

# Will focal therapy become a standard of care for men with localized prostate cancer?

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## SUMMARY

The current treatment choice for men with localized prostate cancer lies between active surveillance and radical therapy. The difference between these two extremes of care is 5% in terms of cancer-related absolute mortality at 8 years. It is generally accepted that this small difference will decrease for men diagnosed in the prostate-specific-antigen era. Radical therapy is associated with considerable adverse effects (e.g. incontinence, impotence, rectal problems) because it treats the whole gland, and damages surrounding structures in up to half of men. Men are being diagnosed at a younger age with lower-risk disease, and many have unifocal or unilateral disease. We propose a new concept whereby only the tumor focus and a margin of normal tissue are treated. This paradigm might decrease adverse effects whilst, at the same time, retaining effective cancer control. The arguments for and against active surveillance and radical therapy are reviewed in this article, with focal therapy presented as a means for bridging these two approaches.

**KEYWORDS** focal therapy, hemiablation, multisequence MRI, prostate cancer, template biopsies

## REVIEW CRITERIA

The information for this review was compiled by searching the PubMed and MEDLINE databases for articles published until 5 February 2007. Electronic early-release publications were also included. Only articles published in English were considered. The search terms used included "prostate cancer" in association with the following search terms: "PSA screening", "natural history", "prostatectomy", "radiotherapy", "active surveillance", "watchful waiting", "transperineal biopsy" and "MRI".

## CME

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## Learning objectives

Upon completion of this activity, participants should be able to:

- 1 List the reasons cited for whole-gland therapy for localized prostate cancer.
- 2 Identify the components of active surveillance for localized prostate cancer.
- 3 List the side effects associated with whole-gland therapy.
- 4 Identify the modalities suitable for focal therapy for prostate cancer.
- 5 List the features not amenable to focal therapy in men with localized prostate cancer.

## INTRODUCTION

A difficult therapeutic dilemma awaits any man diagnosed with localized prostate cancer. Following all staging investigations, the patient will eventually be forced to choose between radical therapy and active surveillance (AS). The former maximizes the chance of cure, but with near certainty of either sexual or urinary morbidity.<sup>1,2</sup> With the latter, genitourinary function is preserved in exchange for the psychological and health care burden of intensive surveillance.<sup>3,4</sup> As prostate-specific antigen (PSA) screening becomes more widespread, it is likely that this therapeutic dilemma will challenge a greater number of men. Screening has the effect of identifying cancers that are of lower risk in men who are younger, compared with older men who are diagnosed outside screening programs.<sup>5</sup> In these younger men, the benefits associated with treating low-risk disease will be less than those with more-severe disease,<sup>6,7</sup> and,

at the same time, the desire to preserve sexual and urinary function will be greater.<sup>8</sup>

In this article, we assert that using a novel approach—that we shall term ‘focal therapy’—might be almost as effective as using radical (whole gland) treatment whilst matching the low adverse effects associated with AS. In other words, compared with patients treated with whole-gland therapy, a significant proportion of men with organ-confined, low to moderate risk prostate cancer who undergo ablation of only malignant tumor foci will be conferred acceptable freedom from disease progression and will have a high probability of preserving genitourinary and bowel function. A departure from standard care as extreme as the one we propose requires a robust justification. To that end, we will start by discussing the merits and limitations of both whole-gland therapy and AS.

#### JUSTIFYING WHOLE-GLAND THERAPY

There are four reasons why whole-gland therapy has been the standard of care for so long. First, prostate cancer has always been regarded as multifocal. Histological studies, however, have shown that a considerable number of men diagnosed in a contemporary setting have unilateral or unifocal disease. In men undergoing radical prostatectomy, 10–40% have unilateral disease<sup>9–14</sup> and 10–44% have unifocal tumors.<sup>15–18</sup> These data raise the possibility that half-gland treatment (hemiblation) or focal ablation of tumor foci alone might be possible for between 10% and almost 50% of patients who would currently receive whole-gland treatment. Nonetheless, these studies might still underestimate the extent of unilateral or unifocal disease. Men who are advised and agree to undergo surgery are the product of numerous selection events that are likely to over-represent the proportion with multifocal disease. This hypothesis is not easy to prove because evaluating whole-gland histology in those successfully managed by AS regimens is clearly impossible. Indirect retrospective evidence, however, has shown that men who chose radical treatment were more likely to have high-risk disease.<sup>19</sup> In addition, a prospective study in men who underwent diagnostic saturation biopsies indicated that those who had radical prostatectomy not only had higher Gleason scores, but also had larger cancer volumes at higher clinical stage than those who did not have prostatectomy.<sup>20</sup>

