An algorithm for managing the failure of external beam radiotherapy in prostate cancer

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OBJECTIVE

To present a management algorithm for men with prostate cancer recurring after external beam radiotherapy (EBRT), based on a review of published reports, to assist clinicians in identifying men who are suitable for salvage therapy and to help them to decide which type of salvage treatment is most likely to confer the desired outcome with the minimum of harm.

METHODS

Men with radiorecurrent prostate cancer require special consideration; they tend to be older, have more comorbidity and have worse disease than their contemporaries having primary treatment. Salvage treatment is compromised by the irradiated pelvis, resulting in increased treatment toxicity. Using the Pubmed database and reference lists of key articles, we identified studies relating to the management of radiorecurrent prostate cancer; the findings were incorporated into a management algorithm and summary table of treatments.

RESULTS

The American Society for Therapeutic Radiology and Oncology criteria, which define biochemical failure has now been superseded by the Phoenix definition (nadir prostate-specific antigen [PSA] plus 2 ng/mL).

Biochemical follow-up after EBRT should be 3-monthly until the PSA level has reached a stable nadir after withdrawing androgen suppression. Contrast-enhanced dynamic magnetic resonance imaging (MRI) is an accurate tool and can be used for both the diagnosis and staging of patients with prostate cancer, in conjunction with prostate biopsies. Prostate biopsies should only be considered >2 years after EBRT to avoid false-positive results. In addition to MRI, high-risk cases being considered for salvage therapy should be considered for laparoscopic lymph-node dissection to exclude micrometastases. Deferred androgen suppression, laparoscopic or open radical prostatectomy, cryotherapy and high-intensity focused ultrasound all seem reasonable salvage treatment approaches.

CONCLUSION

Through improved methods of detection, including frequent PSA measurements, modern imaging and carefully obtained biopsies, those with radiorecurrent disease can be identified before their disease has spread. Rigorous staging will exclude those with micrometastases. The minimally invasive salvage therapies seem to offer an advantage over salvage surgery to patients in whom the benefits and harms are so finely balanced.

KEYWORDS

prostate cancer, radiotherapy failure, salvage treatment

INTRODUCTION

Patients with radiorecurrent prostate cancer require special consideration; they will generally be older than those men receiving primary therapy, and will inevitably have disease of a higher grade and stage. Radiation doses might have been inadequate or poorly targeted, and many patients will not have benefited from developments such as three-dimensional conformal radiotherapy (RT), intensity-modulated RT or dose escalation. Patients who develop biochemical failure (BF) might do so because of recurrence in the prostate, metastases, or both, and thus require careful staging. Finally, if men who have recurrent disease confined to their prostates are treated, that treatment will be given within an irradiated field. The consequences of this are that the toxicity of salvage treatment, whatever its method, will be greater than the toxicity associated with that same treatment given in a primary setting. The result is that even in men who have been appropriately selected, the balance of harm and benefit remains delicately poised.

We present a management algorithm based on a review of published reports that should assist clinicians in identifying men who are suitable for salvage therapy, and help them to decide which type of salvage treatment is most likely to confer the desired outcome with the minimum of harm.

METHODS

Using the Pubmed database and reference lists of key articles, we sought studies relating to the management of radiorecurrent prostate cancer. Furthermore, specific searches were made in individual subject areas (e.g. prostate cancer and RT failure, and MRI). We present the results of our findings, focusing attention on the diagnosis of failed external beam RT (EBRT), staging of radiorecurrent disease and salvage treatment. The findings were incorporated into our proposed treatment algorithm (Fig. 1) and a summary of the different treatments (Table 1).

RESULTS

The American Society for Therapeutic Radiology and Oncology (ASTRO) produced criteria to define BF after RT [1]. The
### MANAGING THE FAILURE OF EBRT IN PROSTATE CANCER

<table>
<thead>
<tr>
<th><strong>AN ALGORITHM FOR MANAGING THE FAILURE OF EXTERNAL BEAM RADIOTHERAPY IN PROSTATE CANCER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance programme</strong></td>
</tr>
<tr>
<td>PSA at initial visit 6 weeks after treatment then 3-monthly Androgen deprivation continues for = 2 years PSA 3 monthly until after ‘PSA bounce’ Once stable nadir reached – 6 monthly PSA RECORD PSA nadir If PSA rises – repeat 3 monthly Annual PSA if stable after 5 years</td>
</tr>
<tr>
<td><strong>Biochemical definition of recurrence: Nadir PSA plus 2 ng/ml</strong> Proceed to prostate biopsies if salvage considered Consider template biopsies if negative with persistent rise in PSA</td>
</tr>
<tr>
<td><strong>Staging</strong> Contrast enhanced dynamic MRI prostate Laparoscopic pelvic lymph node dissection and Bone scan in high risk cases (PSA &gt; 10 ng/ml, Gleason ≥ 7, T3, PSADT &lt; 1 year)</td>
</tr>
<tr>
<td><strong>Risk assessment</strong> <strong>Low risk</strong> – PSA &lt; 5 ng/ml &amp; Gleason score ≤ 6 &amp; ≤ T2 &amp; PSADT &gt; 1 year <strong>Moderate risk</strong> – Those with PSA &gt; 5, Gleason &gt; 7 who aren’t high risk patients <strong>High risk</strong> – 2 of: PSA &gt; 10 ng/ml, Gleason ≥ 8, T3, PSADT &lt; 10 months</td>
</tr>
<tr>
<td><strong>Treatment options</strong> All treatment options available should be discussed with the patient. Treatment options include: Deferred androgen suppression Salvage open / laparoscopic radical prostatectomy Salvage prostate cryotherapy Salvage high-intensity focused ultrasound</td>
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</tbody>
</table>

### FIG. 1.

An algorithm for managing the failure of external beam radiotherapy in prostate cancer.

