Overview

A Systematic Review of the Role of Imaging before Salvage Radiotherapy for Post-prostatectomy Biochemical Recurrence

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Abstract

A substantial proportion of patients who have undergone a radical prostatectomy for localised prostate cancer will have either persistently detectable prostate-specific antigen (PSA) levels or a delayed rise in PSA. The optimum treatment for these situations is not known. The key question is whether the PSA is reflective of local or distant progression. For salvage radiotherapy to be most effective, treatment should be considered before the PSA level is allowed to rise too high, when disease is more likely to be confined to the prostate bed. However, at low PSA levels, current imaging techniques are poor at detecting disease, making it difficult to differentiate local and distant recurrences and to target the radiotherapy appropriately. We review current and investigational imaging techniques, including bone scan, computed tomography, magnetic resonance imaging, positron emission tomography and Prostascint, assessing their utility in the situation of biochemical recurrence after radical prostatectomy.

Key words: Biochemical recurrence; bone scan; PET-CT; prostascint; prostate cancer; salvage radiotherapy

Statement of Search Strategies Used and Sources of Information

The studies used as the basis for this review were identified by searching PubMed for articles published before March 2009. The keywords used for the search were: prostatectomy, salvage radiotherapy, PSA relapse, biochemical recurrence, bone scan, CT, MRI, capromab, Prostascint and PET. Related studies and articles identified in these publications were also reviewed.

Introduction

Radical prostatectomy and radical radiotherapy (using conformal external beam radiotherapy and/or brachytherapy) are definitive treatments for localised prostate cancer. Both of these modalities offer long-term tumour control in most patients. In patients receiving primary surgery there is the option of following up with radiotherapy as either adjuvant or salvage treatment if there is suspicion of residual or recurrent local disease. Adjuvant radiotherapy is considered after radical prostatectomy for men with an undetectable or barely detectable prostate-specific antigen (PSA) level, but with high-risk pathological features. Salvage radiotherapy after radical prostatectomy is used in the situation of either a persistently detectable PSA level or a delayed rise in PSA level after a period of an undetectable level.

There has been debate as to whether selective adjuvant radiotherapy for high-risk patients after radical prostatectomy is better than salvage radiotherapy for patients who develop biochemical relapse at a later date. This issue was addressed by a comparative study of post-prostatectomy radiotherapy from two institutions, one adopting a prospective policy of adjuvant radiotherapy and the other salvage radiotherapy. The salvage group underwent radiotherapy after longer postoperative intervals (median 40.3 vs 2.9 months; \( P < 0.0001 \)) and had higher PSA values before starting radiotherapy (4.5 vs 0.86 ng/ml; \( P = 0.003 \)). Both groups were routinely treated to a minimal total dose of 60 Gy. Multivariable modelling of biochemical relapse-free...
survival found only the PSA value before radiotherapy to be statistically significant ($P < 0.0001$). Radiotherapy was equally effective in either setting when the pre-radiotherapy PSA level was $<1$ ng/ml [1]. This was a non-randomised study and there are concerns that the adjuvant radiotherapy group was not strictly adjuvant (rather early salvage treatment) given that the median pre-radiotherapy PSA level in this group was 0.86 ng/ml.

More recently there have been two randomised studies published that showed that adjuvant radiotherapy can reduce the risk of PSA failure or clinical progression in patients with capsule breach, seminal vesicle invasion or positive surgical margins [2,3]. Updated results from the Southwest Oncology Group (SWOG) 8794 trial confirm survival benefits with adjuvant radiotherapy for patients with pathological T3 disease [4]. Of 425 eligible men, 211 were randomised to initial observation and 214 to adjuvant radiation. Of the patients under observation, 70 eventually received radiotherapy. The hazard ratios for metastasis-free and overall survival were 0.71 ($P = 0.016$) and 0.72 ($P = 0.022$) respectively, in favour of adjuvant treatment.

