Intra-prostatic cancer recurrence following radical radiotherapy on transperineal template mapping biopsy: implications for focal ablative salvage therapy

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Abstract

Background: Men who fail external beam radiotherapy (EBRT) are usually placed on delayed hormone therapy. Some of these men have localised recurrence that might be suitable for further local therapy. We aimed to describe patterns of recurrence, and suitability for focal ablative therapy, in those undergoing transperineal template prostate-mapping (TTPM) biopsies.

Method: 145 consecutive patients (December 2007-May 2014) referred with suspicion of recurrence due to rising PSA after EBRT or brachytherapy who underwent TTPM-biopsies. Suitability for focal ablative therapy required the cancer to be either unifocal or unilateral, or bilateral/multifocal with one dominant index lesion and secondary lesions with Gleason score 3+3=6 with no more than 3mm cancer core involvement.

Results: The mean age was 70.7 (SD 5.8) years. Median PSA at time of TTPM-biopsy was 4.5 (IQR 2.5-7.7). Overall, 75.9% (110/145) were suitable for a form of focal salvage treatment; 40.7% (59/145) were suitable for quadrant ablation, 14.5% (21/145) hemiablation, 14.5% (21/145) bilateral focal ablation and 6.2% (9/145) for index lesion ablation.

Conclusion: Three quarters of patients who have localised radio-recurrent prostate cancer may be suitable for focal ablative therapy to the prostate based on transperineal template prostate mapping biopsies.

Introduction

Men who receive primary radiotherapy for localised prostate cancer may develop recurrence as detected by biochemical criteria within 8 years[1]. Most men who fail radiotherapy are currently placed on delayed androgen deprivation therapy (ADT). There are several well-known side effects with ADT; hot flushes (50-80%), breast tenderness/enlargement (up to 60%), lethargy [2] (most), erectile dysfunction/decreased libido (10-17%)[3], osteopenia/osteoporosis with consequent fracture (19%)[4], variable cognitive impairment[5] , and metabolic syndrome (>50%)[6]. Further, the development of castrate resistance requires expensive second and third line treatment including chemotherapy and patients are not expected to survive more than 24-36 months without further therapy. [7 8 9]

Current salvage therapies include radical prostatectomy, whole-gland brachytherapy, cryotherapy or high intensity focused ultrasound (HIFU). However, these treat the whole prostate and significant risk of incontinence and rectal injury is possible.[10 11] These risks may be minimised by targeting only the area of recurrence, using focal ablative salvage therapies (FAST)[12] such as Cryosurgery, HIFU, high and low dose rate brachytherapy and stereotactic body radiation therapy. For FAST to be delivered appropriately, an accurate determination of the presence or absence of recurrence as well as delineation of any recurrence is necessary.

We aimed to evaluate the patterns of radiorecurrence and hence the proportion of patients that might be suitable for FAST based on transperineal template prostate-mapping (TTPM) biopsies.

Methods

The University College London Hospitals Joint Research Office granted ethics exemption for this study. A retrospective review of our institutional TTPM-biopsy registry identified 145 consecutive patients referred with suspicion of radio-recurrent prostate cancer due to rising PSA following EBRT or brachytherapy who underwent TTPM-biopsies (December 2007- May 2014). All patients underwent mpMRI using 1.5T MRI without an endo-rectal coil. All patients had distant disease ruled out according to standard approaches to staging at the time in our institution which was based on a combination of radioisotope FDG/18F-Choline PET/CT scans and bone-scan. PSMA PET scans were not available during this period. All patients with positive scans were discussed at MDT where scans were reviewed before proceeding to biopsy.

TTPM-biopsy

A 5mm transperineal brachytherapy grid was used to take biopsies under general anaesthetic using ultrasound guidance. Biopsies were taken in 20 sectors as per Onik et al.[13]. Antibiotic prophylaxis was single-dose gentamicin, cefuroxime, and metronidazole at the time of induction. Biopsy cores were analysed and reported by two dedicated expert uro-pathologists with over 10 years of experience. Pathologists were aware of clinical details.

