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

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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 3 + 3 and cancer core involvement 3 mm. Binary logistic regression modelling was used to determine variables predictive of 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 practice 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.

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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 radiotrace bone scan in any man with a Gleason score ≥7 on any histology, prostate-specific antigen ≥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,
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
definitive treatment. Fourth, it is clearly important to remember that while defining the patient population is important and facilitates decision making in clinical practice and research, focal therapy has no long-term outcomes on disease control and is thus not yet considered standard care. Finally, there is no gold standard control with outcomes on disease control and is thus not yet considered practice and research, focal therapy has no long-term

| Table 1 – Baseline characteristics in 291 men undergoing transperineal template prostate-mapping biopsy |
|----------------------------------------------------------|
| **Baseline characteristics**                          | **Value** |
| Age, yr, median (IQR) (overall range)                  | 61 (9) (40–81) |
| Serum PSA, ng/ml, median (IQR) (overall range)          | 6.8 (5.5) (2.1–24.8) |
| Prostate volume, ml, median (IQR) (overall range)       | 35.0 (18) (15–113) |
| PSA density, ng/ml per cubic centimetre, median (IQR) (overall range) | 0.17 (0.14) (0.02–0.99) |
| Initial biopsy strategy, no. (%)                        | TRUS biopsy 267 of 291 (92) |
| Gleason (if positive on TRUS-guided biopsy), no. (%)    | TTPM biopsy 24 of 291 (8) |
| TRUS biopsy                                             | 63 of 233 (27) |
| 3 + 3                                                   | 56 of 233 (24) |
| 3 + 4                                                   | 46 of 233 (20) |
| 4 + 3                                                   | 10 of 233 (4) |
| Missing                                                 | 17 of 233 (7) |
| TRUS-guided biopsies                                    | Total cores, no., median (IQR) (overall range) 10 (4) (3–18) |
| Total positive cores, no., median (IQR) (overall range) | 2 (2) (1–10) |
| Positive cores, %, median (IQR) (overall range)         | 6.0 (6.5) (1.2–24.0) |
| MCL, mm, median (IQR) (overall range)                   | 3 (4) (1–14) |
| % MCL, median (IQR) (overall range)                     | 25 (30) (1–100) |
| TRUS biopsy laterality, no. (%)                         | Unilateral 199 of 233 (85) |
| Bilateral                                               | 23 of 233 (10) |
| Missing                                                 | 11 of 233 (5) |
| Radiologic (MRI) stage, no. (%)                         | T1c 85 of 239 (36) |
| T2a                                                     | 105 of 239 (44) |
| T2b                                                     | 70 of 239 (11) |
| T2c                                                     | 5 of 239 (2) |
| T3a                                                     | 17 of 239 (7) |
| Risk group (NCCN) after TRUS biopsy, no. (%)            | Low 102 of 233 (44) |
| Intermediate                                            | 98 of 233 (42) |
| High                                                    | 16 of 233 (7) |
| Missing                                                 | 17 of 233 (7) |

| Table 2 – Details of transperineal template prostate-mapping biopsies in 291 men |
|----------------------------------------------------------|
| **Characteristics**                                      | **Value** |
| Reason for undergoing TTPM biopsies, no. (%)             | Positive TRUS biopsy 233 of 291 (80) |
| Risk stratification                                     | Risk stratification 69 of 291 (24) |
| Focal therapy                                           | 164 of 291 (56) |
| Negative TRUS biopsy, persistent risk                    | 34 of 291 (12) |
| Diagnostic (no previous TRUS biopsy)                     | 24 of 291 (8) |
| TTPM biopsies                                           | Total cores, no., median (IQR) (overall range) 29 (18) (10–0) |
| Core density (biopsies per cubic centimetre, median (IQR) (overall range) | 1.1 (1.2) (0.4–7.5) |
| Positive cores, no., median (IQR) (overall range)        | Total positive cores, no., median (IQR) (overall range) 8 (5) (2–31) |
| MCL, mm, median (IQR) (overall range)                    | Positive cores, %, median (IQR) (overall range) 6 (6.8) (0.6–74.0) |
| % MCL, median (IQR) (overall range)                      | MCL, mm, median (IQR) (overall range) 50 (55) (3–100) |
| Gleason (TTPM biopsies), no. (%)                         | Gleason (TTPM biopsies), no. (%) 52 of 291 (18) |
| No cancer                                               | 3 + 3 96 of 291 (33) |
| Score 7                                                 | 127 of 291 (44) |
| 3 + 4                                                   | 119 of 291 (41) |
| 4 + 3                                                   | 8 of 291 (3) |
| 4 + 4                                                   | 1 of 291 (0.3) |
| Not gradable                                            | 15 of 291 (5) |
| Risk group (NCCN) after TTPM, no. (%)                   | Risk group (NCCN) after TTPM, no. (%) 70 of 239 (29) |
| Low                                                     | Intermediate 144 of 239 (60) |
| High                                                    | High 20 of 239 (8) |
| Missing                                                 | Missing 5 of 239 (2) |
| TTPM laterialy, no. (%)                                  | TTPM laterialy, no. (%) 94 of 239 (39) |
| Unilateral                                              | Right 45 of 239 (19) |
| Bilateral                                               | Left 49 of 239 (21) |
| Bilateral                                               | Bilateral 145 of 239 (61) |
| TTPM = transperineal template prostate mapping; TRUS = transrectal ultrasound; IQR = interquartile range; MCL = maximum cancer length; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network. Note: Of men with positive TRUS biopsy, 25 (12%) had a negative TTPM biopsy. | TTPM = transperineal template prostate mapping; TRUS = transrectal ultrasound; IQR = interquartile range; MCL = maximum cancer length; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network. Note: Of men with positive TRUS biopsy, 25 (12%) had a negative TTPM biopsy. |