Moreover, within the concept of ‘multifocality’ is the inclusion of small tumors that could represent clinically insignificant or ‘indolent’ disease. One group showed that, other than the largest tumor, 80% of tumor foci have a volume of less than 0.5 cc.<sup>21</sup> With the accumulating evidence that shows that progression is mediated by index tumors of large volume (>0.5 cc) and high grade (Gleason score  $\geq 7$ ),<sup>22,23</sup> it could be argued that small, low-grade foci could be kept under surveillance.<sup>24–26</sup> Such a claim regarding tumor volume is contentious, and there are data that show no such relationship between increasing tumor volume and outcome after radical treatment.<sup>27</sup> Despite this controversy, the notion that large, high-grade tumors drive the natural history in those men with aggressive disease raises the possibility that not all foci need to be treated.<sup>18</sup> Rather than ablate all tumor foci, it might be reasonable to destroy only the index tumor(s) and to place patients on AS for the untreated areas.

The second group of evidence used to justify whole-gland therapy are data indicating field effect changes in normal tissue adjacent to cancer foci.<sup>28–30</sup> For prostate cancer, most of the evidence for field effect points to changes in the immediate vicinity of the cancer focus; therefore, it is assumed that an adequate margin around the malignant focus would be included in focal therapy. Although other studies have demonstrated subtle changes in areas distant from cancer foci, the relevance of such changes and their natural history are unknown.<sup>31</sup> If cancer within the prostate is progressing slowly in the majority of cases, then it is arguable whether these supposed field effect changes will be clinically relevant in the lifetime of a man after he has undergone focal therapy. Regardless, when field change occurs in other cancerous organs, such as the bladder, breast, colon, and kidney, it tends to be ignored when applying treatment. Treatment for the majority of these patients is zonal or regional, with surveillance of the remaining tissue. The objectives are to preserve function, body image and quality of life, whilst reducing the probability of disease-specific progression. In the treatment of breast cancer, it is recognized that adjuvant radiotherapy is required after wide local excision. For other cancers, such as colon and renal cancer, adjuvant radiotherapy might not be needed, and this could also be the case for prostate cancer when focal therapy is used. If recurrence

rates are high in the untreated tissue, however, adjuvant radiotherapy could be administered in lower doses with little additional toxicity.<sup>32</sup> Such an approach would deal with field effect changes in prostate cancer in a similar manner to that of breast cancer therapy. Nonetheless, if this additional therapy resulted in levels of adverse effects equivalent to those of radical treatment, then focal therapy would be deemed to have failed.

Third, it is asserted that prostate cancer cannot be reliably localized within the gland so whole-gland treatment is required. There is a growing amount of evidence from developments in prostate mapping biopsies, as well as from MRI studies, that indicates that this position is increasingly difficult to defend. These techniques will be discussed later. Fourth, whole-gland therapy has been justified because focal therapy has not been possible until relatively recently. The attributes of surgical and radiotherapeutic methods mean that subtotal treatment is not currently possible. It is the refinement of ablation therapies—cryosurgery, high-intensity focused ultrasound (HIFU), photodynamic therapy and radiofrequency therapy—that ablate small discrete areas of tissue and leave adjacent tissue viable that has made it possible to at least conceptualize a novel approach to this condition.

#### LIMITATIONS OF WHOLE-GLAND THERAPY

The best information on the superior efficacy of whole-gland therapy compared with that of AS comes from a Scandinavian randomized controlled trial of radical prostatectomy versus watchful waiting.<sup>7</sup> At a median follow-up of 8 years, random allocation to surgery was associated with a reduction in disease-specific mortality from 14% to 9% ( $P=0.01$ ). This significant difference has increasingly been used to justify the superiority of radical surgery over surveillance.<sup>33</sup> There are two reasons why this justification should be tempered. First, the Scandinavian trial was largely based on patients with clinically palpable disease. Only 12% of the patients had PSA-detected disease and 20% had PSA levels greater than 20 ng/ml. These data are not readily translated compared with data obtained in the PSA-screening era.<sup>34</sup> Second, PSA screening results in over-detection of indolent cancer,<sup>35</sup> which introduces a lead-time bias of at least 10 years.<sup>36</sup> With a more favorable course for disease detected by screening, we

would expect a mortality rate of around 7–11% at 15 years in patients on watchful waiting,<sup>37</sup> and possibly a lower mortality rate in those with low-risk disease.<sup>38</sup>

Disease-specific mortality would be different for low to moderate risk patients placed on AS regimens rather than on 'watchful waiting'. Modern AS regimens involve radical delayed intervention targeted to those who progress during close observation. Evaluation of progression is based on digital rectal examination, a biochemical PSA doubling time (PSADT) of less than 3 years, or a histological grade or burden progression on repeat biopsy. This regimen contrasts with traditional watchful waiting, whereby palliative treatment is instituted in those with symptomatic progression. Cohort studies assessing true AS have shown a disease-specific mortality of only 0–1% at 8 years.<sup>3,4,39</sup> Clearly, the weakness of this approach is the use of surrogate markers such as PSADT, which are derived from predictors of poor outcome after radical treatment. The Toronto AS series switched mid-way through the study from a PSADT of 2 years to one of 3 years, in order to relax the rules for intervention. The PSADT of 3 years is also based on data provided by D'Amico *et al.*,<sup>40</sup> which showed that, before surgery, a PSA velocity of 2 ng/ml per year predicted poor outcome; this result has contentiously been equated with an approximate PSADT of 3 years if the initial PSA was 6 ng/ml.<sup>3</sup> Equally, mortality rates of less than 1% for AS regimens perhaps indicate an early success of this approach, despite such reservations.