Outcome measures

Risk stratification was performed according to a TTPM-biopsy risk scoring system previously validated and used in prior studies. [14] Patients were deemed high-risk if PSA >/=20ng/ml, Gleason >/=8, stage T2c-3a, intermediate-risk if PSA 10-20ng/ml, Gleason =7, or T2b and low-risk PSA <10ng/ml, Gleason </=6, stage T1-T2a. Suitability for focal therapy required the cancer (of any risk) to be unifocal, or unilateral, or bilateral/bifocal with at least one neurovascular bundle avoided, or bilateral/multifocal with one dominant index lesion and secondary lesions having no more than 3mm of Gleason 3+3=6 disease.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, IBM Corporation, New York) and the R language environment (R Core Team 2015, version 3.6.3.). In order to assess whether certain clinical characteristics might predict those patients not suitable for FAST, we conducted a univariate and multivariate logistic regression (odds radios [OR] with 95% confidence intervals [95% CI]) using clinically relevant variables (see Table 5). A two-tailed $p<0.05$ was considered statistically significant. Factors with $p<0.05$ were retained in the final model.

Results

Baseline demographics

The mean age was 70.7 (SD 5.8) years. The mean time from radiotherapy to biochemical failure was 64.2 (SD 34.5) months. Baseline D'Amico risk score was available for 121 patients prior to radiotherapy (Table 1). Seventeen patients (11.7%) were on androgen deprivation therapy (ADT) at the time of biopsy.

Primary outcome

Overall 75.9% (110/145) were suitable for a form of FAST. 40.7% (59/145) were suitable for quadrant ablation, 14.5% (21/145) for hemiablation, 14.5% (21/145) for bilateral focal ablation and 6.2% (9/145) for index lesion ablation. 8.3% (12/145) were suitable for whole-gland treatment only. (Table 2).

Secondary outcomes

3.4% (5/145) were classified as low risk. 17.9% (26/145) were intermediate risk and 62.8% (91/145) were high risk. All low risk patients were suitable for quadrant ablation. All intermediate risk patients were suitable for a form of focal salvage treatment. For high risk patients, 86.8% (79/91) could have a form of FAST (p=0.15 Fishers exact test) (Tables 3 & 4).

Second, on multivariable analyses, age and total number of positive cores on TTPM biopsy were significant in predicting those not suitable for a form of FAST, (odds ratio 0.77 [95% CI 0.62-0.92 p=0.007] and 1.16 [95% CI 1.01-1.37 p=0.04]), respectively. On univariable analysis there were several factors significant in predicting those not suitable for FAST (Table 5).

Complications included haematospermia 0.7% (1/145), 1.4% (2/145) dysuria, and urine retention 0.7% (1/145). Erectile function was not recorded.

Discussion

In summary, approximately 75.9% (110/145) of patients who have biochemical failure following primary radiotherapy for prostate cancer, were suitable for a form of focal salvage treatment as characterised by a very detailed mapping biopsy of the prostate.

Our study had some limitations. First, we have not been able to compare TTPM-biopsy with radical prostatectomy specimens as none had salvage surgery. Whilst one study reports on recurrent prostate tumors after radiation therapy being bulky, bilateral, high grade and proximal to the urethra which may limit focal salvage therapy[15] it has previously been shown that TTPM-biopsy has high diagnostic accuracy when compared to whole-mount specimens [13 16]. Therefore, any patients selected for focal salvage therapy would not ideally be those with high grade bulky bilateral disease or peri-urethral disease; the latter which could also impact on toxicity. Our study has shown that MCCL and number of positive cores are predictors for those not suitable for a form of FAST, however our sample

size was quite limited as there were only 12 patients requiring whole gland treatment. This could also be the reason for a limited number of baseline or pre-biopsy patient characteristics predicting those not suitable for a form of FAST.

Second, after radiotherapy there can be delayed tumour regression and conversion to negative biopsies at a mean time of 30 months. However, these studies are based on transrectal biopsies which has known errors of sampling, inappropriate conclusions about histological changes following radiotherapy may have been reached[17]. Within our study the mean time between radiation therapy and repeat biopsy was 82.5 months with only two patients biopsied before 30 months. Our histopathologists have over ten years' experience in identifying recurrent prostate cancers and associated Gleason grades. We were not able to obtain pre-EBRT diagnostic MRIs for these men to correlate whether areas of tumour recurrence were related to the index lesion; often these men had systematic TRUS-biopsy with no targeting.