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

| Table 3 – The proportion of men suitable for focal therapy following positive transperineal template prostate-mapping biopsy |
|----------------------------------------------------------|
| **Focal strategy**                                       | **Value, no. (%)** |
| Suitable for focal therapy                               | 220 of 239 (92) |
| Not suitable for focal therapy                           | 19 of 239 (8) |
| Unilateral disease (Fig. 2a and 2b)                      | 126 of 239 (53) |
| Suitable for focal therapy                               | 53 of 239 (22) |
| Unifocal ablation (Fig. 2b)                              | 73 of 239 (31) |
| Not suitable for focal therapy                           | 0 (0) |
| Bilateral disease (Fig. 2c–2f)                           | 94 of 239 (39) |
| Suitable for focal therapy                               | 33 of 239 (14) |
| Not suitable for focal therapy                           | 61 of 239 (26) |
| Not suitable for focal therapy                           | 19 of 239 (8) |

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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 treating 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 perspective.

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

| NCCN category based on TTPM biopsy | Unsuitable for focal therapy, no. (%) | Suitable for focal therapy, no. (%) | Spearman rank order correlation (expected cell frequency < 5), p value |
|------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------------------------------------|
| Low                               | 3 of 70 (4)                           | 67 of 70 (96)                       | Pearson chi-square, p = 0.179                                       |
| Intermediate                      | 10 of 140 (7)                         | 130 of 140 (93)                     | p = 0.001                                                          |
| High                              | 5 of 18 (28)                          | 13 of 18 (72)                       | p = 0.001                                                          |
| Low and high                      | 3 of 70 (4)                           | 67 of 70 (96)                       | p = 0.017                                                          |
| Low and intermediate              | 15 of 158 (10)                        | 143 of 158 (91)                     | p = 0.017                                                          |
| High                              | 13 of 210 (6)                         | 197 of 210 (94)                     | p = 0.001                                                          |
| High                              | 5 of 18 (28)                          | 13 of 18 (72)                       | p = 0.001                                                          |

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)

| Variables | Odds ratio | p value |
|-----------|------------|---------|
| Age       | 0.000      | 0.989   |
| PSA       | 0.000      | 0.996   |
| Total number of cores | 0.000      | 0.972   |
| Number of positive cores | 0.000      | 0.972   |
| Maximum cancer length | <0.001     | 0.989   |
| Gleason score (with respect to Gleason 6) | <0.001     | 0.979   |
| Volume    | 1.779      | 0.995   |
| Stage (with respect to stage T1c) | 1.000      |         |
| Stage T2a | 0.000      | 0.982   |
| Stage T2b | 0.000      | 0.987   |
| Stage T2c | 0.000      | 0.989   |
| Stage T3a | 0.000      | 0.991   |
| NCCN risk (with respect to low risk) | 1.000      |         |
| Intermediate | 0.000      | 0.979   |
| High      | <0.001     | 0.995   |

Variables for binary logistic regression model based on TRUS biopsy parameters

| Variables | Odds ratio | p value |
|-----------|------------|---------|
| Age       | 1.023      | 0.665   |
| PSA       | 0.938      | 0.362   |
| Volume    | 0.997      | 0.908   |
| Stage (with respect to stage T1c) | 0.007      |         |
| Stage T2a | 0.253      | 0.298   |
| Stage T2b | 0.041      | 0.084   |
| Stage T2c | 0.001      | 0.001   |
| Stage T3a | 0.000      | 1.000   |
| NCCN risk (with respect to low risk) | 0.835      |         |
| Intermediate | 2.306      | 0.548   |
| High      | <0.001     | 1.000   |
| Total number of cores | 1.019      | 0.475   |
| Number of positive cores | 0.937      | 0.254   |
| Maximum cancer length | 0.870      | 0.481   |
| TTPM Gleason score (with respect to Gleason 6) | 1.472      | 0.733   |
| Gleason 7 | 0.000      | 1.000   |

Variables for binary logistic regression model based on TTPM parameters

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.