The decision to choose radical therapy is confounded not only by the lack of clear evidence for a survival benefit, but also by the degree of morbidity. The adverse effects of radical therapy are caused by the inevitable injury of surrounding structures—such as the pelvic nerves and/or ganglia, bladder neck, bladder, seminal vesicles, rhabdosphincter, Denonvilliers' fascia, and rectum—when delivering treatment to the whole gland. Although the toxicity profile depends on the treatment modality, the different whole-gland treatments share a remarkable similarity. In summary, radiotherapy causes, on average, moderate recto-anal toxic effects and urinary problems in almost 50% of patients in the short term, with nearly all suffering minor symptoms.<sup>41</sup> These adverse effects improve over time, although bowel toxicity can persist in 5–20%

of patients in the long term.<sup>42</sup> Surgery causes fewer rectal problems than does radiotherapy, but a third of men suffer chronic urinary symptoms. Importantly, both modalities give rise to impotence in at least half of those treated.<sup>43,44</sup> Efforts to reduce morbidity have centered on refining methods of surgery (i.e. laparoscopic and robotic prostatectomy) or radiotherapy (i.e. intensity modulation and conformal) to restrict damage to surrounding structures. The implementation of these techniques in radical therapy has not reduced genitourinary toxic effects, and has produced limited overall success.<sup>45–47</sup>

### RATIONALE AGAINST ACTIVE SURVEILLANCE

There are three reasons why patients should undergo any treatment other than AS. First, we do not know which groups of patients are suitable for this regimen. Some prognostic indicators can independently predict risk of recurrence after radical treatment for localized disease, such as PSA levels greater than 10 ng/ml, PSADT less than 3 or 4 years, presence of tumor in 50% or more of a single biopsy core, 50% or more positive cores, and Gleason grade 7 or more.<sup>48–53</sup> Most AS regimens exclude men who have any of the aforementioned risk factors at presentation; those excluded would, therefore, be more likely to benefit from treatment. A considerable proportion of these men would be eligible for some form of focal treatment that would aim to control their moderate-risk or high-risk disease but at the same time limit adverse effects.

Second, some men who are deemed to be at low risk and are recruited into an AS program will cross over to radical therapy. Current estimates of the numbers of these men vary and probably reflect differences in enrollment criteria and surveillance intensities. One UK series has recently updated its figures. Over a short follow-up period (median 22 months), the authors reported a crossover rate of 19.9% (65/326)—9.8% (32/326) demonstrated biopsy progression, 10.1% (33/326) progressed on PSADT (greater than 4 years) and 12.9% (42/326) progressed on PSA velocity (>1 ng/ml per year).<sup>4,39</sup> A Canadian series that studied 299 men over a longer duration (median 64 months follow-up) reported a 22% crossover rate.<sup>3</sup> The authors reported that 15% of patients progressed on PSA biochemical parameters, 4% on histological measures, and 3% clinically. Interestingly, a further 1.6% and 12% of

men from the respective series opted for radical treatment despite showing no signs of progression. The follow-up period for both series is too short, however, and it might be possible that higher rates of progression will be observed after 10–15 years.<sup>54</sup> There is evidence that men who choose AS do so to avoid the adverse effects and inconvenience associated with radical treatment.<sup>8,55,56</sup> It is likely that these very men would value the harm:benefit profile that we anticipate would be possible with focal therapy, and may be willing to undergo disease characterization with imaging and mapping biopsies at diagnosis or at time of progression in order to assess suitability for this therapy.

Third, the intensive AS follow-up regimen, which includes clinical examination and PSA measurements (every 3–4 months) with regular prostate biopsy (at year 1 and then every 3 years), carries notable physical burden.<sup>3,4</sup> It is possible that focal therapy might require a similar post-treatment surveillance regimen for the remaining untreated tissue, although the intensity of surveillance and biopsy frequency might differ.

