, our own experience with 23 patients is not large, it is substantially larger than any other centre and so our approach is perhaps worth describing. We perform the procedure transperineally. Some patients have a patent lumen and voiding difficulty; others have an obliterated outlet and will never have voided, and so the possibility exists of coincidental SWI. Whether or not they had SWI before revision of their VUA they certainly have a very high risk of this afterwards and so all patients should be counselled that they should expect to have a two-stage procedure with revision of the VUA first, and then implantation of an AUS 3–6 months later.

Revision of the VUA is preformed through a transperineal incision. The bulbo-membranous urethra is mobilised up to the site of the obliteration and transected. In most patients the problem starts at the level of the anastomosis and extends proximally, suggesting that an anastomotic disruption occurred; or some other problem arose with the bladder neck reconstruction; or that intrapelvic haematoma–fibrosis may be the cause of the problem. As mentioned above, the radiological appearance is that of a funnelled bladder neck. When there is a contracture this funnelling is usually part of it. All scarred tissue needs to be excised until a relatively healthy ‘bladder neck’ can be defined or created. This is generally very far forwards in the anterior triangle of the perineum and so consequently it is usual to have to separate the crura for access, and common to have to perform an inferior wedge pubectomy to allow sufficient access to be able to create an adequate bladder neck. This is not an easy procedure to perform. We find that revision of a VUA in such patients is substantially more difficult than performing an average bulbo-membranous anastomotic urethroplasty for a pelvic fracture urethral injury which seems, at first sight, to be a very similar undertaking.

In those patients who have complete obliteration of the bladder neck, it must be defined by other means. We identify where the bladder neck should be by cystoscopy through the suprapubic track that these patients inevitably have, and then pass a
spinal needle through the perineal incision and into the bladder, where we guess the bladder neck might be, having mobilised and retracted the urethra (Fig. 7). When the suprapubic cystoscopy shows a satisfactory position of the needle, we then pass a scalpel beside the needle to open up the bladder neck (Figs 8, 9) and then introduce a gorget to open the area widely (Figs 10, 11). The bladder neck fibrosis is then incised or excised as necessary (Fig. 12) and the VUA can then be made (Fig. 13).

In the absence of radiotherapy, transperineal revision of the VUA is usually successful, although we have had to do a further revision in two patients out of a total of 17. After salvage radiotherapy, we have revised the VUA for BNC in six patients with success in four. All patients with a satisfactory result (21 of 23) have subsequently required implantation of an AUS to restore continence.

Others have been able to reconstruct the bladder outflow by endoscopic [115] or by open means [111], with preservation of
continence without the need for an AUS, albeit in just a few patients.

We have already referred to the role of salvage RRP in the treatment of local recurrence after primary irradiation and the higher morbidity associated with it; and also that the adverse effects of postoperative radiotherapy have a particular propensity to affect anastomoses. It is perhaps worth stressing that after prior irradiation all complications, medical and surgical, are as much as 10-times more common and that ‘the burden of therapy and sequelae is more significant’ [116].

BNC and prostatic urethral stenosis after primary radiotherapy, cryotherapy and HIFU

This is an altogether different problem compared with post-surgical BNCs [66–68,78]. Not only is the extent of the contracture or stenosis worse but there are the problems of healing because of their previous treatment. These patients tolerate a suprapubic catheter badly and so there is pressure to provide a surgical cure, but this is technically much more difficult due to the poor and unpredictable vascularity of the bulbar urethra. Furthermore, in some patients, there are additional problems of obesity and other comorbidities that make them unsuitable for surgery. In addition, all patients have a degree of bladder dysfunction, usually a small capacity, thick walled, high pressure, and contracted bladder because of their radiotherapy. In our view, it is not even worth considering reconstructive surgery unless the patient has at least a bladder capacity of ≥200 mL, measured with the patient conscious and active, not under general anaesthesia; and a reasonably well-preserved urethra. Otherwise, the patient should be counselled to accept a supra-vesical diversion (such as a Mitrofanoff procedure), if a suprapubic catheter is intolerable.

