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Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study

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Abstract

Background: Although localised prostate cancer is multifocal in most instances, the index lesion might be responsible for disease progression.
Objective: To determine the early genitourinary functional and cancer control outcomes of index lesion ablation.
Design, setting, and participants: This was a single-centre prospective development study in which 56 men were treated (July 2009–January 2011). The mean age was 63.9 yr (standard deviation 5.8) and median prostate-specific antigen (PSA) was 7.4 ng/ml (interquartile range [IQR] 5.6–9.5). There were seven (12.5%) low-risk, 47 (83.9%) intermediate-risk, and two (3.6%) high-risk cancers.
Intervention: Multiparametric magnetic resonance imaging (mpMRI) and prostate biopsies to localise disease, followed by index lesion ablation using high-intensity focused ultrasound.
Outcome measurements and statistical analysis: Primary outcomes were genitourinary side effects measured using validated questionnaires. Secondary outcomes included absence of clinically significant disease at 12 mo.
Results and limitations: The composite of leak-free, pad-free continence, and erections sufficient for penetration decreased from a baseline frequency of 40/56 (71.4%) to 33/56 (58.9%) at 12 mo. Pad-free and leak-free, pad-free continence was preserved in 48/52 (92.3%) and 46/50 (92.0%) patients, respectively. Erections sufficient for intercourse were preserved in 30/39 (76.9%) patients. The median PSA nadir decreased to 2.4 ng/ml (IQR 1.6–4.1). At 12 mo, 42/52 (80.8%) patients had histological absence of clinically significant cancer and 85.7% (48/56) had no measurable prostate cancer (biopsy and/or mpMRI). Two (3.6%) patients had clinically significant disease in untreated areas not detected at baseline. The main study limitation is the short follow-up duration.
Conclusions: Index lesion ablation had low rates of genitourinary side effects and acceptable short-term absence of clinically significant cancer. Comparative effectiveness trials are required to assess cancer control outcomes against radical therapy.

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Patient summary: In this study we looked at whether it is possible to treat the largest and highest-grade tumour in men who have more than one known prostate tumour. We show that the side effects of targeted ablation were low, with acceptable rates of early cancer control. Larger studies with longer follow-up are needed.
Trial registration: NCT00988130

1. Introduction

For the last 100 yr, treatments for localised prostate cancer have had the whole prostate as their therapeutic target. The utility of a whole-organ approach to prostate cancer treatment has recently been brought into question. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) failed to demonstrate an overall statistically significant survival benefit associated with radical prostatectomy when compared to a conservative strategy [1], although survival benefits were seen in the intermediate- and high-risk subgroups. This confirmed the findings from the Scandinavian Prostate Cancer Group SPCG-4 trial of watchful waiting versus radical prostatectomy in men with high-risk prostate cancer [2]. However, the risk of incontinence and erectile dysfunction associated with radical whole-gland therapy is 15–20% and 30–60%, respectively [3], with significant other complications [4].

Focal therapy involves targeting individual areas of cancer while preserving the majority of the prostate tissue and therefore minimising the collateral damage to surrounding structures such as the external urinary sphincter, bladder neck, neurovascular bundles, and rectum [5,6]. Support comes from studies in which tissue preservation was applied but all known cancer was targeted [7–9]. These studies had very low side-effect profiles and cancer-free rates consistently between 80% and 90%.

Concern regarding focal therapy has centred on the knowledge that prostate cancer is multifocal in origin. In prostate cancer, a larger dominant lesion is often accompanied by two or three smaller low-grade lesions. A hypothesis has emerged that the largest lesion in the prostate—the index lesion—drives disease progression [10]. The index lesion tends to be associated with the highest Gleason grade, harbours other pathological determinants of progression, and has been associated with lymph node metastases on genetic profiling [11,12]. If the index lesion could be isolated with reasonable precision and treatment directed to it alone, then the oncological efficacy of whole-gland treatment might be matched while minimising the risk of side effects. To the best of our knowledge, this is the first prospective study testing this hypothesis.

2. Patients and methods

2.1. Study design and conduct

Our single-centre study was a prospective development study according to the IDEAL (Idea, Development, Exploration, Assessment, and Long-term) guidelines for evaluating innovation in surgery [13]. The trial was approved by Local Research Ethics Committee A of the University College London Hospitals.

2.2. Patient population

Treatment-naïve men recently diagnosed with low-, intermediate-, or high-risk nonmetastatic prostate cancer (prostate-specific antigen [PSA] $\leq$20 ng/ml, Gleason $\leq$ 4 + 3, stage $\leq$T3aN0M0) were eligible (Fig. 1).

2.3. Study interventions

2.3.1. Cancer localisation

Prostate cancer was localised using multiparametric magnetic resonance imaging (mpMRI) and transperineal template prostate mapping (TPM) biopsies [14] (n = 24) and/or transrectal ultrasound (TRUS)-guided biopsies (n = 22). TPM biopsies were carried out under general or spinal anaesthesia, with the prostate sampled at 5-mm intervals.

The index lesion was identified according to the following criteria. First, if an mpMRI lesion was visible on at least two sequences (equivalent to Prostate Imaging Reporting and Data System score of 4 or 5), the dominant biopsy findings had to be concordant with that lesion location. Second, the dominant histological lesion was assigned in the following manner whether an mpMRI lesion was present or not (TPM biopsies were required if an mpMRI lesion was not present):

(1) If the prostate only harboured Gleason 6 disease, then the index lesion was the lesion with the maximum cancer core length (CCL_{max}) provided all other lesions on biopsy located in another quadrant of the prostate had CCL_{max} $\leq$5 mm.
(2) If there was grade heterogeneity between individual lesions, then the lesion with the highest Gleason grade was regarded as the index lesion provided it had no more than Gleason 4 + 3 and the other lesions had no more than Gleason 3 + 3 AND CCL_{max} $\leq$5 mm.

2.3.2. Treatment

Focal ablation of the index lesion was performed using transrectal high-intensity focused ultrasound (HIFU; Sonablate 500, Focus Surgery, Indianapolis, IN, USA) (Supplementary materials). Untreated areas could contain secondary small-volume (CCL $\leq$5 mm) Gleason 3 + 3 disease [14], high-grade prostate intraepithelial neoplasia, and/or atypical small acinar proliferation (Fig. 2).

2.3.3. Follow-up

Contrast-enhanced MRI was carried out at 10–14 d to evaluate the area of ablation, demonstrated by a confluent perfusion deficit (Fig. 3). Clinical review at 1, 3, 6, 9, and 12 mo assessed adverse events, serum PSA, and responses to validated questionnaires. Phosphodiesterase-5 inhibitor (PDE5-I) use was permitted at any time point before treatment and during follow-up to aid erectile function. At 6 mo, mpMRI followed by biopsies targeted to the treated area was scheduled, with a minimum sampling requirement of one core for every 1 ml of residual tissue. Repeat treatment using focal HIFU for treated or untreated areas that