### FOCAL THERAPY

It seems reasonable to hypothesize that if a treatment were available that had virtually no genitourinary adverse effects, could be administered as a day-case procedure, and had proven acceptable levels of oncological efficacy, men would choose this option rather than the only current non-radical therapeutic alternative that is AS. The question of whether or not focal therapy is a desirable avenue for scientific enquiry remains pertinent. To date, only two studies have addressed the issue of focal therapy in prostate cancer. Onik *et al.* reported results on hemiablation by the use of cryotherapy,<sup>57</sup> and published a subsequent update on 42 men who completed at least 1 year of follow-up.<sup>58</sup> In total, 95% of men had a stable PSA level, as defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria.<sup>59</sup> Moreover, 9.5% (4/42) of patients required subsequent whole-gland treatment because of cancer detected in the untreated half of the prostate. This group had repeat transrectal ultrasound (TRUS) biopsy, rather than transperineal template biopsies, to initially verify unilateral disease. At a subsequent stage in the study, the investigators changed to using template biopsies to verify unilateral cancer. Interestingly, of those

men who were potent before hemiablation, 78% (25/32) maintained potency—a considerably high figure considering that whole-gland cryosurgery carries impotence rates in the order of 90%. Although the results from this series were promising, the lack of clear recruitment data, lack of true trial conditions and institutional review board approval, the poor reporting of adverse effects, and the lack of consistent biopsy technique used to verify unilateral cancer, were important limitations. Bahn and coauthors have recently reported on another series of men treated with hemiablation by cryotherapy.<sup>60</sup> At a mean follow-up of 70 months, biochemical disease-free status, according to the ASTRO definition, was maintained by 92.8% (26/28) of patients, and a 96.0% (24/25) negative-biopsy rate was observed. The one positive-biopsy patient was subsequently treated with full-gland cryoablation and remains disease free. Potency was maintained by 48.1% (13/27) of patients and another 40.7% (11/27) were potent with oral pharmaceutical assistance, yielding a total potency-preservation rate of 88.9%. These results are also encouraging, although, as well as the limitations described for the study by Onik *et al.*, the Bahn study had an additional limitation. The investigators used color Doppler-guided TRUS biopsies to verify unilateral disease as well as post-treatment success, but this technique does not carry the necessary accuracy for cancer detection.<sup>61,62</sup>

#### Selecting the right patients for focal therapy

To deliver focal therapy, particular precision is required in localizing the tumor and defining its limits within the gland in order to be confident that other areas are free of clinically important disease (Figure 1). This localization can be done in one of two ways: MRI and transperineal biopsies that use a brachytherapy template.

Prostate imaging has evolved from addressing questions related to locoregional staging to addressing questions that relate to tumor burden and localization of tumor foci within the gland. Advances in MRI have facilitated more-accurate localization of small cancers. Developments such as better resolution from 3 Tesla imaging and the combination of modalities (e.g. T2-weighted imaging, dynamic-contrast enhancement, spectroscopy, and diffusion imaging), so-called multisequencing, should deliver greater accuracy MRI, although this hypothesis has yet to be proven. MRI is not currently

suitable for focal therapy because accuracy rates vary between 40% and 90%. The accuracy limitation in previous studies was due to a number of factors, such as the criteria used to define significant tumors (many studies excluded foci <0.5 cc), whether only peripheral zone tumors were included in the analysis, the method of analysis (studies vary between dividing the gland into 2 to as many as 14 zones), the modality of MRI used, whether endorectal coils were used, and whether the reference standard was TRUS biopsy or whole-mount histology (the latter clearly decreasing the accuracy rate).<sup>63–66</sup> Furthermore, the accuracy for detecting large and high-Gleason-grade tumors is better than that for low-Gleason-grade and small tumors.<sup>67,68</sup> Definitions of true positives have also varied because suspicious areas on imaging do not always correlate to millimeter accuracy with those on step-section histology. When stricter definitions are used, accuracy rates fall.<sup>69</sup> All these limitations within the current literature are obviously important caveats for the use of MRI in localizing cancer foci for the purpose of focal therapy, because it is crucial that all significant tumors are detected. This detection is problematic because the definition of a significant tumor is in itself controversial.

Transperineal biopsies that use a brachytherapy template to direct the needle can be employed to ensure systematic sampling of the whole gland every 5 mm; this approach obtains three-dimensional coordinates of all cancer foci. An accuracy of 95% for detection of all cancer foci was achieved by simulating the technique on computer models that used information derived from whole-mount prostate samples.<sup>70</sup> The prostate is known to move and distort during transperineal needling, and this factor was not considered in the computer model.<sup>71</sup> Another group demonstrated an accuracy of 87% for transperineal ultrasound-guided template biopsy in men before they received radical prostatectomy. This study did not biopsy at every 5 mm grid coordinate, however, which may account for the lower accuracy.<sup>72</sup> Some studies have demonstrated that template biopsies carry no extra risk compared with transrectal biopsies, whilst others have reported an increased rate (about 10%) of urinary retention.<sup>73,74</sup> If multifocal disease were discovered and the patient opted for prostatectomy, it is unclear whether periprostatic fibrosis would affect subsequent surgery. Some groups have shown no particular

effect of fibrosis on surgery,<sup>74</sup> whilst others have reported that surgery is slightly more difficult in such cases but does not increase morbidity.<sup>75</sup> Nonetheless, the requirement for general or regional anesthesia in order to take 20–40 biopsies for a 20–40 cc prostate obviously adds to the health care and financial burden. This cost will need to be taken into account in any assessment of focal therapy. Despite these reservations, it is our belief that, until imaging can accurately define intraprostatic disease, template biopsy carries adequate accuracy to define areas of cancer and facilitate the delivery of focal therapy.