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Consensus conference defined failure as occurring when there were three consecutive increases in PSA after the PSA nadir (backdated to a midpoint between the nadir and the first increase). These criteria have permitted valid comparison between studies that have assessed the outcome of RT for men with prostate cancer. Whilst the ASTRO criteria represent a real and important development in this regard they have received some comment and criticism. These concerns can be summarized as follows. First, PSA increases are difficult to interpret when temporary androgen deprivation is used in a neoadjuvant or adjuvant setting [2,3]. Second, the use of ASTRO criteria to diagnose treatment failure might result in a delay of the diagnosis, as they require three successive PSA increases. Third, false-positive errors can result if three small PSA increases are recorded in a patient with a low PSA level. As a result, several alternative definitions have been proposed; notably Thames et al. [4], in a study of 4839 men treated with EBRT only, found that four definitions of the 102 tested were more accurate in predicting failure than the ASTRO definition, i.e. two PSA increases of ≥ 0.5 ng/mL backdated, a PSA level at or greater than the absolute nadir plus 2 ng/mL at the ‘call date’, and PSA level at or greater than the current nadir plus 2 ng/mL or 3 ng/mL at the ‘call date’. A second ASTRO/Radiation Therapy Oncology Group (RTOG) Consensus Conference took place in Phoenix, Arizona in January 2006, to revise the ASTRO definition [5]. The new definition of BF after EBRT with or without hormonal therapy was agreed to be an increase of ≥ 2 ng/mL above the nadir PSA, dated at the time of identification. This has become known as the ‘Phoenix’ definition.

Other PSA-related predictors of treatment failure have been identified. These could be used in conjunction with PSA and biopsy results to assess the probability of treatment failure, although they are now less useful, as the androgen deprivation which accompanies modern RT protocols rapidly results in low levels of PSA. PSA nadir values of < 0.5 ng/mL have repeatedly been shown to predict treatment success [6–8]. Cook et al. [6] found the mean nadir PSA for patients with local failure to be 1.1 ng/mL, and 2.2 ng/mL for those who developed metastatic disease. The time to a nadir PSA level has also been shown to be an independent predictor of treatment failure, with shorter times indicating a worse outcome [8,9]. Ray et al. [8] found that patients with PSA nadirs achieved in < 6 months of treatment had an 8-year biochemical disease-free survival (bDFS) rate of 27% and a metastasis-free rate of 66%. The equivalent DFS rates of patients with PSA nadirs achieved in > 2 years were 75% and 99%, respectively. This perhaps reflects the faster cell turnover in aggressive cancers, making them initially more sensitive to the DNA damage induced by RT. Unrecognized metastasis and radio-resistance probably explain the poor prognosis in these tumours.

### FOLLOW-UP SCHEDULES AFTER EBRT

Early follow-up schedules after RT for prostate cancer tend to be designed to identify and treat any treatment-related toxicities. These, if present, are likely to be most problematic for the patient in the first 3–6 months. Once acute toxicities have resolved the follow-up tends to be structured to identify and document the PSA nadir. After the nadir has been established, the follow-up should be designed to identify biochemical recurrence at an early stage without overburdening patients with unnecessarily frequent testing. The European Association of Urology (EAU) guidelines suggest a follow-up at 3, 6 and 12 months, followed by 6-monthly reviews for a further 2 years, followed by annual review. The EAU also regard a rising PSA level (as per the ASTRO definition) as the most valuable clinical predictor of recurrent disease. The Royal College of Radiologists’ Clinical Oncology Information Network guidelines on the management of prostate cancer cite the ASTRO definition of BF and
their guidelines for follow-up. They recommend PSA measurements at 3- or 4-month intervals for the first 2 years after RT, and 6-monthly measurements thereafter [10].

There are data to aid the design of follow-up schedules; e.g. the mean time to reach the PSA nadir in those who develop local recurrence has been shown to be 17 months in one large series [6]. The mean time to PSA nadir in those who did not recur was 24 months. Thus 3- to 4-monthly PSA measurements until 2 years after RT seem justifiable. Kuban et al. [11] found that the period during which patients had the greatest risk of BF was 18–42 months after treatment; 3- to 4-monthly PSA measurements are therefore also worthwhile throughout this period. The effect of stopping androgen deprivation should also be considered, including the effect of the ‘PSA bounce’ phenomenon, seen in 20–30% of patients (depending on the definition used). Thus, to also reduce testing in stable patients and distinguish those having a ‘PSA bounce’ rather than BF, PSA measurements should be 3- to 4-monthly on discontinuing androgen deprivation, until the PSA level reaches a stable nadir. Once reached, the frequency can be reduced to 6-monthly until 5 years after treatment have elapsed, when measurements can be annual. In the presence of an increasing PSA level, the frequency of testing should revert to 3- to 4-monthly to detect impending BF.