In those with a contracture limited to the bladder neck and the prostatic and membranous urethra, salvage RRP gives the best results in our experience, although this can be extremely difficult to accomplish. The prostate is commonly shrivelled up under the inferior pubic arch and difficult to define; it is plastered to the rectum and densely adherent to the retropubic space. The anastomosis of the bladder to the urethra is often technically difficult.

We have performed this in nine patients with success in six, one of whom required implantation of an AUS to restore continence and complete the reconstruction. The other three patients developed recurrent contractures. As always, those who have had pure EBRT are the easiest to deal with. Those who have had EBRT and then either salvage HIFU or BT are more difficult. It is easy to appreciate why urologists prefer to persevere with endoscopy or the use of UroLume stents against all the odds for their success [117].

URORECTAL FISTULA

This is the least common but the most incapacitating of all the complications of the treatment of prostatic disease. It is also the only complication to have been reported regularly since RP began [40–43]. As with strictures, there are several other causes of URF and like strictures there has been a considerable rise in the reported incidence of URF after the treatment of prostate cancer in recent years, presumably because RRP is much more commonly performed; because when radiotherapy is used the dose is greater; because there is an increasing use of multi-modal treatment; and because of the increased use of salvage treatment. Before 1977, 3.8% of URFs were associated with radiation treatment; since then the percentage has risen to 49.6% [118].

The diagnosis of URF is straightforward: the patients present with urine leakage through the rectum. Some also have pneumaturia and/or faecaluria but this is very much less common, unlike vesico-colic fistulae due to diverticular disease or cancer of the sigmoid colon when these two symptoms tend to predominate. Thus in URF, the flow gradient is predominantly from the bladder to the bowel [119]. When faecaluria is present, it is an adverse prognostic feature [120].

URF after RRP

This usually follows a direct injury to the rectum at the time of the RRP. It is reported to occur in ≤1% of cases [70,90,121,122], although it is not always clear if this figure
FIG. 14. A URF (A) between the rectum (B) and the VUA (C) after RRP.

FIG. 15. An endoscopic view through the suprapubic track of the same patient as in Fig. 14. The fistula is at A. There is the tip of a cystoscope in the bladder neck (B).

FIG. 16. Transperineal repair of a URF. 1. The perineal body is exposed through perineal/peri-anal inverted-U-shaped incision. The perineal body is clearly demonstrated between the bulbar urethra anteriorly within bulbospongious and the anal canal posteriorly within its sphincter mechanism; and between the surgeon’s index and middle fingers, which are in the ischia-rectal fossa on either side.

refers to perioperative rectal injury, early postoperative transient fistulation that may heal spontaneously, or an established URF that will not. It is important to note that there is no term that distinguishes between these two types of ‘fistula’: the early postoperative ‘leak’ that may heal spontaneously, usually within 3 months, before the track has epithelialised, and an established URF that has epithelialised and that will therefore not close spontaneously.

As with BNC, rectal injury is reported to be less common after laparoscopic and robotic RRP [70,90,121,122]. It is more common after perineal [40–42,120] RP and much more common after salvage RRP [116].

If a rectal injury is recognised and repaired at the time then in many, if not most instances, the repair heals and a URF does not develop [120,121,123]. A covering colostomy is not necessary [122] unless the patient is having a salvage RRP after previous failed EBRT, when it probably is. If the injury goes unrecognised or if an attempted repair fails, a URF may result. This becomes apparent 1–6 weeks postoperatively, usually at 2–3 weeks. The first sign is usually urine leakage from the rectum. When faecaluria occurs, the clinical picture tends to be more ominous as the fistula tends to be larger and the leak is less likely to be contained [121]. As a result, faecal leakage leads not only to local infection and abscess formation, which discharges through the suture line of the bladder neck reconstruction or the VUA or both; it might also lead to severe sepsis and to Fournier’s gangrene. With prompt attention, including a defunctioning ileostomy or colostomy in those at risk of serious sepsis, spontaneous healing will occur in 50–75% [120–124]. An ileostomy is quicker and easier to perform (laparoscopically) and reverse, and is advisable if faecal diversion is expected to be temporary; a colostomy is better if it is likely to be permanent.