The volume of tissue that could be destroyed before focal therapy develops into whole-gland treatment is unknown. Whether maximum tissue ablation should be set at 75%, 50% or lower will, in part, be determined by other considerations when selecting patients, primarily the proximity of tumor foci to the external sphincter and neurovascular bundles. The physician will need to ensure that the sphincter and at least one neurovascular bundle is preserved in order to minimize adverse effects.

#### Refining the focal therapy intervention

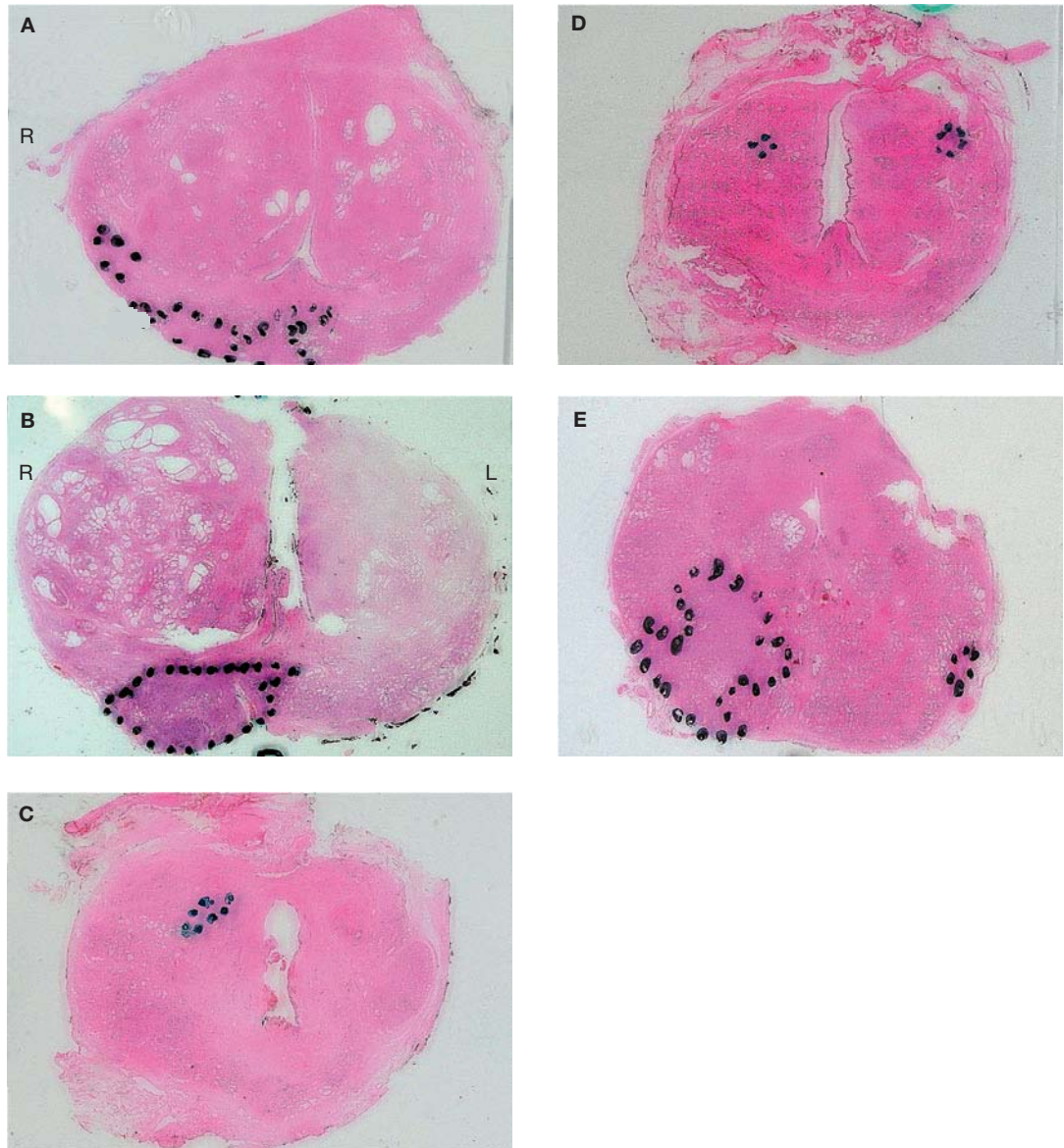
One of the main hurdles to implementing focal therapy was the lack of technologies available that could treat in a focal manner. The modalities cryosurgery, HIFU, photodynamic therapy and radiofrequency ablation are capable of creating localized necrosis within the prostate in a relatively controlled manner.<sup>76</sup> In theory, focused radiotherapy and field-limited dosimetric brachytherapy could also be used for focal ablation. A detailed discussion of these modalities is beyond the scope of this article, but each modality has its own advantages. HIFU offers the prospect of a truly minimally invasive approach, with no breach of mucosa or skin, whilst allowing real-time ultrasound feedback of thermal effects and thus, indirectly, tissue destruction.<sup>77</sup> The problems of translating images from one device to another (as is necessary with HIFU) is overcome in cryosurgery and photodynamic therapy, provided that the set-up of patient and equipment used at the time of the template biopsies is replicated when employing the subsequent modality. If and when MRI can accurately locate tumors, image-registration software will be required to translate magnetic resonance images onto ultrasound devices in order to drive greater ablative precision.