The UK RADICALS study will further address this issue. It is open to patients after radical prostatectomy where there is uncertainty about the need for postoperative radiotherapy. Patients are randomised between immediate radiotherapy to the prostate bed and delayed radiotherapy on PSA relapse. A second randomisation among patients receiving radiotherapy is between no androgen deprivation therapy vs short-term (6 months) and long-term (2 years) endocrine treatment. Given the uncertainty around adjuvant and salvage treatment after prostatectomy, eligible patients should be encouraged to take part in this study.

About 25–40% of patients will experience recurrence after radical prostatectomy, manifested by a rising PSA level, often without clinical or radiological evidence of disease. Treatment for men with a detectable PSA level after radical prostatectomy for prostate cancer remains controversial. In the absence of metastatic disease, a rising PSA level is interpreted as locally persistent or recurrent disease, and salvage radiotherapy could theoretically control the local disease. However, if metastatic disease were found to be present, radiotherapy to the prostate bed would be unnecessary and merely expose the patient to additional morbidity. There is currently no consensus regarding the use of imaging techniques before embarking on a course of salvage radiotherapy and despite it being a relatively common clinical situation, the decision as to which further investigations, if any, are requested is left to individual clinicians. This overview aims to review the current evidence for the use of imaging before salvage radiotherapy for a persistently detectable PSA level and a delayed rise in PSA level after radical prostatectomy.

**Definition of Biochemical Recurrence**

Any detectable level and/or rising PSA after radical prostatectomy should be considered as persistent or recurrent disease. The precise definition of biochemical failure varies from study to study. Although previous studies have suggested a threshold of $\geq 0.4$ ng/ml for biochemical failure, more recent work suggests that a PSA level of $>0.2$ ng/ml is an appropriate threshold to define PSA recurrence, as these patients had a 3-year PSA progression of 100% (95% confidence interval 87–100%) [5]. A European Consensus statement on the management of PSA relapse in patients with prostate cancer also defined PSA relapse after radical prostatectomy as a value of 0.2 ng/ml with one subsequent rise [6]. Ultrasensitive PSA assays that detect serum PSA levels $<0.01$ ng/ml may detect relapse several months or even years earlier than conventional assays, but the clinical usefulness is limited by higher rates of false-positive results.

It should be noted that the PSA level does not always correlate well with the tumour burden and that there are numerous examples of metastatic disease in the absence of significantly elevated PSA levels, particularly when the tumours are poorly differentiated.

The 2004 European consensus suggested that secondary treatment after local failure of radical prostatectomy should be initiated when PSA levels reach 1.0–1.5 ng/ml and salvage radiotherapy should be considered with or without hormonal therapy [6]. However, more recent reports suggest that results are best when the PSA level is $<0.5$ ng/ml and the general feeling is that the lower the PSA level at the time of salvage, the better the result [7].

**Significance of Biochemical Recurrence**

Although biochemical recurrence is accepted as a surrogate end point for defining treatment outcome and as an indication for salvage treatment, the clinical significance in terms of overall and clinical disease-free survival remains unclear. Even in men who develop biochemical recurrence, clinical progression may take many years to manifest and, hence, the benefit of local treatment in terms of prostate cancer-specific mortality is questionable. In one series of 1132 patients, those with rising serum PSA levels after radical prostatectomy had a 10-year survival rate of 88% compared with 93% for those without biochemical recurrence ($P = 0.94$) [8]. A report from Johns Hopkins Hospital showed that when 304 patients with PSA-only recurrence were observed without treatment, only 34% developed clinically evident metastatic disease at an average of 8 years and the median time to death after the development of metastases was 5 years. In survival analysis, a time to biochemical progression of less than 2 years ($P < 0.001$), a Gleason score of 8–10 ($P < 0.001$) and a PSA doubling time of less than 10 months ($P < 0.001$) were predictive of the probability and time to the development of metastatic disease [9].

