Prostate Cancer Tumour Features on Template Prostate-mapping Biopsies: Implications for Focal Therapy

Paras B. Singh, Chukwuemeka Anele, Emma Dalton, Omar Barbouti, Daniel Stevens, Pratik Gurung, Manit Arya, Charles Jameson, Alex Freeman, Mark Emberton, Hashim U. Ahmed

Keywords:
Prostate cancer, Biopsy, Diagnosis, Pathology, Surgery, Therapy

Abstract

Background: Focal therapy is being offered as a viable alternative for men with localised prostate cancer (PCa), but it is unclear which men may be suitable.

Objective: To determine the proportion of men with localised PCa who are potentially suitable for focal therapy.


Intervention: TTPM biopsies using a 5-mm sampling frame.

Outcome measurements and statistical analysis: Suitability for focal therapy required the cancer to be (1) unifocal, (2) unilateral, (3) bilateral/bifocal with at least one neurovascular bundle avoided, or (4) bilateral/multifocal with one dominant index lesion and secondary lesions with Gleason /3 + 3 and cancer core involvement /3 mm. Binary logistic regression modelling was used to determine variables predictive for focal therapy suitability.

Results and limitations: The median age was 61 yr, and the median prostate-specific antigen was 6.8 ng/ml. The median total was 29 cores, with a median of 8 positive cores. Of 239 of 291 men with cancer, 29% (70 men), 60% (144 men), and 8% (20 men) had low-, intermediate-, and high-risk PCa, respectively. Ninety-two percent (220 men) were suitable for one form of focal therapy: hemiablation (22%, 53 men), unifocal ablation (31%, 73 men), bilateral/bifocal ablation (14%, 33 men), and index lesion ablation (26%, 61 men). Binary logistic regression modelling incorporating transrectal biopsy parameters showed no statistically significant predictive variable. When incorporating TTPM parameters, only T stage was a significant negative predictor for suitability (p = 0.001) (odds ratio: 0.001 [95% confidence interval, 0.000–0.048]). Limitations of the study include potential selection bias caused by tertiary referral practise and lack of long-term results on focal therapy efficacy.

Conclusions: Focal therapy requires an accurate tool to localise individual cancer lesions. When such a test, TTPM biopsy, was applied to men with low- and intermediate-risk PCa, most of the men were suitable for a tissue preservation strategy.

© 2013 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Division of Surgery and Interventional Science, University College London, 3rd Floor, Charles Bell House, 67 Riding House Street, London, W1P 7NN, UK. Tel. +44 0 34479194; Fax: +44 0 34479303. E-mail address: hashim.ahmed@ucl.ac.uk (H.U. Ahmed).

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.
1. Introduction

Localised prostate cancer (PCA) treatment currently involves surgery or radiotherapy applied to the whole prostate regardless of the location or volume of individual PCA lesions. Although there is a survival benefit from this approach in men with intermediate- and high-risk disease, radical whole-gland therapies are associated with a significant risk of rectal complications, incontinence, and impotence [1,2]. Tissue-preserving focal therapy, in which only areas of known cancer are targeted, may improve the therapeutic ratio [3–7]. A number of early-phase studies have shown that preservation of genitourinary function can be high following focal therapy, although cancer control in the medium and long term is yet to be fully evaluated [8–11].

One of the key challenges with focal therapy is to accurately identify the population of men who are potentially suitable for tissue preservation. Some practitioners have argued that focal therapy is an alternative in men suitable for active surveillance [3,5,12], while others have argued that focal therapy should be investigated as a potential alternative to radical therapy in those men likely to benefit from treatment [4,6,12,13]. This argument incorporates the concept of ablating the index cancer lesion, which usually harbours the highest grade and largest cancer volume [14]. A number of ethics committee-approved trials are currently recruiting men with intermediate- and high-risk disease and treating them in an index lesion-ablative manner [15–17].

Therefore, the population of men who are potentially eligible for focal therapy is likely to vary with respect to risk group and is dependent on the focal therapy strategy. Studies using whole-mount prostatectomy specimens to estimate this population might incorporate selection bias, since men would have chosen surgery rather than any number of other treatment modalities. We sought to evaluate the proportion of men suitable for focal therapy based on transperineal template prostate-mapping (TTPM) biopsies, as this test can be applied to all men prior to treatment.