#### Testing the focal therapy hypothesis

Given the points we have raised, we believe that the time is right to propose the following hypothesis: men with localized low to moderate risk prostate cancer who are managed with focal therapy will experience lower rates of genitourinary and rectal adverse effects than men managed with whole-gland therapy, and will have comparable rates of freedom from disease progression.

The most promising way to achieve a marked reduction in treatment-related morbidity might be to direct the therapy at the tumor and not at the whole gland. The first question lies in whether, by preserving most of the prostate and its surrounding structures, the morbidity associated with treatment could be reduced to low levels. The second question is whether such a method would have efficacy for cancer control with respect to recurrence or to biochemical progression-free survival and cancer-specific mortality. Certainly, according to the best data available, a reduction in recurrence and mortality of a few percentage points would render focal therapy equivalent to traditional radical treatments.

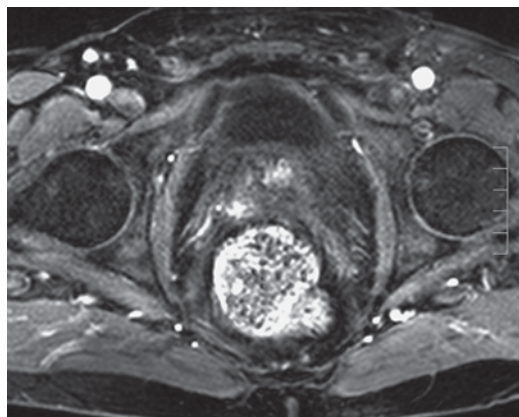
Focal therapy may not be suitable in those men who have large-volume, multifocal, high-Gleason-score disease. For these men, radical treatment would be ideal. Current diagnostic and staging evaluation methods do not have sufficient precision to identify this group. Instituting a technique for precisely localizing and characterizing cancer areas would identify high-risk men more clearly. Equally, by subjecting all men at diagnosis to the level of precise localization that we suggest, the low-risk group—suitable for AS—could also be more clearly defined from the outset. The histological progression rate in patients on current AS regimens might be reduced if it is accepted that a proportion of those who progress had higher-risk disease that was missed on initial TRUS biopsy.<sup>78,79</sup> Treating high-volume disease that has been well characterized and shown to have a low Gleason score might also reduce the number of patients who exhibit biochemical progression. Furthermore, those men on AS who then progress could undergo precise disease characterization at that time in order to stratify them into those suitable for either focal therapy or whole-gland treatment. In other words, selective delayed intervention could involve focal therapy and not just radical treatments.



**Figure 1** Radical prostatectomy step sections. **(A)** This sample shows unilateral prostate cancer (two foci indicated by dotted lines, both Gleason score 7). This case would have been suitable for hemiablation. **(B)** This sample shows unilateral, unifocal prostate cancer (indicated by dotted line; Gleason score 7). This case would have been suitable for hemiablation or focal ablation. **(C)** This sample shows unilateral, unifocal, low-volume prostate cancer (indicated by dotted line; Gleason score 7). This case would have been suitable for focal ablation. **(D)** This sample shows bilateral, low-volume prostate cancer (indicated by dotted lines; Gleason score 7). This case would have been suitable for bilateral focal ablation. **(E)** This sample shows bilateral prostate cancer. The lesion on the right is of large volume, with a Gleason score of 7 (the index lesion). The lesion on the left is of low volume (<0.5 cc), with a Gleason score of 6. This case may have been suitable for either bilateral focal ablation or focal ablation of only the index lesion.