Third, we have used the same risk classification as in the primary setting[18 19]. Whilst this has not been validated in the radiorecurrent setting, it might be argued that any recurrent cancer following radiotherapy will be more aggressive compared to similar histological phenotypes in the primary setting.

Fourth, high-risk radiorecurrent prostate cancer, whilst theoretically being suitable for FAST, may have a higher risk of micro-metastatic disease and therefore it is questionable whether these men should receive further local treatment. Novel modalities like PET-PSMA or whole-body MRI might help in this setting as they have been reported to be more accurate than current staging scans. We are currently testing the hypothesis that local salvage ablation might be beneficial in the metastatic setting within the FORECAST study[20]. It must also be noted that although some patients may benefit from a form of FAST, some patients such as those over 75 years with significant comorbidity and a PSA doubling time of greater than 2 years following EBRT, may be able to remain under observation without ADT thus reducing toxicity of any further treatment.

In order for patients to be eligible for FAST, radiorecurrent disease must be accurately characterised. This is important as we have shown that higher number of positive cores and MCCL were predictors in those who would not be suitable for a form of FAST. This can be done with TTPM-biopsy or using mpMRI followed by targeted and systematic biopsies. Whilst mpMRI has been reported to have high sensitivity and specificity of up to 86-100% [17 21] for the detection of radiorecurrent cancer, these studies have used transrectal ultrasound biopsy, which can miss disease. One study found that TTPM-biopsy detected 85.7% of clinically significant radiorecurrent cancers compared with 77.9% with

mpMRI-targeted biopsy. **Error! Bookmark not defined.**

Several studies have examined the benefit of FAST in radiorecurrent disease; 5-year biochemical disease-free survival ranges being 47-55%, respectively. There were severe urinary, gastrointestinal and sexual toxicity rates in the range of 0-33.3%[22] although likely lower than those reported from whole-gland salvage treatments.[23] The location of recurrent tumours can also determine which salvage ablative treatment to use. HIFU is reported as causing more toxicity for anterior tumours, whereas cryotherapy can be accurately targeted into these tumours thereby potentially decreasing toxicity and improving oncological outcome. Our FOCal RECurrent Assessment and Salvage Treatment study will assess the role of whole-body MRI for staging, the role of image-targeted biopsies compared to TTPM-biopsies and the early outcomes of FAST in men with proven localised, locally advanced as well as metastatic radiorecurrent prostate cancer (clinicaltrials.gov number: NCT01883128)[24].

Conclusion

Radio-recurrent cancer may be suitable for focal ablative salvage treatment. Accurate characterisation of radiorecurrent disease is necessary. TTPM biopsies has shown that three quarters of men with localised recurrence might be suitable for a focal salvage therapy. The effectiveness of this treatment is still to be determined.

Conflicts of Interest and other funding

Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Ahmed currently receives funding from the Wellcome Trust, Medical Research Council (UK), Cancer Research UK, Prostate Cancer UK, The Urology Foundation, BMA Foundation, Imperial Health Charity, NIHR Imperial BRC, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed is a paid medical consultant for Sophiris Biocorp and Sonacare Inc. Ahmed, is a proctor for HIFU and cryotherapy and paid for training other surgeons in these procedures. Ahmed is paid proctor for Rezum for the treatment of benign prostate hyperplasia.

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Emberton and Freeman have loan notes/stock options in Nuada Medical Ltd (UK).

Heather Payne has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Bayer, Ferring, and Novartis.

None of the other authors have anything to declare.

Role of Funding Source

None of the funding sources had any role or input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

[1] Kuban DA, Thames HD, Levy LB, et al. Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. Int J Radiat Oncol Biol Phys 2003;57(4):915-28.

[2] Crook JM, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N. Engl. J. Med. 2012;367:895–903

[3] Potosky AL, Knopf K, Clegg LX, et al. “Quality-of-life outcomes after primary androgen deprivation therapy: Results from the prostate cancer outcomes study.” *J Clin Oncol* 19 (2001): 3750-3757.