Typically an established post-surgical URF is small, sometimes only apparent as an area of tethering on rectal examination, usually no more than a few millimetres and almost always <3 cm, even when there has been complete anastomotic breakdown, cavitation and infection [119]. It is usually found, radiologically or endoscopically (Figs 14, 15), to arise from the base of the bladder close to the posterior quadrant of the anastomosis rather than from the anastomosis itself [119].

Spontaneous closure of an URF [43,120] only occurs within ~3 months of the original surgery before the track has epithelialised, or otherwise only temporarily. There is no report of an established URF closing spontaneously and permanently [and no suggestion at all that a post-irradiation URF will do so] [118,119,125–128]. Thus, although a colostomy and an indwelling catheter may be necessary in a patient with extravasation of urine and faecal leakage in the early postoperative period after a RRP, they are only of value thereafter to control symptoms. As the flow gradient is from the urinary tract to the rectum, an indwelling catheter is more likely to be helpful than a colostomy.

Various techniques have been described to treat URF, but there are three main approaches: the transperineal repair [43,118–120,125–137]; the York Mason trans-ano-rectal sphincter-splitting approach and variations on that theme [128–130,138–152]; and the Parks per-ano rectal advancement flap that also has its variants [130,153–157]. The published information available would suggest that the success rates of all three approaches are high, approaching 100%. Local application of various types of glue have been reported to be successful in three small series [158–160], albeit less successful but with a much lower morbidity. Needless to say not every patient who may be suitable for surgery wants it and there are occasional reports of patients who manage for years with conservative management [119,161].

The advantages of the transperineal approach are that the urinary tract and the rectum can be separated, and both sides of the fistula closed independently. Also, a tissue flap can be interposed to minimise the risk of recurrence, when necessary (Figs 16–22). The flap is usually the gracilis muscle [118–120,125–137] but tunica vaginalis has also been described [162]. Access to the rectum with the transperineal approach is excellent and the rectal defect is relatively easily closed in two layers. The bladder base or anastomotic defect is more difficult to close because there is less flexibility and mobility of the tissues, and so
FIG. 17. Transperineal repair of a URF. 2. The perineal body is divided to separate the urethra and bulbospongiosus from the anal sphincter mechanism (visible – A) and, higher up, the levatores ani, up to the level of the fistula.

FIG. 18. Transperineal repair of a URF. 3. The fistula (A) is exposed, between the levators (B), having mobilised around it. (It is unusual to be able to expose it as clearly as this!).

FIG. 19. Transperineal repair of a URF 4. The fistula has been transected and there is a pair of forceps in the rectal defect.

FIG. 20. Transperineal repair of a URF 5. The mobilisation continues proximally up to healthy tissue, so that the rectum is fully mobilised. The margins of the levators are again clearly visible (A).

FIG. 21. Transperineal repair of a URF 6. Both sides of the fistula have been closed. The rectal closure is clearly seen (A). The bladder closure is less obvious but is indicated by a stay-suture (B). The levators (C) are then approximated to separate the two suture lines to complete the repair.

FIG. 22. Transperineal repair of a URF 7. When necessary the gracilis muscle is mobilised on its vascular pedicle through two incisions along its length, proximally over its vascular pedicle and distally just above its insertion, where it is divided. The muscle flap (A) is then re-deployed to the perineum for interposition between the bladder and the rectum.
it can often only be closed in one layer. The urethra itself is not usually seen unless it is specifically exposed to deal with an associated BNC or a completely disrupted anastomosis. This approach is generally favoured by those urologists who perform URF surgery themselves, probably because it is a ‘classical’ urological approach [128].