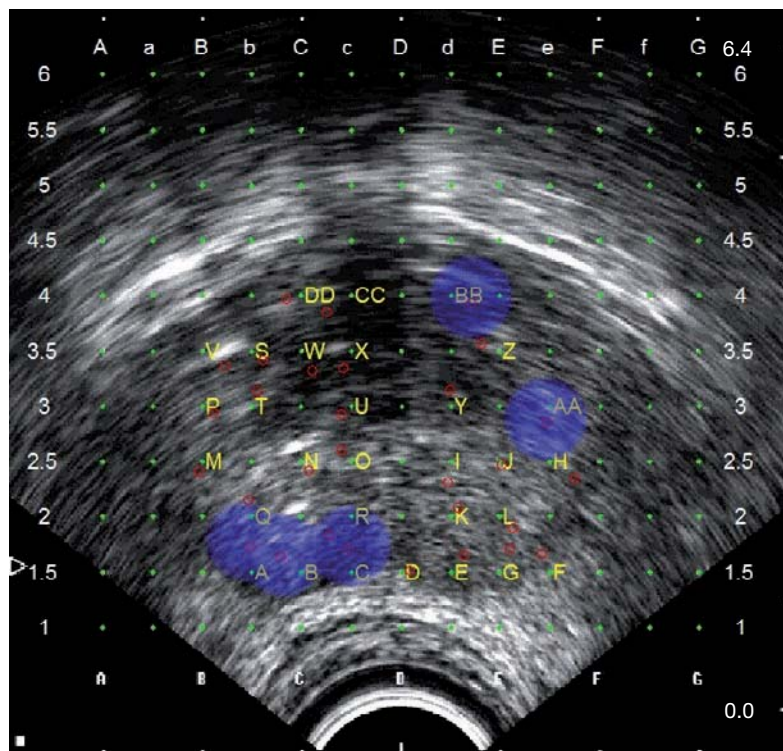
Localization of disease is going to rely heavily on multisequence MRI and prostate mapping using template biopsies (Figures 2 and 3). It is our expectation that these two technologies should be complementary when used together, at least until other technologies are available.

If more-precise ablation is required, then treatment of designated areas within the prostate presents a challenge for the use of HIFU, for reasons of image registration. Treatment should also reflect the inherent sampling inaccuracy of transperineal biopsies, and should be performed



**Figure 2** MRI scan (1.5 Tesla, 15°, T1-weighted dynamic contrast-enhanced (gadolinium) VIBE image) demonstrating avidly enhancing bilateral lesions (right base and left anterior; same patient as in Figure 3). Abbreviation: VIBE, volumetric interpolated breath-hold examination.

with an adequate margin of 5–10 mm. It is envisaged that this sampling inaccuracy is probably the least challenging element of the initiative, whilst verifying treatment success is probably the most difficult aspect. The correct initial approach would ideally use all the available detection methods—PSA, histology and MRI. As some prostate tissue is left untreated in focal therapy, absolute values of PSA will be insufficient for verifying treatment success. Equally, failure defined on the basis of PSA kinetics, the parameters of which are currently defined from values in post-radical-treatment cohorts, might not apply. Indeed, the use of PSA kinetics and absolute values of PSA as surrogate markers of success for radical treatments is in itself controversial.<sup>80</sup> Post-treatment PSA kinetics that are measured during AS (e.g. doubling time, velocity) might be more useful for the assessment of focal therapy. Evaluation of PSA density changes (i.e. calculated using the volume of untreated prostate tissue) is also needed in any trial of focal therapy. In addition, if nonsignificant tumor is left untreated, then positive histology should clearly not be regarded as failure, and factors used to define high-risk disease in TRUS biopsy samples may have to be employed. In this respect, the ineffectiveness of MRI in identifying low-volume, low-Gleason-grade disease could be an advantage for focal therapy in early-diagnosis cases (by excluding indolent disease), and follow-up MRI could provide the optimal solution between



**Figure 3** Template mapping biopsies demonstrating 4 cores positive for adenocarcinoma out of a total of 30 cores. Blue areas represent cancer areas (cores A, B, C and AA are Gleason grade 3+4=7, whilst core BB is Gleason grade 3+3=6). A, B and C represent one cancerous area, whilst AA and BB represent another. In this case, MRI detected both areas before template biopsies were performed.

detection of significant disease that requires treatment and overdetection of disease that should be monitored.