A retrospective study of men who received salvage radiotherapy found the following clinicopathological features to predict for progression after radiotherapy: Gleason score of 8–10, negative surgical margins, seminal vesicle invasion, PSA level greater than 2 ng/ml or a PSA doubling time of less than 10 months [10]. In contrast, however, local recurrence without metastases is suggested
by a > 10 month PSA doubling time, a Gleason score of 7 or less, a positive surgical margin, negative seminal vesicles and negative lymph nodes [7,11]. On the basis of this observation, a nomogram has been constructed with the intention of optimising patient selection for salvage radiation [7].

The key question remains whether a PSA rise is reflective of local or distant progression. There is some evidence that local progression is a more dominant component of failure than metastasis. In a post-mortem study, residual prostatic cells were found in the prostate bed in 50% of cases [12] and biopsy studies also showed that in 38–50% of cases there was evidence of adenocarcinoma in the urethrovessical junction and prostate bed with or without abnormal digital rectal examination [13,14]. In addition, it has been observed that after salvage local radiotherapy, the PSA level falls significantly in up to 80% of cases, suggesting that local persistence or progression is a major component of the rising PSA level [15,16]. Analysis of patterns of failure in the SWOG 8794 study showed the likelihood of local vs distant failure at 10 years to be dependent on the post-surgical PSA level. For PSA levels <0.2 ng/ml, local failures occurred in 20% of patients who did not receive radiotherapy, compared with 12% of distant failures. In patients with post-surgical PSA levels >1.0 ng/ml, the corresponding figures were 28% vs 44% [17].

With the development of intensity-modulated radiotherapy and image-guided radiotherapy, there is the potential to escalate the dose of radiotherapy in areas of known disease recurrence, so that accurate identification of local recurrence with pelvic imaging might improve the effectiveness of tumour eradication. It has been shown that increasing the dose of salvage radiotherapy from 60 to 70 Gy improves 5-year biochemical relapse-free survival from 25 to 58% [18]. This highlights the importance of imaging studies not only in excluding metastatic disease, but also in identifying the location of small foci of locoregional disease that can be targeted with intensity-modulated radiotherapy and treated to higher doses, improving the chance of long-term control.

**Investigations**

The major objective of investigations is to rule out the presence of metastatic disease, which would obviate the need for local radiotherapy. However, the yield of conventional investigations is extremely low for men with PSA-only progression. There are difficulties in interpreting the literature, particularly due to the typically small sample sizes and the heterogeneity of study populations (pre-treatment, post-radiation, postoperative persistent or recurrent PSA). There is also a significant variation in defined end points (clinical, biochemical and pathological) and in the length of follow-up reported. One particular problem is how to report the sensitivities and specificities of different techniques, given that there is no definitive way of confirming the results. Many publications use a clinical or biochemical response to subsequent local salvage radiotherapy as evidence of a locoregional recurrence and equate this response with the pre-salvage imaging results to ascertain the predictive value of the technique.

**Transrectal Ultrasonography and Biopsy**

Transrectal ultrasonography (TRUS) of the prostatic fossa in association with TRUS-guided needle biopsy is considered more sensitive than a digital rectal examination for detecting local recurrence, especially if PSA levels are low. The most common site for a positive biopsy is the vesico-urethral anastomosis (VUA), followed by the anterior or posterior bladder neck [19]. Local recurrence on TRUS is usually represented by a hypoechoic lesion or a fullness of the VUA. However, TRUS is unlikely to detect minimal tumour mass at very low PSA levels (<1 ng/ml) and the role of a biopsy of the VUA remains unclear, specifically whether there is really a need to take a biopsy in the event of PSA failure.

Evidence from case series of men with post-radical prostatectomy biochemical recurrence suggest positive biopsy rates of between 38 and 55%, often requiring biopsies on more than one occasion [13,14,19–21]. The problem is that a positive biopsy does not preclude metastatic disease and a negative biopsy does not preclude local recurrence, so treatment decisions cannot be based on these results. Our recommendation is that TRUS biopsy should not be routinely carried out in PSA failure after surgery.