This proposal would result in more visits for the patient than with the current EAU guidance. The benefit of these additional tests cannot be established until they have been prospectively studied. However, we suggest that the additional burden of blood tests would seem a small cost compared to a potentially avoidable delay in diagnosis and progression to metastatic disease.

MRI

MRI, particularly using endorectal coils (erMRI), is increasingly recognized as a potential diagnostic tool for prostate cancer. A recent study compared the accuracy of erMRI, sextant-core biopsies and DRE in the diagnosis of cancer, comparing the results to tumour sites in radical prostatectomy (RP) specimens [12]. They found that for locating cancer erMRI contributed statistically significant and clinically important improvements to a DRE or TRUS and biopsy findings. This approach was also used in a study of patients after EBRT failed [13]; the accuracy of erMRI for detecting tumour was high (area under curve, AUC, of 0.61–0.75), although these authors reported a fair degree of interobserver variability in the interpretation of erMRI. They concluded that erMRI should be incorporated into the criteria used to select patients for salvage therapy.

**TABLE 1 The characteristics of salvage treatment options for radiorecurrent prostate cancer**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred androgen suppression</td>
<td>Observation until PSA or PSADT pass a defined threshold; androgen ablation thereafter</td>
<td>Suitable for most patients; Avoids toxicity of treatment in many; Cheap</td>
<td>Palliative not curative</td>
<td></td>
</tr>
<tr>
<td>Salvage RP</td>
<td>Surgical excision of irradiated prostate</td>
<td>Curative in accurately staged patients; 43% biochemically disease-free at 10 years</td>
<td>High levels of morbidity; High chance of extra-prostatic disease; Few surgeons offer procedure; Few surgeons offer procedure</td>
<td>Patient unable to tolerate haemodynamic compromise</td>
</tr>
<tr>
<td>Salvage cryotherapy</td>
<td>Percutaneous lethal freezing of prostate under image guidance</td>
<td>40% biochemically disease-free at 5 years; Low perioperative morbidity</td>
<td>Incontinence &amp; perineal pain problematic; Poorer outcome than surgery</td>
<td>Involvement of seminal vesicles; Ano-rectal absence/pathology (applies to all TRUS-guided methods)</td>
</tr>
<tr>
<td>Salvage HIFU</td>
<td>Transrectal thermal destruction of prostate using focused ultrasound</td>
<td>Well tolerated by patients; Accurate conformal planning; 38% disease-free at 40 months; Lower morbidity than RRP &amp; cryotherapy</td>
<td>Bladder neck stenosis/slough problems; Long-term outcome not reported</td>
<td>Heavy prostatic calcification; Prostate volume &gt;40 mL after cytoreduction</td>
</tr>
<tr>
<td>Salvage brachytherapy</td>
<td>Permanent radioactive implants in previously irradiated gland</td>
<td>34–53% disease-free at 5 years. Very well tolerated</td>
<td>Only two reports</td>
<td>LUTS and previous TURP (relative)</td>
</tr>
<tr>
<td>RITA</td>
<td>Transrectal delivery of thermal energy</td>
<td>Similar to those of HIFU</td>
<td>Few reports with no long-term follow-up</td>
<td></td>
</tr>
</tbody>
</table>

PROSTATE BIOPSIES

On a biochemical diagnosis of treatment failure, prostate biopsies should always be obtained to confirm the histological diagnosis of prostate carcinoma if salvage treatment is
being considered. The interpretation of prostate biopsies after EBRT can be problematic and was well studied by Crook et al. [6]. False-negatives occur due to sampling error in up to 19% of cases and false-positives and indeterminate biopsies also frequently occur due to delayed tumour regression. Nevertheless the biopsy status at 24–36 months after treatment is an independent predictor of outcome [6]. The high false-negative rate seen by Crook et al. might be due to the number of cores taken. Generally six cores were taken (range 4–7) [6], which was fairly standard for the time. Modern biopsy regimens, e.g. the Vienna nomogram, recommend more cores, to increase the diagnostic yield [14]. This approach is likely to be just as valid after RT. Patients with abnormalities on MRI can also have directed biopsies to increase the diagnostic yields. Those with negative biopsies, whose biochemical results suggest failure, might benefit from more extensive transperineal template-guided biopsies to detect occult recurrences. This clinical picture can also arise when local control is successful but occult metastatic disease is present. This should be suspected when the PSA level is increasing and the biopsies and MRI do not identify tumour. A bone scan might also be unhelpful due to a low disease burden. In these cases the choices are to repeat the biopsies after an interval (4–6 months) in the hope of identifying local disease, or, assuming micrometastatic disease, start a programme of deferred androgen suppression. To avoid biopsies, serial dynamic contrast-enhanced MRI might also have a role [12]. The management should be planned on an individual basis.