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References

[1] Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367: 203–13.
[2] Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013;368: 436–45.
[3] Lindner U, Trachtenberg J, Lawrentschuk N. Focal therapy in prostate cancer: modalities, findings and future considerations. Nat Rev Urol 2010;7:562–71.
[4] de la Rosette J, Ahmed H, Barentsz J, et al. Focal therapy in prostate cancer: report from a consensus panel. J Endourol 2010;24: 775–80.
[5] Eggener S, Salomon G, Scardino PT, de la Rosette J, Polascik TJ, Brewster S. Focal therapy for prostate cancer: possibilities and limitations. Eur Urol 2010;58:57–64.
[6] Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2013.05.048.
[7] Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol 2007;4:632–42.
[8] Lindner U, Weersink RA, Haider MA, et al. Image guided photo-thermal focal therapy for localized prostate cancer: phase I trial. J Urol 2009;182:1371–7.
[9] Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011;185:1246–54.
[10] Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int 2012;109:1648–54.
[11] Ahmed HU, Hindley RC, Dickinson L, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 2012;13:622–32.
[12] Eggener SE, Scardino PT, Carroll PR, et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol 2007;178:2260–7.
[13] Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med 2009;361:1704–6.
[14] Ahmed HU, Arya M, Freeman A, Emberton M. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? Lancet Oncol 2012;13:e509–17.
[15] Dickinson L, Ahmed HU, Kirkham A, et al. A multi-centre prospective development study evaluating focal therapy using high intensity focused ultrasound for localised prostate cancer: the INDEX Study. Contemp Clin Trials 2013;36:68–80.
[16] Ahmed HU, Emberton M. An evaluation of lesion control using focal ablation with high intensity focused ultrasound in the treatment of non-metastatic progressive prostate cancer [identifier NCT00987675], ClinicalTrials.gov Web site. http://clinicaltrials.gov/show/NCT00987675.
[17] Ward JF. Regional cryoaulation for localized adenocarcinoma of the prostate[identifier NCT00877682], ClinicalTrials.gov Web site. http://clinicaltrials.gov/show/NCT00877682?term=NCT00877682&rank=1. Accessed 31 October 2012.
[18] Barzell WE, Melamed MR, Cathcart P, Moore CM, Ahmed HU, Emberton M. Identifying candidates for active surveillance: an evaluation of the repeat biopsy strategy for men with favorable risk prostate cancer. J Urol 2012;188:762–7.
[19] Kirkham AP, Haslam P, Keanie JY, et al. Prostate MRI: who, when and how? Report from a UK consensus meeting. Clin Radiol 2013;68:1016–23.
[20] Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol 2011;186:458–64.
[21] Ahmed HU, Emberton M, Kepner G, Kepner J. A biomedical engineering approach to mitigate the errors of prostate biopsy. Nat Rev Urol 2012;9:227–31.
[22] Crawford ED, Rove KO, Barqawi AB, et al. Clinical-pathologic correlation between transperineal mapping biopsies of the prostate and three-dimensional reconstruction of prostatectomy specimens. Prostate 2013;73:778–87.
[23] Bott SR, Ahmed HU, Hindley RG, Abdul-Rahman A, Freeman A, Emberton M. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. BJU Int 2010; 106:1607–11.

[24] Karavitakis M, Winkler M, Abel P, Livni N, Beckley I, Ahmed HU. Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy. Prostate Cancer Prostatic Dis 2011;14:46–52.

[25] Catto JW, Robinson MC, Albertsen PC, et al. Suitability of PSA-detected localised prostate cancers for focal therapy: experience from the ProtecT study. Br J Cancer 2011;105:931–7.

[26] Mayes JM, Mouraviev V, Sun L, Tsivian M, Madden JF, Polascik TJ. Can the conventional sextant prostate biopsy accurately predict unilateral prostate cancer in low-risk, localized, prostate cancer? Urol Oncol 2011;29:166–70.

[27] McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009; 374:1105–12.

[28] Puech P, Potiron E, Lemaitre L, et al. Dynamic contrast-enhanced-magnetic resonance imaging evaluation of intraprostatic prostate cancer: correlation with radical prostatectomy specimens. Urology 2009;74:1094–9.

[29] Turkbey B, Mani H, Aras O, et al. Correlation of magnetic resonance imaging tumor volume with histopathology. J Urol 2012;188: 1157–63.

[30] Arumainayagam N, Ahmed HU, Moore CM, et al. Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. Radiology 2013;268: 761–9.