**Skeletal Scintigraphy (Bone Scan)**

Skeletal scintigraphy (bone scan) is probably the most common study requested in the setting of a rising PSA level after prostatectomy. The documentation of bone metastases would obviate the need for salvage radiotherapy. However, in a series of 93 men with PSA-only recurrence, the probability of a positive bone scan was less than 5%, unless the serum PSA value was above 40 ng/ml [22]. There was a similar (5–8%) rate of indeterminate scans, raising questions over the specificity of bone scans in this situation. The lowest serum PSA value associated with a positive bone scan in the absence of adjuvant hormone therapy was 46 ng/ml. This level is well above the threshold at which salvage radiotherapy is normally considered.

These findings have been confirmed by a more recent study that showed that bone scans were unlikely to be positive unless the PSA doubling time was less than 6 months. In patients with biochemical recurrence after prostatectomy, the rate of positive bone scans was 26% if PSA doubling time was less than 6 months, but only 3% if greater than 6 months [23]. A rapid slope of rise of PSA of 0.50 ng/ml per month has also been shown to be predictive of a positive examination [24]. Gomez et al. [25] found a 33% positivity rate of bone scans taken on 35 patients with biochemical recurrence, but no patient with a PSA level <7 ng/ml had a positive scan.

These studies suggest that a bone scan should only be considered if there are symptoms of bone disease, a very high baseline PSA level (>10 ng/ml) or a high PSA velocity (>0.5 ng/ml/month). A nomogram has been suggested to predict the likelihood of a positive bone scan result in patients with elevated PSA after prostatectomy [26]. Different ranges of postoperative PSA, Gleason score and
surgical margins were grouped together with postoperative reference points, such as trigger PSA (the value prompting the bone scan request), PSA velocity, PSA slope and PSA doubling time. On multivariate analysis, PSA slope, PSA velocity and trigger PSA predicted for a positive bone scan. For trigger PSA levels of 10 ng/ml or less (median 8.4 ng/ml), bone scans were positive in only 4% of cases.

It should be noted that there have been recent improvements in bone scanning techniques with the availability of multiple rotational views, especially relevant to imaging the sacrum behind the bladder, a common source of metastases in prostate cancer.

Abdominopelvic Computed Tomography

Computed tomography plays an important role in detecting pelvic and retroperitoneal nodal disease in the initial staging of prostate cancer, with a reported sensitivity of 78% and specificity of 97% [27]. However, the sensitivity of abdominopelvic computed tomography for the detection of low-volume recurrent disease is limited, particularly when PSA levels are low. Studies have shown computed tomography to be positive in only 11–14% of men with biochemical relapse after radical prostatectomy [24,28]. The mean PSA value associated with a positive computed tomography examination was 12.4 ng/ml and the mean PSA velocity was 30.6 ng/ml/year [28]. One of the problems with computed tomography is that soft tissue density is often seen in the prostate bed, particularly around the bed of the seminal vesicles, and this scar tissue may be confused with local recurrence (see Fig. 1a).

Even in biopsy-proven pelvic recurrence, computed tomography has a low sensitivity; in a group of 22 post-radical prostatectomy patients with biochemical recurrence and local disease confirmed on TRUS biopsy, only 36% had findings consistent with recurrence on retrospective review of pelvic computed tomography examinations [29].

In summary, there is no role for routine computed tomography in biochemical progression/recurrence, unless perhaps if there is a high PSA value or velocity. The computed tomography examination does, however, play an important role in radiotherapy treatment planning to define the prostate bed target volume (see Fig. 1b).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has gained increasing favour in the evaluation of the postoperative patient with biochemical recurrence. Endorectal coil MRI has been shown to be a useful method in evaluating local recurrence in men with a rising PSA level [30]. Local recurrences have been shown to be isointense on the T1-weighted images and hyperintense on the T2-weighted images compared with adjacent muscle and the recurrences enhance with gadolinium administration.

