available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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

Paras B. Singh [a], *Chukwuemeka Anele* [b], *Emma Dalton* [b], *Omar Barbouti* [b], *Daniel Stevens* [c], *Pratik Gurung* [a], *Manit Arya* [d,e], *Charles Jameson* [f], *Alex Freeman* [f], *Mark Emberton* [a,d], *Hashim U. Ahmed* [a,d,*]

[a] *Division of Surgery and Interventional Sciences, University College London, London, UK;* [b] *Medical School, University College London, London, UK;* [c] *Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK;* [d] *Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK;* [e] *Barts Cancer Institute, Queen Mary, University of London, London, UK;* [f] *Department of Histopathology, University College London Hospitals NHS Foundation Trust, London, UK*

Article info

Article history:
Accepted September 25, 2013
Published online ahead of print on October 6, 2013

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.
Design, setting, and participants: Our institutional transperineal template prostate-mapping (TTPM) biopsy registry of 377 men from 2006 to 2010 identified 291 consecutive men with no prior treatment.
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 $\leq 3+3$ 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.

* 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).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2013.09.045

Please cite this article in press as: Singh PB, et al. Prostate Cancer Tumour Features on Template Prostate-mapping Biopsies: Implications for Focal Therapy. Eur Urol (2013), http://dx.doi.org/10.1016/j.eururo.2013.09.045

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 radioisotope bone scan in any man with a Gleason score $\geq$7 on any histology, prostate-specific antigen $\geq$10 ng/ml, or clinical/MRI T stage $\geq$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 $\leq$3 + 3 and cancer core involvement $\leq$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,

Please cite this article in press as: Singh PB, et al. Prostate Cancer Tumour Features on Template Prostate-mapping Biopsies: Implications for Focal Therapy. Eur Urol (2013), http://dx.doi.org/10.1016/j.eururo.2013.09.045