[4] Shahinian VB, Kuo YF, Freeman JL, et al. “Risk of fracture after androgen deprivation for prostate cancer.” *N Engl J Med* 352 (2005): 154-164.

[5] Jamadar RJ, Winters MJ, Maki PM. “Cognitive changes associated with ADT: A review of the literature. .” *Asian J Androl* 14 (2012): 232-238.

[6] Braga-Basaria M, Dobs AS, Muller DC, et al. “Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. .” *J Clin Oncol* 24 (2006): 3979-3983.

[7] Ryan CJ, Smith MR, de Bono JS, et al. “Abiraterone in metastatic prostate cancer without previous chemotherapy.” *N Engl J Med* 368 (2013): 138-148.

[8] James ND, Spears MR, Clarke NW, et al. “Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019).” *Eur Urol.* 67 (2015): 1028-1038.

[9] Shore N, Higano CS, George D et al. Concurrent or layered treatment with radium-223 and enzalutamide or abiraterone/prednisone: real-world clinical outcomes in patients with metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2020 May 13.

[10] Punnen S, Cooperberg MR, D'Amico AV, et al. “Management of biochemical recurrence after primary treatment of prostate cancer: a systematic review of the literature. .” *Eur Urol.* 64 (2013): 905-915.

[11] Crook JM, Zhang P, Pisansky TM et al. “A Prospective phase 2 trial of transperineal ultrasound-guided brachytherapy for locally recurrent prostate cancer after external beam radiation therapy (NRG Oncology/RTOG-0526). .” *Int J Radiat Oncol Biol Phys* 103 (2019): 335-343.

[12] Kanthabalan A, Arya M, Punwani S, et al. Role of focal salvage ablative therapy in localised radiorecurrent prostate cancer. *World J Urol* 31 (2013): 1361-1368.

[13] Onik G, Barzell W. “Transperineal 3D mapping biopsy of the prostate: An essential tool in selecting patients for focal prostate cancer therapy.” *Urol Oncol* 26 (2008): 506-10.

[14] Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol 2011;186(2):458-64.

[15] Leibovici D, Chiong E, Pisters LL, et al. “Pathological characteristics of prostate cancer recurrence after radiation therapy: implications for focal salvage therapy. .” *J Urol* 188 (2012): 98-102.

[16] Kara T, Akata D, Akyol F et al. “The value of dynamic contrast-enhanced MRI in the detection of recurrent prostate cancer after external beam radiotherapy: Correlation with transrectal ultrasound and pathological findings.” *Diagn Interv Radiol* 17 (2011): 38-43.

[17] Crook JM, Perry GA, Robertson S et al. “Routine prostate biopsies following radiotherapy for prostate cancer: Results for 226 patients. .” *Urology* 45 (1995): 624-631.

[18] Kanthabalan A, Peters M, Van Vulpen et al. “Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer.” *BJU Int.* 120 (2017): 246-256.

[19] Peters M, Kanthabalan A, Shah TT, et al. Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: Presentation of risk scores for individual patient prognoses. Urol Oncol. 2018;36(1):13.e1-13.e10.

[20] Kanthabalan A, Shah T, Arya M, et al. “The FORECAST study - Focal recurrent assessment and salvage treatment for radiorecurrent prostate cancer.” *Contemp Clin Trials.* 44 (2015): 175-186.

[21] Parekh A, Graham PL, Nguyen PL. “Cancer control and complications of salvage local therapy after failure of radiotherapy for prostate cancer: A systematic review..” *Seminars in Radiation Oncology* 23 (2013): 222-234.

[22] Duijzentkunst DA, Peters M, van der Voort van Zyp JR, Moerland MA, van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: A comprehensive review. World J Urol 2016;34(11):1521-31.

[23] Castro Abreu AL, Bahn D, Leslie S, et al. “Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy.” *BJU Int* 112 (2013): 298-307.

[24] Ahmed HU, Berge V, Bottomley D, et al. “Prostate Cancer RCT Consensus Group. Can we deliver randomized trials of focal therapy in prostate cancer? .” *Nat Rev Clin Oncol.* 11 (2014): 482-491.