Endorectal MRI may also have a role in defining target volumes for salvage radiotherapy after prostatectomy. In a substantial number of cases, remnants of the seminal vesicles are identified. Sella et al. [30] reported that seminal vesicle remnants were seen on 20% of MRIs carried out after prostatectomy. This residual seminal vesicle needs to be included in the salvage radiotherapy target volume if pathologically involved [31]. Similarly, any postoperative remnants of prostatic tissue should be included. MRI identified an area of local recurrence in 39 of 41 patients defined as having a local relapse based on positive biopsy results, a PSA decline after salvage radiotherapy or serial imaging showing tumour enlargement [30]. In a recent study, Miralbell et al. [32] showed that MRI can identify residual disease with PSA levels ranging from 0.05 to 13.3 ng/ml (median 0.87 ng/ml), typically in the inferior and posterior region of the VUA.

Advances in MRI, such as higher strength magnets, promise improved resolution, which may reduce the need for the endorectal coil and enable better coregistration with computed tomography planning scans. MRI also plays a role in the evaluation of the axial skeleton for bone metastases, particularly if the bone scan is equivocal (see Fig. 2).

The utility of MRI can be improved by using alternative imaging agents and acquisition techniques. Dynamic contrast-enhanced MRI (DCE-MRI) enables the evaluation of vascular parameters such as flow and permeability while contrast is infused over a period of time. There is emerging evidence that this technique is more sensitive than conventional T2-weighted MRI in the diagnosis of prostate

Fig. 1. (a) Computed tomography scan from a patient with biochemical relapse after prostatectomy, showing residual seminal vesicles and surgical clips. (b) Computed tomography radiotherapy planning scan delineating the clinical target volume (CTV) and the planning target volume (PTV).
cancer and also in the assessment of relapse after radiotherapy [33,34]. Patients about to undergo prostatectomy were imaged with conventional and DCE-MRI and the location of the tumour on imaging was compared with subsequent histology. DCE-MRI was more sensitive for tumour localisation than T2-weighted MRI (50% vs 21%, \( P = 0.006 \)) with similar specificity (85% vs 81%, \( P = 0.593 \)) [35]. However, these findings are not universal: a prostate biopsy study did not confirm significant improvements in sensitivity of DCE-MRI over T2-weighted MRI, and the specificity may even be less [36]. In a group of patients at high risk of post-prostatectomy recurrence, DCE-MRI has been correlated with TRUS biopsy and found to have a sensitivity of 71% and a specificity of 94% in predicting recurrence [37]. Vascularity and contrast enhancement can be reduced in patients who have received androgen ablation, which may limit the application of this technique.

A quicker and more simple technique that does not require contrast infusion is diffusion-weighted imaging (DWI). Apparent diffusion coefficient maps are produced that enable a quantitative assessment of the prostate or prostate bed. It has been shown that combined T2 and DWI-MRI is better at detecting cancer in the peripheral zone of the intact prostate than T2 imaging alone, improving the sensitivity from 54 to 81% with only a slight loss in specificity (84 to 91%) [38,39]. As with most techniques, studies have concentrated on the initial staging and diagnosis of prostate cancer and it remains to be shown whether there is a role for DWI-MRI in biochemical recurrence post-prostatectomy.

The use of superparamagnetic iron oxide nanoparticle contrast agents has been shown to improve the sensitivity of MRI in the detection of lymph node metastases. These nanoparticles are internalised by macrophages within lymph nodes and result in changes in the magnetic properties. In a study of 80 patients with T1-3 prostate cancer who subsequently underwent surgical lymph node resection or biopsy, conventional MRI detected pathologically involved nodes with a sensitivity of 35.4%, compared with 90.5% for MRI with nanoparticle contrast agents [40]. This technique warrants further investigation in post-prostatectomy patients with biochemical recurrence.

Positron Emission Tomography

The use of conventional positron emission tomography (PET) tracers such as \(^{18}\)F-fluorodeoxyglucose (FDG) in urological tumours is limited by a relatively low uptake by the primary tumour (due to a low glycolysis rate in most prostate cancers) and the renal excretion of the isotope, resulting in collection in the bladder, thus obscuring any local uptake. It cannot reliably differentiate between primary prostate cancer, benign prostatic hyperplasia and postoperative scar. Although PET has a lower sensitivity for bone metastases than a radionuclide bone scan, there may be some value in the assessment of metastatic disease, particularly with the improved resolution obtained with computed tomography fusion scans.