When URF closure is performed by, or together with, a colorectal surgeon, the York Mason or one of its variants, and more recently the Parks approach are more commonly adopted. The specific advantage of the Parks repair is that it is minimally invasive and endoluminal. Another advantage is that failure does not compromise a subsequent transperineal repair. The disadvantage of both the Parks and the York Mason procedures is that access to the urinary component of the fistula is poor. At least one group openly acknowledges that it makes no attempt at all to close the urinary side of the fistula and relies entirely on a careful layered closure of the rectum for the success of the specific procedure [151]. Furthermore, the exposure does not allow an interposition flap. An additional incision and exposure of the fistula is necessary for this. The specific disadvantage of the York Mason and similar approaches, is the risk to the anal sphincter because of its division. Although there is no mention of complications with the anal sphincter-splitting approaches in the urological literature [138–152], the York Mason procedure is now obsolete [163,164].

in colo-rectal practice, at least in part because of the substantial incidence of anal sphincter incompetence [163,164] and recto-cutaneous fistulisation [165,166].

With all of these procedures, a covering colostomy is usually performed either at the time of the repair or, more commonly, beforehand and then closed a few months later. This means that for many, if not most patients, these are three-stage procedures [126–128], although a single-stage approach, without a colostomy unless positively indicated, is advocated by some [119,128,139].

In 2002, we described complete success in closing the fistula in 14 patients with post-RRP URF, with ≥2 years of follow-up with this three-stage approach of covering colostomy, repair with an interposition gracilis flap and then closure of the colostomy [131]. In 2011, we updated our experience with an additional 40 patients [119]. The URF was again cured in all patients but on this occasion it was without a covering colostomy in six patients and without an interposition gracilis flap in 11.

This is because it is possible, in patients with a post-surgical fistula, to separate the urinary and the rectal suture lines longitudinally and to close the space between them with the levators, having carefully preserved them during the preliminary dissection. Thus, it is entirely possible to repair these in one stage, without the need for a gracilis or other interposition flap, without risk to the anal sphincter, as in the York Mason approach, and without a colostomy in those patients who did not need one in the acute phase after the injury.

**URF after primary radiotherapy, cryotherapy or HIFU**

This group is entirely different [33,45,46,57,67,68,116,118,119,125–127,167–170]. They have active disease in many instances. The incidence is up to 10–times higher than in non-irradiated patients [116] and is higher still in those who have combinations of treatment, approaching 100% when EBRT and BT are followed by salvage HIFU [33]. The URF is generally larger, between 0.1 and 4 cm in diameter, but usually ≥2 cm, with palpable fibrosis around it on rectal examination. Tissue elasticity and mobility is grossly limited and healing is impaired by the irradiation. Other complicating factors include irretrievable damage to the anal sphincter and severe anal stenosis but these are rare [45,46].

The fistula usually develops 17–37 months after radiotherapy and typically follows a biopsy of the anterior rectal wall in patients with irradiation proctitis and recurrent rectal bleeding [167,169,170]. Therefore, this should be avoided if at all possible, although close surveillance of the rectum is clearly important because of the significant risk of rectal cancer in this group of patients, as discussed above. The onset is much less dramatic than in post-surgical URF and is rarely life-threatening in the same way and does not require a covering colostomy [119,126–128], except for postoperative patients after salvage RRP after previous (failed) EBRT. That said, many authors seem to regard it as essential.