2. Methods

This study received exemption from ethics committee approval from the University College London Hospitals Joint Research Office. Our institutional TTPM biopsy registry includes all cases having this procedure. The majority of these patients were tertiary referrals to our institution with previous transrectal ultrasound–guided biopsies. TTPM biopsies were conducted using a method previously described, with cores taken every 5 mm throughout the prostate using a template grid (Fig. 1) [18]. Antibiotic prophylaxis was used with single-dose cefuroxime, gentamicin, and metronidazole at the time of induction. The complications were assessed on immediate postoperative findings and any hospital readmissions and were enquired of the patient at the 4–6-wk follow-up visit. The cancer risk group was determined using the US National Comprehensive Cancer Network (NCCN) guidelines. Locoregional radiologic staging was performed using prostate magnetic resonance imaging (MRI), and distant metastases were ruled out using a pelvic MRI and radiisotope bone scan in any man with a Gleason score ≥7 on any histology, prostate-specific antigen (PSA) ≥10 ng/ml, or clinical/MRI T stage T3a. The T stage was based on MRI characteristic only and not on histology [19].

Toxicity data were collected retrospectively through review of clinic notes and are reported for completeness, although they may be subject to recall bias. Criteria used to decide suitability for focal therapy were those used in prospective ethics committee–approved trials actively recruiting during the period of this study, with pathologic tumour features characterised according to a combination of cancer core length and Gleason grade [20] (Fig. 2). We have reported the results of two of these studies [9,11]. A third trial treating the index lesion is currently closed for analysis [18]. Our current multicentre focal therapy trial incorporates all these focal therapy strategies and will aim to recruit 150 men [20].

In summary, suitability for focal therapy required the cancer to be (1) unifocal, (2) unilateral, (3) bilateral/bifocal with at least one neurovascular bundle avoided, or (4) bilateral/multifocal with one dominant index lesion and secondary lesions with Gleason ≤3 + 3 and cancer core involvement ≤3 mm. The avoidance of the neurovascular bundle was based on ensuring that the posterior left or right quadrant of prostate tissue was not ablated. We accept that the neurovascular bundle is not a discrete bundle but has a more complex diffuse anatomic distribution. We felt that the avoidance of a posterior quadrant at least would avoid most of the ipsilateral nerves in question.

Because of the nonparametric nature of the data, a chi-square test or Spearman rank order for correlation was used, depending on expected values in the two-by-two tables. Cancer risk groups, in addition, were dichotomised at the low/intermediate and intermediate/high thresholds to reflect two schools of thought about the placement of focal therapy. First, some practitioners believe that focal therapy is an alternative for only those men suitable for active surveillance. Second, others have argued that focal therapy is an alternative for men with clinically significant cancer as a strategy that might overcome the harms of treatment but retain the cancer control benefits. A binary logistic regression model was also used, since the predictor variables were a combination of continuous and categorical variables and not normally distributed. Each logistic regression model used nine predictor variables. All tests were two-tailed and performed within SPSS statistical software v.17.0 (2010; IBM Corp., Armonk, NY, USA), and significance was defined as a p value <0.05.

3. Results

An unselected cohort of 377 men referred to our institution underwent TTPM biopsy between 2006 and 2010; of these men, 291 had no previous treatment and formed our cohort for analysis (Fig. 3, Tables 1 and 2). The side-effects of TTPM included perineal ecchymosis in 100% of the men (291 of 291); mild, self-resolving haematuria in most; haematuria requiring admission in 2% (6 of 291); urinary retention in 7% (20 of 291); urinary tract infection in 1% (3 of 291); scrotal skin cellulitis in 0.3% (1 of 291); and no sepsis. We did not routinely collate data on erectile dysfunction at baseline or follow-up, so the actual number with haematospermia is unknown.