\(^{11}\)C-labelled choline is incorporated into cell membranes as phosphatidylcholine (membrane lipid synthesis is

![Fig. 2. This post-prostatectomy patient was observed to have a biochemical recurrence with a prostate-specific antigen level of 0.4 ng/ml. (a) A magnetic resonance imaging scan showed no evidence of tumour recurrence, pelvic lymphadenopathy or bone metastases. (b) A bone scan revealed a solitary focus of increased uptake in the posterolateral aspect of the right eighth rib. Plain films of this area were unremarkable. In the absence of other abnormal foci, this probably represents a benign cause and is not convincing for skeletal metastases.](image-url)
activated during cell proliferation) and has the advantage of a virtual absence of urinary radioactivity. $^{11}$C-choline has been studied as a PET tracer in prostate cancer, showing avid uptake by the tumour and involved lymph nodes, but little background uptake (non-specific uptake is seen in the intestines). This technique may prove useful in preoperative assessment of lymph node involvement in prostate cancer or for restaging tumours with increasing serum PSA levels. $^{11}$C-choline PET may be able to detect local recurrences or distant metastases in about half of patients [41], although the yield in patients with low PSA levels may be lower. Modern PET/computed tomography fusion imaging techniques may give improved results, localising recurrent disease in up to 70% of patients with biochemical relapse. There are reports of a sensitivity of as high as 91% in the detection of tumour recurrence in patients with PSA levels <2.5 ng/ml [42]. Scattoni et al. [43] evaluated the detection of lymph node metastases with $^{11}$C-choline PET/computed tomography examinations in patients with biochemical relapse by correlation with lymph node dissection. Nineteen of 21 patients (90%) with positive $^{11}$C-choline PET/computed tomography had nodal metastases of prostate adenocarcinoma at histological evaluation [43]. However, a cautionary note is identified by Schilling et al. [44], who found that three of 10 patients with positive examinations showing pelvic nodal metastases had no tumour confirmed on pathology, suggesting a worrying false-positive rate.

It should be noted that $^{11}$C has a short half-life of about 20 min, compared with 110 min for $^{18}$F. This raises practical problems for such tests and essentially restricts usage to facilities with a local cyclotron.

To this end, $^{18}$F-choline PET/computed tomography has been investigated and found to detect disease relapse in 43% (24/56) of patients with increased PSA levels after radical prostatectomy. The sensitivity of this technique was closely linked to PSA levels, with a sensitivity of 20% if PSA <1 ng/ml, but over 80% if PSA >5 ng/ml [45]. A similar study in 100 patients with biochemical recurrence (which included patients treated by radiotherapy and endocrine therapy as well as radical prostatectomy) concluded that $^{18}$F-choline PET/computed tomography would probably not detect recurrence unless the PSA level was over 4 ng/ml [46].

Another potentially useful PET tracer is $^{11}$C-acetate, the uptake of which is linked to proliferation via acetyl-coenzyme-A activity. It may have a role in prostate cancer, where higher sensitivities than FDG-PET have been shown [47]. As with radiolabelled choline, there is minimal excretion of the tracer into the renal collecting systems. Similar success rates to $^{11}$C-choline PET have been seen in identifying sites of recurrence in biochemical relapse after radical prostatectomy, with 73% anatomical site definition.

A recent study casts some doubt over the reliability of PET in evaluating recurrence after prostatectomy. Twenty patients with PSA levels <1 ng/ml after radical prostatectomy received PET/computed tomography studies with either $^{18}$F-choline or $^{11}$C-acetate. Only half were found to have abnormal PET tracer uptake, although 15 of 18 who also underwent endorectal MRI examinations had evidence of local recurrence [48].