RE-STAGING AFTER DIAGNOSIS OF BIOCHEMICAL FAILURE

We described the increasing value of MRI in the diagnosis of recurrent prostate cancer. After RT, MRI is also perhaps the best method of local staging. Improved scanners and scanning techniques have increased the accuracy of these studies, particularly through the use of larger magnets and the increasing use of contrast agents to produce dynamic scans [15]. In their study of patients after EBRT failed, Sala et al. [13] also assessed the accuracy of eMRI for detecting extracapsular extension (AUC 0.76–0.87) and seminal vesicle invasion (AUC 0.70–0.76). MRI can also detect abnormal lymph nodes, based on size criteria, but the accuracy of this method has been shown to be poorer than histological staging after laparoscopic pelvic lymph node dissection (LPLND) [16]. Further improvements in MRI might overcome the poor accuracy in lymph node staging with the use of highly lymphotropic superparamagnetic nanoparticles (ferumoxtran-10). In a study by Harisinghani et al. [17], MRI with nanoparticle contrast media had a significant advantage over conventional MRI. All patients with histologically confirmed positive lymph nodes were identified with the technique, and there was a clear and significant advantage comparing node for node (sensitivity 90.5% vs 35.4%, P < 0.001). In summary, MRI can contribute to both the diagnosis and staging of radiorecurrent prostate cancer. Further developments in MRI, including the use of 3-T magnets and spectroscopy, will further improve its accuracy, and thus its use is bound to increase with time.

PROSTASCINT SCAN

The ‘Prostascint’ scan has been evaluated and approved by the United States Food and Drug Administration for use in the staging patients with prostate cancer, but it is not in routine clinical use. The accuracy of this scan has been assessed in several studies (reviewed in [15]). Most of these studies contained few patients or relied on retrospective multicentre data, with a poor correlation between scan data and pathological examination of pelvic lymph nodes. Few studies compared imaging and pathology, but Hinkle et al. [18] studied 51 patients with high-risk prostate cancer who had extended LPLND. They found that the sensitivity, specificity, accuracy and positive predictive value of the Prostascint scan compared with histopathology was 75%, 86%, 81% and 79%, respectively. This compared to a combined accuracy of CT, MRI and ultrasonography of the pelvis of only 48% in the same group. However, Porsky et al. [19], who studied the accuracy of the scan compared to the exact location of the positive result, found the Prostascint scan to have a sensitivity of only 17% and a positive predictive value of 11%. There are no studies specifically targeting irradiated patients being considered for salvage treatment.

LPLND

LPLND in the context of salvage therapy for irradiated patients has been reported to be feasible, although more technically challenging than in unirradiated patients [20,21]. This is due to a loss of the normal tissue planes between the neurovascular structures and the lymph node packet, which was smaller and more fibrotic than normal. In each series patients with occult nodal metastases were identified in appropriately screened patients who would have otherwise been offered local salvage RP. The procedure was well accepted by patients and not associated with significant complications. Anecdotally the LPLND in irradiated patients has been associated with more complications, highlighting the need for these procedures to be carried out by experienced laparoscopists. Further research in this area is required.

There is some controversy about the extent of LPLND in the management of primary tumours. This also potentially applies in the salvage setting. While it has been established that the extended LPLND (obturator, hypogastric nodes, common and external iliac nodes) gives a larger yield of nodes and a higher node positivity rate than the modified LND (obturator and hypogastric nodes only), the morbidity of the extended LPLND was far greater than that of the modified technique (37% vs 2%), and the extended LPLND offered no advantage over modified LPLND in diagnosing positive lymph nodes when the results were analysed by prognostic factors [22]. The use of radioisotope sentinel LPLND allows sentinel nodes outside the obturator and hypogastric groups to be identified using a laparoscopic γ-probe. Corvin et al. [23] found that 48% of their patients had sentinel nodes outside the obturator fossa. Those with a positive node on frozen-section analysis had extended LPLND. Three of the 10 metastases they identified lay outside the modified LPLND template. They did not report significant lymphocele with the extended LPLND. In a similar study, Jeschke et al. [24] found that 54% of their patients had sentinel lymph nodes exclusively outside the obturator fossa. Eight of 11 metastases were also found exclusively outside the obturator fossa. They recommended either sentinel LPLND, extended where necessary, or extended LPLND as the ideal approach. This approach is probably also valid in the salvage setting, although the morbidity of an extended dissection in an irradiated field needs further study.

It was previously established that nodal dissection is unnecessary in those patients with primary tumours with a PSA level of
<10 ng/mL and a Gleason score of ≤6 [25]. However, it is not clear whether this restriction should also apply to those with radiorecurrent disease. The same question can be asked about the extent of LPLND in those with radiorecurrent disease. However, the morbidity associated with LPLND is similar to that of some of the minimally invasive therapies. This might encourage some to choose treatment (with a risk of nodal disease) over accurate staging.

In summary, we conclude that as laparoscopy is now available to most urology departments managing prostate cancer, LPLND is an ideal mode of staging biopsy-proven radiorecurrent cancer in those considering salvage treatment with a negative MRI, particularly when the PSA level is >10 ng/mL and of Gleason ≥7. However, patients should be carefully counselled as to the risks of the procedure and those of the proposed treatment, should the LPLND show no evidence of metastasis. Those undertaking LPLND after RT should be experienced in the procedure in the unirradiated patient.

BONE SCAN

There have been no specific studies to assess the need for radionuclide bone scans to identify patients with bony metastases in those being considered for salvage treatment. Guidance has been issued based on retrospective series of newly diagnosed patients with prostate cancer. One recent example suggested that bone scans are only necessary if the PSA level is >20 ng/mL, and the disease stage T4 and Gleason score ≥7 [26]. Many of these patients would not be evaluated for salvage therapy. Bone scans in patients being considered for salvage therapy should probably include those with Gleason 7 disease or worse, a PSA level of >10 ng/mL or a PSA doubling time (PSADT) of <1 year.