Ninety-two percent of men with cancer (220 of 239 men) on TTPM biopsy were suitable for at least one form of focal therapy: hemiablation (22%, 53 of 239 men), unifocal ablation (31%, 73 of 239 men), bilateral/bifocal ablation (14%, 33 of 239 men), and index lesion ablation (26%, 61 of 239 men) (Table 3). Based on univariate analysis, being in the NCCN high-risk group was a statistically significant predictive factor for men not suitable for focal therapy,
Modified Barzell Zones

1. Left Parasagittal Anterior Apex
2. Left Parasagittal Anterior Base
3. Right Parasagittal Anterior Apex
4. Right Parasagittal Anterior Base
5. Midline Apex
6. Midline Base
7. Left Medial Anterior Apex
8. Left Medial Anterior Base
9. Right Medial Anterior Apex
10. Right Medial Anterior Base
11. Left Lateral
12. Right Lateral
13. Left Parasagittal Posterior Apex
14. Left Parasagittal Posterior Base
15. Right Parasagittal Posterior Apex
16. Right Parasagittal Posterior Base
17. Left Medial Posterior Apex
18. Left Medial Posterior Base
19. Right Medial Posterior Apex
20. Right Medial Posterior Base

Clinically insignificant disease
- Gleason = 3+4 AND/OR
- Max Cancer length 4-5mm

Gleason >/= 4+3 AND/OR
- Max cancer length >/=6mm

Fig. 1 – Template prostate-mapping biopsies. (a) Biopsies are taken every 5 mm through a template brachytherapy grid using a method described by Winston Barzell. Biopsies are still taken every 5 mm throughout the prostate, and two biopsies are taken from the same grid coordinate if the prostate is longer than the length of one core biopsy [19]. (b) Regional method used on template-mapping biopsy. Although 5-mm sampling is carried out, the biopsies are batched into 20 zones to limit pathology burdens. The colour coding of individual lesions/zones is based on Kirkham et al. [19]. In this case, index lesion ablation could be targeted to the left peripheral zone lesion and the low-volume, low-grade cancer in zone 20 left untreated. Reprinted from [18] with permission from Elsevier.
although numbers were small (Table 4). When dichotomising between low- and intermediate/high-risk groups, the proportion of men suitable for focal therapy decreased from 99% (84 of 85 men) to 91% (94 of 106 men), respectively \((p = 0.005)\). When dichotomising between low/intermediate-risk compared with high-risk groups, 95% (166 of 175 men) compared with 75% (12 of 16 men) were suitable for focal therapy \((p = 0.002)\).

On binary logistic regression modelling that incorporated transrectal biopsy parameters, we found no statistically significant predictive factor for focal therapy suitability. However, when TTPM biopsy variables were used instead, stage (specifically, radiologic T2c) was a significant negative predictor \((p = 0.001)\) (odds ratio: 0.001 [95% confidence interval, 0.000–0.048]) (Table 5).

4. Discussion

Approximately 90% of men presenting with low- and intermediate-risk disease in our cohort were suitable for at least one focal therapeutic strategy using TTPM biopsy as a means to localise individual PCa lesions.

Our study has a number of limitations. First, as a tertiary centre, we had men presenting to us who were interested in focal therapy. This situation might have led to selection bias, as men with larger cancer burdens on transrectal biopsy may not have sought further risk stratification or trials in focal therapy. This bias is difficult to quantify. Second, as there is no clear consensus as to which risk category for focal therapy should be investigated [3–6,15,16], our inclusion of intermediate- and high-risk groups may be controversial. We have tried to reflect this lack of consensus by describing all risk groups in an open manner. Third, although we found that clinical T stage was the only negative predictor for suitability of focal therapy, it must be noted that clinical T stage does not correlate very well with final pathologic stage or final oncology outcome after
therapy strategies are based on our prospective trials and are thus not just theoretical concepts. We have previously shown that of men with low- and intermediate-risk disease who have undergone radical prostatectomy, between 51% and 68% would have been suitable for a form of focal therapy including index lesion ablation [23,24]. Other
researchers have identified that only one-fifth to one-third of men may be suitable [25]. These differences may be due to controversy surrounding the concept of the index lesion and whether it is safe to leave low-grade, low-volume lesions untreated. We have included this concept as a focal therapeutic strategy, since men are currently being treated in this manner within the context of ethics committee–approved trials [17–19]. Indeed, many focal therapy series in which transrectal biopsy is used to localise lesions are likely to be treated by an index lesion ablation de facto.