The urinary tract defect is far less amenable to closure than in the non-irradiated patient because of both its size and the limited tissue pliability. Consequently, some authors have used a buccal mucosal graft, supported by a gracilis flap, to close the defect [118,125–127,137]. We prefer salvage RRP, if the prostate is still present as the cancer is still active in a significant percentage of patients but would consider the buccal mucosal graft/gracilis flap approach in patients with a URF after a salvage RRP if the bladder-base defect is large. We find that an ileocystoplasty is usually a better alternative – accepting that it is a trans-abdominal procedure and therefore a greater burden to the patient – because the ilium has very predictable and reliable blood supply and because a cystoplasty also deals with the thick walled small capacity bladder due to irradiation cystitis which is almost always present.

Our recent experience is of 17 patients [119]. All patients underwent MRI as well as cysto-urethrography and endoscopy. As a result two distinct sub-groups could be identified: nine patients, generally those with a purely post-irradiation fistula, with a direct communication between the prostatic urethra and the rectum, without an intervening cavity; and eight patients who had an intervening cavity, generally those who had had salvage cryotherapy or HIFU in addition. In the patients with no cavity there was a definable, albeit usually small, residual prostate in all (Figs 23,24). In the patients

*FIG. 23. An image from a retrograde urethrogram of a patient with a ‘simple’ URF after EBRT. There is no cavitation, just a direct communication (A) between the prostatic urethra (B) and the rectum (C). Same patient as in Fig. 24.*
with a cavitating fistula, there was no discernible discrete prostate, just a cavity that effectively extends from the eroded posterior pubic symphysis around the pelvic side walls and into the anterior aspect of the rectum (Figs 25, 26).

In the patients without cavitation our preference is for a salvage RRP rather than an attempt to close the fistula as for a post-surgical URF, for the reasons given above. The rectal defect is then closed with inverting interrupted mattress sutures; the omentum is mobilised and deployed as an interposition flap; and the VUA is then made (Figs 27–30). In the patients with a cavity, the wall of the cavity and the material contained within it is excised transperineally,

FIG. 24. An image from MRI of a patient with a ‘simple’ URF after EBRT. There is no cavitation, just a direct communication (A) between the prostatic urethra (B) and the rectum (C). Same patient as in Fig. 23.

FIG. 25. A ‘complex’ URF after radiotherapy and salvage HIFU. There is marked cavitation between the bladder and the rectum. Same patient as in Fig. 24.

FIG. 26. A ‘complex’ URF after radiotherapy and salvage HIFU. There is marked cavitation (arrows) between the bladder and the rectum. Same patient as in Fig. 25.

FIG. 27. Salvage RRP 1. The prostate has been removed and the rectum repaired (A). The tip of a silicone Foley catheter is visible in the urethral stump (B) and the shaft of another is seen within the bladder (C).

FIG. 28. Salvage RRP 2. Six parachute sutures are approximating the bladder to the urethra. There is an omental flap in place, between the rectum and the bladder and urethra, ready to wrap around the completed anastomosis. The catheter in the bladder is for demonstration purposes only.
with a gracilis flap to obliterate the cavity, or abdomino-perineally using the omentum rather than the gracilis to obliterate the cavity, but otherwise in the same way (Figs 31–33).

A covering colostomy is not essential [119] but is always safe.

Recovery was slow in all these patients, with delayed healing of the VUA and they required protracted wound drainage and up to 12 weeks of catheterisation before complete healing was shown radiologically and the catheters were removed. Most had limited bladder capacity and poor bladder compliance urodynamically and so had a degree of frequency of urination to stay socially dry. Three of the eight patients with cavitation but only one of the nine patients without cavitation needed an AUS implant for SWI. Interestingly, we have never (yet) had an instance of failed closure of the rectal defect; the problem is always with the VUA. Another interesting point, is that we have found moderate to severe pelvic and perineal pain to be a significant clinical feature in most patients with post-irradiation/cryotherapy/HIFU fistulae and it is gratifying that this is relieved by closure of the fistulae, from the day of surgery.