TREATMENT OPTIONS

Before considering treatment options the effect of BF on the patient’s survival prospects should be assessed. This point was addressed by Lee et al. [27], who studied a cohort of 1786 patients treated with radical RT. Overall and cause-specific survival at 5 years was worse in patients with PSA failure (79.5% vs 87.5%, P < 0.001; and 84.4% vs 99.0%, P < 0.0001). Subgroup analysis showed that PSA failure conferred a statistically significant poorer overall survival in those with high-risk disease and those aged <75 years. Thus salvage treatment is necessary in some and should be targeted at those who have most to gain from it. Perhaps the best way to identify those at greatest risk of clinical treatment failure is the PSADT. Lee et al. [27] studied the PSADT in patients with BF; they found a 5-year rate of true clinical failure of 6.5% for men with a PSADT of >8 months and 88.5% for men with a PSADT of ≤8 months. Thus in men with a rapidly increasing PSA level after EBRT, who have no signs of nodal or bone metastasis, there is a considerable potential for benefit from salvage treatment. These patients are also at most risk from local salvage treatment failure due to unidentified micrometastases.

The management of patients with radiorecurrent tumours might be influenced by EBRT technique or coexisting EBRT toxicity. Toxicity might influence patients to avoid all salvage therapy, so it is important for men to also consider the toxicity of androgen suppression which might be required later. Patients treated with conventional EBRT rather than modern conformal techniques might have more extensive tissue changes in the pelvis that affect open surgery. Those with anorectal toxicity might have increased problems from the transrectally guided therapies, due to the size of the probe. The effect of salvage therapy on patients with urinary frequency or incontinence is not well described for any method and should be studied further. Treatment choice will also be influenced by availability, thus patients should ideally be managed in cancer centres where expertise can be concentrated.

DEFERRED ANDROGEN SUPPRESSION

To date there has been no randomized study to compare delayed vs immediate androgen deprivation in patients with BF after EBRT. Recent data showed that in most cases patients can be safely observed. In their study, Faria et al. [28] retrospectively assessed patients treated with EBRT and who had BF by ASTRO criteria. Those who received treatment had less favourable prognostic characteristics (higher PSA nadir, higher PSA level at BF, shorter PSADT) suggesting that these patients had been selected for treatment based on these criteria. There were no prostate cancer-related deaths in either group over the mean 85 month follow-up. Interestingly, 53% of the untreated group would not have been diagnosed with BF under the definition of nadir + 2 ng/mL PSA, suggesting that the ASTRO definition might over-diagnose BF from a clinical perspective.

Another valuable study by Pinover et al. [29] showed that their policy of deferred androgen suppression in patients with a PSADT of >1 year appropriately avoided treatment, with no significant difference in the numbers with metastases at 5 years. Those with a PSADT of <1 year benefited from early treatment, with a mean time to distant failure of 25 months vs 6 months if untreated (P < 0.02).

Thus for many men the preferable treatment strategy will be a period of observation followed by initiation of androgen suppression at a given level of PSA or PSADT. Delayed treatment avoids the related costs and side-effects of LHRH analogues or antiandrogens, which can include loss of libido, erectile dysfunction, osteoporosis, bone fractures, muscle atrophy, hot flushes, breast tenderness and fullness. There is no consensus on the PSA threshold that should trigger treatment, but Faria et al. [28] imply that their treated group generally had a PSA level of >10 ng/mL and a PSADT of <10 months. Pinover et al. [29] used a PSADT of <12 months; it was previously recommended that patients with a PSADT of <5 months be started on immediate androgen suppression due to the rapid progression of the disease [30]. Equally those who are symptomatic from their disease should start treatment. An EORTC trial to address the question of the timing of androgen suppression after EBRT was started, but failed to recruit patients and was terminated [30]. Thus we are unlikely to obtain definitive evidence on this question in the future. We recommend that patients with, or strongly suspected of having, metastases start androgen deprivation. Patients with a PSADT of <1 year should also start immediate therapy to delay the onset of metastases. There is no clear PSA threshold above which patients should be treated, although values of 10–20 ng/mL have been suggested.

SALVAGE RETROPUBIC RP (RPP)

This procedure is perhaps the only widely accepted salvage therapy. Although it has been shown to give long-term disease control [31,32] surprisingly few patients are so treated. Indeed it was recently noted that <500 procedures were reported [33]. The poor
acceptance of this procedure relates to the significant morbidity associated with it.

The approach to salvage RRP is similar in most reported series; patients tend to have a good functional status and a life-expectancy of >10 years. Patients will all have histologically confirmed residual/recurrent prostate cancer on transrectal biopsy. Patients shown on biopsy or imaging to have involvement of the bladder neck or seminal vesicles have previously been offered cystoprostatectomy, although this is of questionable benefit to the patient. A standard RRP is normally used, although some have combined retropubic and perineal approaches to facilitate careful dissection of the densely adherent prostate and rectum [34]. These RT-related adhesions are the cause of longer surgery and more complications, the latter including rectal injury, prolonged urinary extravasation, anastomotic stricture and urinary incontinence. The incidence of complications was reported in several series and were reviewed well by Touma et al. [35]. Using values from reported case series, the overall complication rates for salvage RRP were estimated; the mean estimated blood loss was 992 mL, with rectal injury in 3.7%, bladder neck contracture in 18% and incontinence (requiring pads) in 45%. Touma et al. also concisely summarized the oncological outcomes from these series. Only 20–39.5% of cases (weighted mean 33%) had organ-confined disease; nearly half had seminal vesicle involvement. There was biochemical clearance of disease in 48.6% of cases if the weighted mean was used from the series reported. This tallies well with the largest series, in which the 10-year BF-free survival rate was 43% [36]. The most recent series published on salvage RRP also had similar overall results, with 47% of patients progression-free at 5 years [37]. Interestingly, none of those with pathological T2N0 tumours and all of those with TxN+ developed recurrence, showing the importance of nodal staging. A preoperative PSA level of <5 ng/mL was highly predictive of localized disease.