Our study has relevance on a number of levels. First, when patients wish to explore focal therapy and are recommended to have a general anaesthetic and multiple biopsies, which carry some additional toxicity, they are likely to want to know the odds that they might be found to have suitable disease for focal therapy. Second, physicians offering template biopsies with a view to focal therapy are better placed to advise and counsel while also being able to make a judgement on whether the additional resources are worthwhile for their particular health care setting. Third, with designs for randomised controlled trials of focal therapy compared with radical therapy being considered, there is a key issue about when to apply a template biopsy with respect to the timing of randomisation. If template biopsies are conducted prior to randomisation, men potentially go through a morbid, high-burden test that will have little clinical relevance if they are randomised to the control arm. If templates are conducted after randomisation and only in the focal arm, but a large proportion of men are then not suitable for focal therapy (therefore, they have radical therapy), this situation would be problematic from an intention-to-treat analysis. Our study has shown that template biopsies after randomisation would not necessarily lead to significant rates of whole-gland therapy in the focal therapy arm.

There are no widely accepted standards for disease localisation in focal therapy, since studies have shown that transrectal biopsy on its own is not sufficient [26]. However, TTPM biopsy is more invasive and requires considerable health care resources. Its major advantage is high sensitivity and negative predictive value for detecting and ruling out significant disease was not left untreated. Since then, evidence on multiparametric MRI shows that this modality might have negative predictive values of 90–95% for ruling out clinically significant PCa (Gleason ≥3+4 and/or lesion ≥0.5 ml) using whole-mount prostatectomy [28,29] or

Table 4 – The relationship of suitability for focal therapy and risk groups following transperineal template prostate-mapping biopsies

<table>
<thead>
<tr>
<th>NCCN category based on TTPM biopsy</th>
<th>Unsuitable for focal therapy, no. (%)</th>
<th>Suitable for focal therapy, no. (%)</th>
<th>Spearman rank order correlation (expected cell frequency &lt; 5), p = 0.017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>3 of 70 (4)</td>
<td>67 of 70 (96)</td>
<td>0.995</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 of 140 (7)</td>
<td>130 of 140 (93)</td>
<td>0.001</td>
</tr>
<tr>
<td>High</td>
<td>5 of 18 (28)</td>
<td>13 of 18 (72)</td>
<td>0.756</td>
</tr>
<tr>
<td>Low and high</td>
<td>3 of 70 (4)</td>
<td>67 of 70 (96)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intermediate and high</td>
<td>15 of 158 (10)</td>
<td>143 of 158 (91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low and intermediate</td>
<td>13 of 210 (6)</td>
<td>197 of 210 (94)</td>
<td>0.001</td>
</tr>
<tr>
<td>High</td>
<td>5 of 18 (28)</td>
<td>13 of 18 (72)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

TTPM = transperineal template prostate mapping; NCCN = National Comprehensive Cancer Network.

Table 5 – The role of transrectal biopsy and transperineal template prostate-mapping biopsy parameters in combination with other clinical baseline parameters to predict subsequent suitability for focal therapy (binary logistic regression)