What is now required is a standardized assessment and clear follow-up of focal therapy under ethical conditions in a well-characterized group of men. In order to test this hypothesis, we propose an approach (Box 1) that closely follows the Medical Research Council's (UK) guidelines for evaluating complex interventions.<sup>81</sup> It is difficult to define which radical treatments should be incorporated in the control arm of a randomized controlled trial. At present, the long-term data support the inclusion of either radical prostatectomy or radiotherapy, and these two options are included in the Prostate testing for cancer and Treatment ( ProtecT) trial. The design of a randomized controlled trial to evaluate focal therapy should, however, also be pragmatic so that participating centers can carry out the type of radical therapy that is best practice for that particular clinician or center, whether it is open, laparoscopic or robotic prostatectomy,

**Box 1** Medical Research Council's (UK) guidelines for evaluating complex interventions.

1. Defining the intervention (Consensus)
  - a. Will focal therapy be acceptable to clinicians managing men with prostate cancer?
  - b. What attributes of focal therapy will make it acceptable to clinicians?
2. Qualitative studies (discrete choice experiments with patient)
  - a. If adverse effects were considerably reduced, to what extent will men with localized low to moderate risk prostate cancer accept focal therapy at the expense of a percentage increased risk in cancer progression or a decrease in life expectancy?
  - b. Will men accept random allocation to either whole-gland treatments or AS and focal therapy if the adverse effects of focal therapy are acceptably lower than those of radical therapy?
3. Evaluation and characterization of prostate cancer
  - a. To what extent can multisequence MRI detect and localize significant prostate cancer in men with high (age-specific) PSA levels?
  - b. Can multisequence MRI provide the three-dimensional data necessary for planning focal therapy?
4. Phase II hemiablation, proof-of-concept trial (using HIFU, cryosurgery or PDT). Do men with unilateral prostate cancer (T2b N0 M0 or less; Gleason score 7 or less; PSA less than 15 ng/ml), when treated with hemiablation, experience:
  - a. Less harm (i.e. fewer treatment-related adverse effects) compared with conventional radical therapies?
  - b. Early benefit (i.e. absence of cancer on post-treatment biopsy)?
  - c. Localization of disease could be performed initially by template biopsies, and subsequently by multisequence-MRI if the latter demonstrates sufficient accuracy.
5. Phase II focal ablation, proof-of-concept trial (using HIFU, cryosurgery or PDT)
  - a. Do men with bilateral prostate cancer (T2c N0 M0 or less; Gleason score 7 or less; PSA less than 15 ng/ml), when treated with focal ablation of cancer foci only, experience less harm (fewer treatment related adverse effects) than those treated with conventional radical therapies, and early benefit (absence of tumor on post-treatment biopsy sample)?
  - b. Bilateral disease should initially be treated if either or both of the neurovascular bundles can be preserved.
  - c. An ablation of only the cancer foci (in unilateral disease) confer decreased morbidity and comparable cancer control to hemiablation?
6. Phase II focal ablation of index tumor—long-term follow-up efficacy trial (using HIFU, cryosurgery or PDT)
  - a. Is focal ablation of the index tumor(s) only, in men with prostate cancer (T2c N0 M0 or less; Gleason score 7 or less; PSA less than 15 ng/ml), efficacious compared with conventional radical therapies, as demonstrated by biochemical progression, histological progression and cancer-specific mortality (i.e. follow-up for untreated areas in similar manner to AS regimens)?
  - b. From current evidence the index tumor would be defined as any focus with either volume greater than 0.5 cc or Gleason score 7 or more.
7. Phase II–III (randomized controlled trial) comparing focal therapy (hemiablation or focal ablation of all tumor foci) with AS or radical treatment (multicenter, minimum 5 years follow-up)
  - a. Primary outcomes: is focal therapy efficacious in terms of disease progression (clinical, biochemical, histological, imaging) and cancer-specific mortality compared with AS or radical therapy?
  - b. Secondary outcomes: how does focal therapy compare with AS and radical therapy in terms of quality of life and psychological burden for patients? How does focal therapy compare with AS and radical therapy in terms of financial burden on the health care system?

Abbreviations: AS, active surveillance; HIFU, high-intensity focused ultrasound; PDT, photodynamic therapy; PSA, prostate-specific antigen.

or conventional external beam, conformal or intensity modulation radiotherapy.

### CONCLUSIONS

The prospect of using focal therapy in treating organ-confined prostate cancer relies on accurate localization of malignant foci so that they can be

treated with an adequate margin. Although focal therapy, if proven efficacious, may require state-of-the-art imaging in order to become accepted as a standard of care in the long term, the time seems right to test the concept, because the technology to both locate and treat the disease to a high level of precision is available to us.

## KEY POINTS

- The current choice for men with localized prostate cancer lies between active surveillance and radical therapy
- Radical therapy carries significant side effects (e.g. incontinence, impotence, rectal problems) because it treats the whole gland and damages surrounding structures in up to half of men
- Active surveillance might exclude men who have risk factors at presentation, and it is likely that those excluded are therefore more likely to benefit from treatment
- The decision to choose radical therapy is not only confounded by the lack of clear evidence for a survival benefit but also the degree of morbidity
- Focal therapy might be almost as effective as radical (whole gland) treatment with similar low adverse effects as seen in those with active surveillance
- A significant proportion of men with organ-confined, low-to-moderate risk prostate cancer may be spared from disease progression and have a high probability of preserving genitourinary and bowel function with focal therapy

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