Laparoscopic salvage RP was also reported from a few cases [38]; this study showed that the procedure was feasible, with no increase in intraoperative complications but reduced blood loss and postoperative pain. Oncological results could not be established with this study due to short follow-up. Two of seven patients had positive margins.

### SALVAGE PROSTATIC CRYOTHERAPY

Rapid freezing of tissues to very low temperatures results in a lethal injury to cells. The modern technique of prostate cryotherapy involves the percutaneous placement of probes under TRUS guidance. Typically six or more probes will be placed along with thermocouples which monitor the temperature at key anatomical points (external urethral sphincter, neurovascular bundles, Denonvilliers’ fascia, prostatic apex). A urethral warming device is used to prevent tissue sloughing. Usually two freeze-thaw cycles, controlled by automated planning software, are used to deliver the treatment.

Pisters et al. [39–47] reported the largest published series of salvage cryotherapy, with = 150 procedures contributing to at least nine original papers. The outcomes were published from this series [43]. The 5-year bDFS rate was 40%, with an overall survival of 73%. The results were better in patients with a PSA level of <10 ng/mL before cryotherapy (5-year DFS 57% vs 23% in the high-PSA group, P < 0.001), a recurrence Gleason grade of <9 (5-year disease-specific survival 46% vs 31% in the high-grade group) and in patients with no extraprostatic disease (5-year DFS 90% vs 69%). The main complications of the procedure were urinary incontinence (73% of patients reporting some degree of incontinence), obstructive symptoms (67%), erectile dysfunction (72%) and severe perineal pain (8%) [46]. Six of 150 patients required major pelvic surgery to manage their complications [41]. While cryotherapy is a minimally invasive technique, Perotte et al. [44] assessed the quality of life of a subset of patients and found high levels of dissatisfaction relating to postoperative complications and treatment failure. Although there have been no similar studies to assess the quality of life in patients after salvage RP with which they could compare, the authors concluded that cryotherapy offered no quality-of-life advantage over salvage RP. Recent data offer a slightly more optimistic view, possibly due to technical improvements in cryosurgical instruments. Robinson et al. [48] studied 46 patients who were treated in a phase II trial of salvage cryotherapy. Quality-of-life scores in these patients returned to preoperative levels by 24 months after cryosurgery in all domains, except for urinary and sexual function; 29% of men reported urinary bother as a ‘moderate-to-big’ problem, and 50% reported sexual bother as a ‘moderate-to-big’ problem.

Recent studies generally show improved oncological efficacy, which might also reflect advances in technology and technique. Chin et al. [49] treated 118 patients, of whom 114 had a nadir PSA level of <0.5 ng/mL. While the median follow-up was only 18.6 months (range 3–54), the bDFS rate was 68%, 55% and 34%, according to the PSA threshold used (4, 2 and 0.5 ng/mL). A pretreatment PSA level of >10 ng/mL, Gleason score >7 before RT and stage T3/T4 disease appeared to predict an unfavourable biochemical outcome. Serious complications included four recto-urethral fistulae (3.3%) and severe incontinence (6.7%).

Recently the experience of a UK centre was reported [50]; 100 patients were closely assessed, with a mean follow-up of 27.5 months; bDFS was defined by a serum PSA level of <0.5 ng/mL. The 5-year biochemical recurrence-free survival was 73% for low-risk, 45% for intermediate-risk and 11% for high-risk patients. The reported complications included incontinence (13%), erectile dysfunction (86%), LUTS (16%), prolonged perineal pain (4%), urinary retention (2%) and rectovesical fistula (1%). The PSA nadir is used frequently as an early surrogate of successful treatment. The value used varies in published reports but it is clear that long-term control is unlikely in those whose PSA nadir level is >1.0 ng/mL. Increasingly, studies like those above are defining success more strictly as a nadir PSA level of <0.5 ng/mL.

In summary, while salvage cryotherapy is less invasive than salvage RRP it is probably less effective, but improvements in technique and better patient selection have led to good results. It is probably the best established minimally invasive treatment for radiorecurrent prostate cancer, and it is supported by guidance from the National Institute of Clinical Excellence (NICE).

### HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)

Initial studies showed HIFU to be a well-tolerated and effective treatment for localized prostate cancer [51–57]. HIFU uses focused ultrasound waves emitted by a transrectal transducer to cause a lethal rise in temperature in the targeted tissue. After
treatment there is coagulative necrosis and eventually cavitation. There are two HIFU devices available, the Ablatherm (EDAP SA, Lyon, France) and the Sonablate (Focus Surgery Inc, IN, USA). The potential advantage of the Sonablate device is the real-time ultrasonography of the treatment zone, which allows HIFU intensity to be modulated according to visual cues. Patients treated with HIFU can be discharged from hospital within a few hours, although a urethral or suprapubic catheter is left for 5–10 days to allow the passage of sloughing tissue. The procedure is generally well tolerated with a low incidence of serious complications.