**Capromab Pendetide Scans**

The $^{111}$In-capromab pendetide scan (ProstaScint®) utilises an IgG monoclonal antibody that binds to the prostate-specific membrane antigen on prostatic epithelial cells, but not to PSA or prostatic acid phosphatase. Prostate-specific membrane antigen is expressed more abundantly in malignant tissue than in normal tissue.

![Fig. 3. (a) $^{111}$In-capromab pendetide (ProstaScint®), (b) computed tomography and (c) fusion images of a patient with prostate-specific antigen relapse after prostatectomy. The computed tomography scan was equivocal but the Prostacint and fused images showed retroperitoneal uptake suspicious for paracaval metastases. (Figure courtesy of ELISAPharma Ltd)
Studies report a sensitivity of 75%, a specificity of 86% and an overall accuracy of 81% in the detection of extraprostatic disease in high-risk prostate cancer patients [49]. ProstaScint/C210 scans have been shown to detect occult metastatic disease in about 25% of men who were thought to have isolated local recurrence. Hence, this technique may play an important role in differentiating local failure from metastatic recurrence after radical prostatectomy to allow for a better selection of patients for salvage radiotherapy (see Fig. 3).

As with the PET techniques, this method of imaging is best utilised with image fusion to compare with anatomical (computed tomography or MRI) images. ProstaScint seems to be sensitive even at low PSA levels, with one study identifying abnormal uptake in 85% of post-prostatectomy patients, with a median relapsed PSA level of 1.2 ng/ml (range 0.2–4.8 ng/ml) [50]. However, in this same study, Prostascint positivity did not predict for a durable response to radiation. This was confirmed by Koontz et al. [51], who found no correlation between Prostascint results and the

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Results</th>
<th>References</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>No. patients</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transrectal ultrasound + biopsy</td>
<td>38–55% positive for local recurrence</td>
<td>[13]</td>
<td>75%</td>
<td>66%</td>
<td>119</td>
<td>Not routinely recommended</td>
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<tr>
<td></td>
<td>Negative biopsy does not preclude local recurrence</td>
<td>[19]</td>
<td>76%</td>
<td>67%</td>
<td>99</td>
<td>No information regarding distant recurrence</td>
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<tr>
<td>Bone scan</td>
<td>5% positive if PSA &lt;40 ng/ml (&lt;1% if PSA &lt;10 mg/ml)</td>
<td>[22]</td>
<td>NA</td>
<td>NA</td>
<td>93</td>
<td>Recommended if: PSA doubling &lt;6 months or PSA velocity &gt;0.5 ng/ml/month or absolute PSA level &gt;10 ng/ml</td>
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<tr>
<td></td>
<td>26% positive if PSA doubling time &lt;6 months, 3% positive if PSA doubling time &gt;6 months</td>
<td>[23]</td>
<td>NA</td>
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<td></td>
<td>None positive if PSA &lt;7 ng/ml</td>
<td>[25]</td>
<td>NA</td>
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<td>Abdominopelvic computed tomography</td>
<td>14–36% positive scans in biochemical recurrence</td>
<td>[29]</td>
<td>36%</td>
<td>NA</td>
<td>22</td>
<td>Not recommended for restaging, but important role in defining salvage radiotherapy target volumes Low sensitivity for detecting local recurrence at low PSA levels</td>
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<td></td>
<td>Negative biopsy does not preclude local recurrence</td>
<td>[24]</td>
<td>NA</td>
<td>NA</td>
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<td>MRI</td>
<td>95% of biopsy-proven local recurrences were visible on MRI</td>
<td>[30]</td>
<td>95%*</td>
<td>100%*</td>
<td>41</td>
<td>May be considered to assess pelvic nodes if rapid PSA rise Useful for identifying residual seminal vesicles DCE-MRI may have higher sensitivity then standard MRI techniques, but still largely investigational</td>
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<td></td>
<td>(DCE-MRI)</td>
<td>[37]</td>
<td>71%</td>
<td>94%</td>
<td>70</td>
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<tr>
<td>Positron emission tomography</td>
<td>11C-choline positron emission tomography reveals positive uptake in about 50% of cases with low PSA levels (&lt;1 ng/ml)</td>
<td>[48]</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
<td>Not routinely recommended Deserves further investigation — seems to be more sensitive than anatomical imaging in some situations, but less sensitive than MRI at detecting local recurrence when PSA &lt;1 ng/ml</td>
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<td></td>
<td>18F-choline: sensitivity dependent on PSA levels</td>
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<td></td>
<td></td>
<td>[43]</td>
<td>64%</td>
<td>90%</td>
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<td></td>
<td></td>
<td>[45]</td>
<td>20–80%</td>
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<tr>
<td>Prostascint® scans</td>
<td>Reports of up to 85% positive uptake at low PSA levels (median 1.2 ng/ml)</td>
<td>[50]</td>
<td>86%</td>
<td>47%</td>
<td>42</td>
<td>Seems to be more sensitive than anatomical imaging at low PSA levels Not routinely recommended</td>
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<td></td>
<td></td>
<td>[49]</td>
<td>75%</td>
<td>86%</td>
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<td></td>
<td></td>
<td>[52]</td>
<td>76%</td>
<td>54%</td>
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PSA, prostate-specific antigen; MRI, magnetic resonance imaging; DCE, dynamic contrast enhanced.

