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Review – Prostate Cancer

The Role of Focal Therapy in the Management of Localised Prostate Cancer: A Systematic Review

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Abstract

Context: The incidence of localised prostate cancer is increasing worldwide. In light of recent evidence, current, radical, whole-gland treatments for organ-confined disease have being questioned with respect to their side effects, cancer control, and cost. Focal therapy may be an effective alternative strategy.

Objective: To systematically review the existing literature on baseline characteristics of the target population; preoperative evaluation to localise disease; and perioperative, functional, and disease control outcomes following focal therapy.

Evidence acquisition: Medline (through PubMed), Embase, Web of Science, and Cochrane Review databases were searched from inception to 31 October 2012. In addition, registered but not yet published trials were retrieved. Studies evaluating tissue-preserving therapies in men with biopsy-proven prostate cancer in the primary or salvage setting were included.

Evidence synthesis: A total of 2350 cases were treated to date across 30 studies. Most studies were retrospective with variable standards of reporting, although there was an increasing number of prospective registered trials. Focal therapy was mainly delivered to men with low and intermediate disease, although some high-risk cases were treated that had known, unilateral, significant cancer. In most of the cases, biopsy findings were correlated to specific preoperative imaging, such as multiparametric magnetic resonance imaging or Doppler ultrasound to determine eligibility. Follow-up varied between 0 and 11.1 yr. In treatment-naïve prostates, pad-free continence ranged from 95% to 100%, erectile function ranged from 54% to 100%, and absence of clinically significant cancer ranged from 83% to 100%. In focal salvage cases for radiotherapy failure, the same outcomes were achieved in 87.2–100%, 29–40%, and 92% of cases, respectively. Biochemical disease-free survival was reported using a number of definitions that were not validated in the focal-therapy setting.

Conclusions: Our systematic review highlights that, when focal therapy is delivered with intention to treat, the perioperative, functional, and disease control outcomes are encouraging within a short- to medium-term follow-up. Focal therapy is a strategy by which the overtreatment burden of the current prostate cancer pathway could be reduced, but robust comparative effectiveness studies are now required.

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1. Introduction

The advent of prostate-specific antigen (PSA) screening has led to stage, grade, and risk migration towards diagnosis of less aggressive prostate cancer (PCa). As a result, men with localised PCa and physicians who advise them face a difficult therapeutic dilemma: surveillance versus radical whole-gland therapy. The available evidence from randomised controlled trials (RCTs) demonstrates that there is little to no difference between these choices in terms of overall and cancer-specific survival after a median of 10 yr of follow-up [1]. In light of these findings, the patient's dilemma is made that much more profound by the significant rates of genitourinary and rectal side effects, which can occur despite technological improvements in surgery and radiation [2–5].

Consequently, there has been interest in focal therapy. This tissue-preserving strategy has at its core the reduction of treatment-related toxicity by minimising damage caused to the prostate and adjacent structures while attempting to retain the benefits of treating cancer [6–9]. This is an approach adapted by many other solid-organ malignancies, including renal, thyroid, breast, liver, and pancreas, but in which PCa has limited evidence and acceptance. Indeed, since whole-mount analysis of radical prostatectomy specimens has shown the presence of multiple foci of disease in most cases, the perception has been that whole-gland therapies are mandatory. However, new evidence suggests that the natural history of the disease is predominantly driven by the largest lesion with the highest grade, the so-called index lesion [10]. Therefore, targeted treatment delivered to the index lesion while sparing the rest of the gland may be a rational approach in men with intermediate- and low-volume, high-risk PCa that has disease suitable for a focal tissue-preserving approach. This proposition could make focal therapy achievable in the majority of men with localised PCa.

At the moment, any approach able to preserve part of the prostatic tissue (eg, "hockey stick" ablation, hemiablation, and focal ablation) is considered *focal therapy*. Many groups have published limited data on outcomes following focal therapy, and many others are actively engaged or considering prospective comparative effectiveness research in this area. It is an opportune time for a systematic review to evaluate the current evidence base and identify strengths and weaknesses and points of uncertainty about focal therapy to guide future trials.

2. Evidence acquisition

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We limited our systematic search to studies reporting on actual focal-therapy outcomes. We report on the following specific categories of data from the identified literature: (1) definition of the ideal candidate for focal therapy, (2) disease localisation, (3) identification of which lesions to target, (4) definitions of success and failure in focal therapy, and (5) morbidity and cancer-control outcomes after focal therapy.

Studies were identified by electronic search of Medline (through PubMed), Embase, Web of Science, and Cochrane Review databases from inception of the each respective database through 31 October 2012, with prespecified English language and human-studies restrictions. In addition, registered trials were retrieved from trials registries (ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number). We conducted a search of ongoing trials to allow us to determine the current thinking on patient eligibility, disease localisation, and types of outcome measures that investigators in this area are currently using. The search strategy was as follows: "PCa" OR "prostatic neoplasms" AND "focal treatment" OR "focal therapy" OR "tissue-preserving/-preservation" OR "subtotal" OR "cryosurgery" OR "cryotherapy" OR "cryoablation" OR "high-intensity focused ultrasound ablation" OR "HIFU" OR "photodynamic therapy" OR "PDT" OR "laser therapy" OR "brachytherapy."

RCTs, prospective development studies, and retrospective case series investigating ablative techniques to treat biopsy-proven PCa in a subtotal manner in the primary or salvage setting were included. Eligibility was reviewed separately by two reporters (M.V. and H.U.A.). In case of disagreement despite further discussion between the two authors, the senior author (T.J.P.) arbitrated. All selected articles were fully reviewed, and data extraction was predefined pro forma. Authors of included studies were contacted when one of the outcomes was not clearly or explicitly reported or when there were concerns about duplicate data sets; one reminder was sent for nonreplies. In cases where no reply was received, we chose not to report uncertain outcomes. When two or more series completely overlapped in time, only the largest series was reported; when the overlapping was partial over a limited time, all studies were reported, and the possible duplication of data was highlighted in the tables.

The primary end point was treatment-related side effects. We defined these in the following manner and differentiated them based on those reported by physicians and those using validated patient-reported questionnaires: leak-free continence, leak-free and pad-free continence, erections sufficient for penetration, and rectal toxicity (diarrhoea, bleeding, pain, rectourethral fistula). Functional outcomes were extracted from each study only when preoperative and postoperative data were available. In other words, only patients with normal function before treatment were considered. For instance, when calculating erectile function outcome, the denominator was represented by the men potent before the operation. Secondary end points were failure defined by residual PCa in the treatment area proven by biopsy, overall complications, quality of life (QOL) outcomes, need for secondary local or systemic treatment, and mortality. Biochemical outcomes also were reported.

The following data were extracted from each study:

- Predefined eligibility criteria
- Participants, including sample size, age, D'Amico or National Comprehensive Cancer Network cancer Risk classification, PSA level, and Gleason grade

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