In the only published series of salvage HIFU, Gelet et al. [58] used the Ablatherm device to treat a group of 71 patients in whom EBRT had failed. At the last follow-up 80% of patients treated had negative biopsies (corresponding to a 73% 30-month actuarial negative biopsy rate) and 61% achieved a PSA nadir of <0.5 ng/mL within 3 months. Despite these results, 56% required adjuvant therapy. It appears the ‘standard cancer evaluation’ used in this study underestimated the presence of micrometastatic disease; they did not use LPLND to stage high-risk patients. At 30 months there was a 38% clinical disease-free rate. Adverse effects of HIFU included bladder neck stenosis (17%), incontinence (grade I, 13%; grade II, 15%; grade III, 7%) and recto-urethral fistula (6%). Four patients (6%) were treated with an artificial sphincter.

HIFU appears to be a feasible salvage treatment when EBRT has failed, and it has been approved by NICE for use in the primary and salvage treatment of prostate cancer. The long-term oncological results require further study, and studies using the Sonablate device for primary and salvage therapy are in progress at our institution. Quality of life studies are also required to establish the acceptance of HIFU amongst patients.

**SALVAGE BRACHYTHERAPY**

Seed-implant brachytherapy has been used in a few studies of patients who have developed biochemical recurrence after EBRT. The two major series give 5-year bDFS rates of 34–53% [59,60]. In the larger series, Grado et al. [60] reported 98% local cancer control and disease-specific survival of 89% and 79% at 3 and 5 years, respectively. Recently, a small series of 17 patients showed an actuarial 4-year survival of 75%, with no prostate cancer deaths or local recurrences. Grade 3 and 4 genitourinary toxicity developed in seven and one patient (6%), respectively. Grade 2 and 3 gastrointestinal toxicity occurred in five and one patient, respectively [61]. Thus brachytherapy appears to be a potentially useful salvage therapy that needs further evaluation.

**RADIOFREQUENCY INTERSTITIAL TUMOUR ABLATION (RITA)**

RITA has been used in several tumours as a noninvasive ablative therapy. Using TRUS guidance, RITA causes targeted tissues to be heated and destroyed by coagulative necrosis, much like HIFU. It has been tested in primary prostate cancer [62–64] and recently a few patients after EBRT failure were treated with RITA [65]. Although 90% of patients had a decrease in PSA level of >50%, and 46% had a decrease of >80%, the authors report none with undetectable levels of PSA and only one had a sustained decrease in PSA level of >80%. While this might be due to the focal nature of their treatment strategy, the impression is that this technique is less effective than other minimally invasive salvage therapies.

**DISCUSSION**

The ASTRO definition of BF has undoubtedly been of enormous benefit to researchers and clinicians. However, a nadir PSA level plus 2 ng/mL is one of several definitions shown to be more accurate than the original ASTRO definition in predicting clinical failure, and it has now been adopted by ASTRO and RTOG after a second consensus conference. This is now commonly known as the ‘Phoenix’ definition of RT failure. The present review suggests that PSA should be measured 3– to 4-monthly during the first 2 years and then continue as such until adjuvant androgen deprivation is discontinued. Once a stable PSA level is reached and any ‘PSA bounce’ has settled, the interval can be reduced to 6-monthly. After 5 years, patients with a stable PSA level can be tested yearly.

Developments in prostate imaging have led to greater levels of accuracy, and the role of MRI in the diagnosis and staging of the disease is now well established. The importance of clinically localized tumour stage before RT as a significant predictor of DFS after salvage treatment has been confirmed in a series of salvage RRP [66]. This finding probably applies to other treatments and to staging before salvage treatment. Those with clinical or radiological extraprostatic disease considering salvage therapy should be warned of the increased likelihood of failure. Also, a significant proportion of patients will be overstaged by clinical examination and imaging. Ward et al. [67], in a large series of clinical T3 primary tumours treated by RP, found that 27% were pathologically T2 and 27% had microscopic nodal metastases. Patients with clinical T3 tumours should thus be offered treatment (and nodal staging) after being warned of the increased risk of micrometastatic disease and local failure. HIFU might offer some advantage in the T3 group, as the extraprostatic disease can be carefully targeted in a precise treatment zone while avoiding damage to adjacent structures.

While the results of the Prostascint scan have been mixed, there is hope that the use of ferumoxtran-10-enhanced MRI might allow noninvasive diagnosis of nodal metastases. Meanwhile, LPLND offers a minimally invasive means of identifying those unsuitable for salvage treatment.