* In a restricted group (see text).
efficacy of salvage radiotherapy – patients with a positive examination for local recurrence had no difference in progression-free survival from those with a negative examination.

As with the novel PET tracer techniques, there have been many small studies published, with a wide range of reported specificity, sensitivity and predictive values [52–55]. The largest of these studies examined 255 patients with biochemical failure and a PSA level ≤4 ng/ml. The sensitivity of Prostascint for detecting disease recurrence was 76%, with a specificity of 54% and a positive predictive value of 90% [52]. However, a recent publication claimed a positive predictive value of only 27% in the ability of Prostascint to detect disease outside the surgical bed, and therefore concluded that salvage radiotherapy should be considered on the basis of a raised PSA level, irrespective of the Prostascint results [55].

Recommendations

Given the previously identified clinicopathological factors that define the risk of metastatic vs local disease, it is tempting to define patient risk groups orientated towards different imaging pathways. Different combinations and sequences of radiographic studies could be recommended based on the likely yield of useful information.

These risk groups might be identified based on:

(1) Pre-surgical prognostic variables (baseline PSA level)
(2) Prostatectomy pathology (Gleason score, margin status, extracapsular extension, seminal vesicle involvement, lymph node status)
(3) Post-prostatectomy variables (time to PSA detection, PSA velocity and doubling time, absolute PSA value at time of testing)

Before proceeding with salvage radiotherapy, a bone scan should be requested in the presence of factors that predict for a high risk of metastatic disease. These include a high initial pre-surgical PSA level (>10 ng/ml) or unfavourable PSA kinetics (PSA velocity >0.5 ng/ml/month) at the time of biochemical relapse.

In patients with factors that indicate a high risk of locoregional recurrence, a prostate MRI examination should be considered. These factors include positive surgical margins, extracapsular extension or seminal vesicle involvement at the time of surgery.

However, for the most part, current practice is to treat with salvage radiotherapy for a rising PSA without the need for imaging or biopsy evidence of local recurrence, accepting that current techniques may not be sensitive enough to detect small volume local disease (see Table 1).

Imaging is primarily aimed at excluding metastatic disease and, hence, identifying patients who would not benefit from salvage radiotherapy. Evidence suggests that bone scan and pelvic nodal assessment with computed tomography or MRI are not necessary before starting radiotherapy unless the PSA velocity is rapid, although there is no well-defined cut-off value. The sensitivity of current imaging techniques in detecting disease recurrence falls short of the sensitivity of PSA detection. Functional imaging techniques, such as PET or antibody scintigraphy, may prove useful in identifying patients with early metastatic disease not evident on current standard imaging. These techniques have been studied, but reports as to their utility in this situation are conflicting and further investigation is warranted.

References


[48] Vees H, Buchegger F, Albrecht S, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. BJU Int 2007;99(6):1415–1420.