CONCLUDING COMMENTS

It is striking how different the impact is on the patient between the complications of surgery on the one hand, and of radiotherapy on the other, especially the combination of EBRT and BT. With a post-surgical urethral stricture, BNC or URF, the patient will recover from his reconstruction within weeks with a reasonable expectation of return to normality, accepting that some will require a subsequent implantation of an AUS for the reconstruction to be complete. With a post-irradiation complication of the same type and same urethrographic magnitude, the patient will take months to recover and rarely returns to normality even though his quality of life may be very much improved. Although the incidence and nature of potential complications are usually carefully discussed with patients with localised prostate cancer before deciding whether surgery or EBRT/BT/HIFU/cryotherapy are to be recommended as primary treatment, we do not think that enough attention is paid...
to counselling patients about the relative impact of those complications and the relative outcome of further treatment in the two groups. In our view, the greater adverse impact of EBRT/BT/HIFU/cryotherapy needs to be stressed, particularly as many patients actively seek out non-surgical treatment to avoid the risks of surgery in the belief that non-surgical treatment carries a lower morbidity.

SUMMARY

- The management of the posterior urethral complications of the treatment of prostate cancer is a ‘growth industry’ in reconstructive urology.
- The complications of surgery for prostate cancer are well understood and relatively easily treated with relatively good or very good results.
- The complications of EBRT, BT, cryotherapy and HIFU for prostate cancer are less well understood and much more difficult to treat with much less satisfactory outcomes.
- Sequential salvage therapy with these methods carries a particularly high morbidity and are a major reconstructive challenge.
- When one of these complications exists, one of the other complications commonly co-exists and all are commonly associated with SWI, which requires further treatment in its own right.
- With EBRT, BT, cryotherapy and HIFU, bladder dysfunction commonly coexists as well, causing a small functional bladder capacity that may make reconstruction unrealistic.
- Most of these problems are associated with, if not a consequence of, local tissue ischaemia, and it is of primary importance to ensure that well vascularised tissue is used for their repair.
- Post-surgical urethral stricture should be treated as for a similarly sited stricture in any other situation but a non-transecting approach seems preferable, if possible.
- Strictures after EBRT, BT, cryotherapy and HIFU may be amenable to an anastomotic repair, if they are short but they are commonly long, dense and obliterative and are therefore best treated with a flap repair because grafts are relatively contraindicated in irradiated tissue.
- Post-surgical BNC that do not respond to a single or occasional endoscopic procedure should be treated by a trans-perineal excision of the contracture and re-anastomosis of healthy urethra to healthy bladder, expecting that the patient will subsequently require implantation of an AUS for SWI.
- Patients with a BNC or prostatic urethral stenosis after EBRT, BT, cryotherapy or HIFU should be considered for a salvage RRP. They should be warned that they may need an AUS, but this is not usually necessary.
- Post-surgical URF are usually simple direct fistulae between the rectum and the bladder base, and are best managed by a one stage trans-perineal repair without an interposition flap or a covering colostomy.
- URF after EBRT, BT, cryotherapy and HIFU are commonly complicated by an intervening cavity. They are best treated by an abdomino-perineal salvage RP, repair of the rectal defect, VUA and an omental wrap if there is a residual discrete prostate. A covering colostomy is not always necessary but is often a sensible precaution.
- When counselling patients about the primary treatment of prostate cancer they should be advised that although the same type of complication may occur after surgical or non-surgical treatment, the scope and scale of that complication, the ease with which it is treated and the degree of restoration of normality after treatment is altogether in favour of surgery in those for whom surgery is appropriate and who are fit for surgery.

CONFLICT OF INTEREST

None declared.

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Abbreviations: BT, brachytherapy; EBRT, external beam radiotherapy; (R)RP, (retropubic) radical prostatectomy; HIFU, high-intensity focused ultrasound; ED, erectile dysfunction; BNC, bladder neck contracture; URF, urorectal fistula; VUA, vesico-urethral anastomosis; SWI, sphincter weakness incontinence; AUS, artificial urinary sphincter.