These improvements in staging combined with new less-invasive therapeutic options such as cryotherapy, HIFU or brachytherapy should alter the benefit/harm ratio in two ways. First, by reducing the proportion of men so treated who will not benefit; and second, by reducing the toxicity experienced by men who are deemed to be appropriate candidates for treatment. The challenge for future management will be to identify the group of patients who lie between those with slow progressing local recurrence, who do not need therapy, and those who have aggressive metastatic disease who will progress despite any local therapy. From our review we can conclude that the patients most likely to benefit from a salvage procedure will have the following features: biopsy-confirmed radiorecurrent prostate cancer, negative lymph nodes on MRI (and LPLND for high-risk cases) and a life-expectancy of ≥ 10 years. The risk of failure of salvage treatment will depend on the clinical stage, Gleason score, volume of disease on biopsy/MRI, PSA and PSADT. To guide patients, risk groups need to be carefully defined based on multivariate analysis of large cohorts of patients. It seems generally accepted that those with low-risk disease (Gleason score ≤ 6, PSA level < 5 ng/mL, PSADT > 1 year, clinical stage ≤ T2) will...
probably fare well with deferred androgen suppression or salvage therapy. Those with high-risk disease, e.g., those with two or more of the following risk factors; Gleason score 8–10, PSA >10 ng/mL, PSADT <10 months and clinical stage T3, will have a high chance of recurrence due to metastatic disease. Some of these patients, identified early, might not have microscopic nodal or bony disease and thus might have the most to gain from treatment, as aggressive metastatic disease is otherwise inevitable. Treatment can more easily be justified in these patients if treatment-related toxicity is minimised. Minimally invasive therapies thus have a more important role in higher risk patients. High-risk patients should also benefit from neoadjuvant and adjuvant androgen suppression, although there are few data at present assessing this directly. The moderate-risk group (everyone else) should probably have salvage treatment, if it is acceptable to the patient, with the aim of curing most patients.

Many patients with BF might not need or will not be suitable for salvage treatment. Clearly this includes patients with metastatic disease, who should start androgen deprivation, and those with a PSADT of <5 months, who should probably be considered to have micrometastases even if they are not necessarily detectable. The patient’s health might be such that aggressive treatment of the cancer offers no overall benefit. Patients might also refuse treatment due to the associated risks of therapy, or they might be unsuitable for treatment due to persistent side-effects from EBRT. Such patients can be managed with deferred androgen suppression. A prospective study is required to determine whether the early oncological results of salvage therapy (i.e., transition of pT1–3 to pT0) translate to improved long-term survival, compared to deferred androgen suppression alone.

In summary, patients treated with RT for prostate cancer should be monitored carefully with 3- to 4-monthly PSA measurements until they have a stable nadir PSA when off androgen suppression. Patients who have an increase in PSA level of 2 ng/mL above the nadir should be fully counselled as to the benefits and risks of salvage treatment. If they agree in principle to salvage therapy, then diagnostic and staging tests should be undertaken. These should include dynamic contrast-enhanced MRI and a set of TRUS-guided prostate biopsies. Areas of suspicion on the MRI should have directed biopsies. Those with histologically confirmed cancer and negative nodes on MRI should be offered LPLND if there are any risk factors (PSA level >10 ng/mL, Gleason ≥7, clinical stage T3, PSADT <1 year). Those with negative biopsies should be considered for re-biopsy. Transperineal biopsies can be used, particularly if there is suspicion of tumour in the anterior part of the gland. Patients should be offered as many treatment options as possible. Thus the management of radio-recurrent prostate cancer should be centralized into cancer centres. Patients can then select the ideal treatment with the assistance of the multidisciplinary team. We hope that this approach will help to rationalize care and improve the outcome in this group of men, who frequently lack the opportunity for cure.

CONFLICT OF INTEREST
Mark Emberton is a paid consultant to Misonix, UK, distributor of the Sonablate device.

REFERENCES
7 Zietman AL, Tibbs MK, Dallow KC et al. Use of PSA to predict subsequent biochemical outcome following external beam radiation therapy for T1–2 adenocarcinoma of the prostate. Radiother Oncol 1996; 40: 159–62
14 Remzi M, Fong YK, Dobrovits M et al. The Vienna nomogram. validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate. J Urol 2005; 174: 1256–60
16 Borley N, Fabrin K, Sriprasad S et al.
Laparoscopic pelvic lymph node dissection allows significantly more accurate staging in 'high-risk' prostate cancer compared to MRI or CT. Scand J Urol Nephrol 2003; 37: 382–6
26 O’Sullivan JM, Norman AR, Cook GJ, Fisher C, Dearnaley DP. Broadening the criteria for avoiding staging bone scans in prostate cancer. A retrospective study of patients at the Royal Marsden Hospital. BJU Int 2003; 92: 685–9
29 Pinover WH, Horwitz EM, Hanlon AL, Uzzo RG, Hanks GE. Validation of a treatment policy for patients with prostate specific antigen failure after three-dimensional conformal prostate radiation therapy. Cancer 2003; 97: 1127–33
30 Parker CC, Dearnaley DP. The management of PSA failure after radical radiotherapy for localized prostate cancer. Radiother Oncol 1998; 49: 103–10


61 Uchida T, Sanghvi NT, Gardner TA et al. Transrectal high-intensity focused ultrasound for treatment of patients with stage T1b–2n0m0 localized prostate cancer: a preliminary report. *Urology* 2002; 59: 394–8


73 Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005; 95: 751–6

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Abbreviations: ASTRO, American Society for Therapeutic Radiology and Oncology; RTOG, Radiation Therapy and Oncology Group; HIFU, high-intensity focused ultrasound; (EB)RT, (external beam) radiotherapy; EAU, European Association of Urology; eMRT, endorectal coil MRI; AUC, area under the curve; LPLND, laparoscopic pelvic lymph node dissection; PSADT, PSA doubling time; BF, biochemical failure; R(RP), retropubic radical prostatectomy; NICE, National Institute of Clinical Excellence; (b)DFS, (biochemical) disease-free survival; RITA, radiofrequency interstitial tumour ablation.