<table>
<thead>
<tr>
<th>Variables based on TRUS biopsy parameters</th>
<th>Odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.000</td>
<td>0.989</td>
</tr>
<tr>
<td>PSA</td>
<td>0.000</td>
<td>0.996</td>
</tr>
<tr>
<td>Total number of cores</td>
<td>0.000</td>
<td>0.990</td>
</tr>
<tr>
<td>Number of positive cores</td>
<td>0.000</td>
<td>0.972</td>
</tr>
<tr>
<td>Maximum cancer length</td>
<td>&lt; 0.001</td>
<td>0.989</td>
</tr>
<tr>
<td>Gleason score (with respect to Gleason 6)</td>
<td>&lt; 0.001</td>
<td>0.973</td>
</tr>
<tr>
<td>Volume</td>
<td>1.779</td>
<td>0.995</td>
</tr>
<tr>
<td>Stage (with respect to stage T1c)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Stage T2a</td>
<td>0.000</td>
<td>0.982</td>
</tr>
<tr>
<td>Stage T2b</td>
<td>0.000</td>
<td>0.987</td>
</tr>
<tr>
<td>Stage T2c</td>
<td>0.000</td>
<td>0.989</td>
</tr>
<tr>
<td>Stage T3a</td>
<td>0.000</td>
<td>0.991</td>
</tr>
<tr>
<td>NCCN risk (with respect to low risk)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.000</td>
<td>0.979</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 0.001</td>
<td>0.995</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables based on TTPM parameters</th>
<th>Odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.023</td>
<td>0.665</td>
</tr>
<tr>
<td>PSA</td>
<td>0.938</td>
<td>0.362</td>
</tr>
<tr>
<td>Volume</td>
<td>0.997</td>
<td>0.908</td>
</tr>
<tr>
<td>Stage (with respect to stage T1c)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Stage T2a</td>
<td>0.253</td>
<td>0.298</td>
</tr>
<tr>
<td>Stage T2b</td>
<td>0.041</td>
<td>0.084</td>
</tr>
<tr>
<td>Stage T2c</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage T3a</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>NCCN risk (with respect to low risk)</td>
<td>0.835</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.306</td>
<td>0.548</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>Total number of cores</td>
<td>1.019</td>
<td>0.475</td>
</tr>
<tr>
<td>Number of positive cores</td>
<td>0.937</td>
<td>0.254</td>
</tr>
<tr>
<td>Maximum cancer length</td>
<td>0.870</td>
<td>0.481</td>
</tr>
<tr>
<td>TTPM Gleason score (with respect to Gleason 6)</td>
<td>0.943</td>
<td></td>
</tr>
<tr>
<td>Gleason 7</td>
<td>1.472</td>
<td>0.733</td>
</tr>
<tr>
<td>Gleason 8</td>
<td>0.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

TRUS = transrectal ultrasound; TTPM = transperineal template prostate mapping; PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Network.
TTPM [30] as a reference standard and thus might have a role in focal therapy disease localisation.

5. Conclusions

The success of tissue-preserving focal therapy is dependent on appropriate patient selection. This selection necessitates an accurate investigative tool that can exclude significant cancer outside the area intended to be ablated while precisely localising individual cancer lesions, which are to be selectively destroyed. When such a test, TTPM biopsy, was applied to men with low- and intermediate-risk PCa, most men were found to be suitable for a tissue preservation strategy. Whether such a tissue-preserving strategy gives long-term favourable oncologic outcomes is currently being evaluated by various ongoing focal therapy trials.

Author contributions: Hashim U. Ahmed had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ahmed, Freeman, Emberton.

Acquisition of data: Ahmed, Singh, Dalton, Stevens, Arya, Freeman, Jameson, Barbouti, Gurung, Anele.

Analysis and interpretation of data: Ahmed, Singh, Arya.

Drafting of the manuscript: Singh, Ahmed.

Critical revision of the manuscript for important intellectual content: Emberton, Ahmed, Singh, Stevens, Arya.

Statistical analysis: Ahmed.

Obtaining funding: Ahmed, Emberton.

Administrative, technical, or material support: Freeman, Jameson.

Supervision: Ahmed.

Other (specify): None.

Financial disclosures: Hashim U. Ahmed certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Mark Emberton and Hashim U. Ahmed received funding from Sonacare Inc. for an investigator-led focal therapy trial using the Sonablate 500 HIFU device; received free use of the Nanoknife device from Angiodynamics for an investigator-led clinical trial of focal therapy; and received funding from the Medical Research Council (UK), Pelican Cancer Foundation, St Peters Trust, Prostate Cancer UK, Wellcome Trust, NIHR-1i4i, and NIHR-HTA. Mark Emberton received consultancy payments from Sonacare, GSK, and Steba Biotech and has share options and is a director in Nuada Medical Ltd. Alex Freeman has share options in Nuada Medical Ltd. Manit Arya received funding from Orchid (a male cancer charity). Barts, and The London Charity.

Funding/Support and role of the sponsor: This study was funded by an MRC fellowship grant awarded to HUA and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

References


