Focal Ablation of Early-Stage Prostate Cancer

Candidate Selection, Treatment Guidance, and Assessment of Outcome

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KEYWORDS

• Prostate cancer • High-intensity focused ultrasound ablation • Cryotherapy • Laser therapy
• Photodynamic therapy

KEY POINTS

- Despite the multifocality of prostate cancer, there is evidence that lesions smaller than 0.5 m^3, or Gleason pattern 3 or less, have a low potential for clinical progression.
- Clinically significant disease is, therefore, often limited to a single index lesion. Focal ablation offers the option to target this index lesion, maintain oncological control, and minimize complications by the preservation of the healthy gland.
- Candidates are selected using template mapping or multiparametric MRI targeted biopsies to identify appropriate index lesions.
- Multiple energy modalities have been tested, including high-intensity frequency ultrasound, cryoablation, laser ablation, photodynamic therapy, focal brachytherapy, radiofrequency ablation, and irreversible electroporation.
- Outcome is assessed by "for cause" biopsy of the ablated area, triggered by prostate-specific antigen measurements or MRI or performed per protocol at 12 months.

INTRODUCTION

Treatment of prostate cancer currently relies on either active surveillance in low-risk disease or strategies that target the whole gland, such as radical prostatectomy or radiotherapy in intermediate-risk to high-risk disease. A limitation of whole-gland treatments has been the risk of genitourinary adverse events related to neurovascular, external urinary sphincter, or bowel or bladder injury. Some have described this approach to be akin to "using a sledgehammer to kill a flea."[1] The necessity to treat the whole organ can be attributed to 2 main issues. First, diagnostic techniques have not previously been accurate enough to localize lesions. Random transrectal ultrasound biopsy techniques (TRUS) do not allow for reliable localization of lesions.[2] In

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addition, imaging until recently had not been able to detect or localize significant lesions reliably.[3] Recent advances in diagnostics, however, with increased used of multiparametric (mp) MRI and targeted biopsies have allowed accurate localization of significant lesions. Second, a common criticism has been that prostate cancer is known to be a multifocal process.[4] It seems, however, that the multifocality is commonly related to secondary lesions that are small and low grade, particularly evident in postmortem studies, cystoprostatectomy, or prostatectomy series.[5] Within this multifocal landscape there is evidence that in many men an index lesion, the largest and highest grade, is the likely key driver of clinical disease progression. Thus, focal index lesion ablation can potentially halt or perhaps delay disease progression without the need for whole-gland treatment.[6] Third, there has been no widely accepted treatment modality that have been fully validated for focal ablation of prostate cancer. Multiple energy modalities have been tested including high-intensity frequency ultrasound (HIFU), cryoablation, interstitial laser ablation, photodynamic therapy (PDT), focal brachytherapy, radiofrequency ablation (RFA), and irreversible electroporation (IRE). With long-term data now available for large focal therapy series and prospective trials, including a randomized controlled trial (RCT),[7,8] there is now a large body of evidence supporting this treatment strategy.

The development of focal ablation has been driven by its significantly lower side-effect profile (erectile, urinary, and bowel dysfunction) compared with radical whole-gland surgery or radiation. In addition, it is a minimally invasive procedure performed in a day-case setting with many returning to normal activities within a few days rather than weeks during or after radical therapy.

CANDIDATE SELECTION

The basis for focal ablation relies on the following premises: candidates for focal ablation have a clinically significant index lesion; there may be other insignificant out-of-field lesions; tests can accurately identify the index lesion; and an appropriate energy modality is used to target and ablate the index lesion effectively and safely for a specific tumor in a particular individual.

The Index Lesion

There is growing acceptance of the index lesion theory of prostate cancer. Prostate specimens often demonstrate multifocal lesions[4] but there is evidence that small and low-grade lesions are clinically insignificant. In vitro studies demonstrate that low-grade lesions (Gleason pattern 3) do not bear the hallmarks of malignancy: self-sufficiency in growth signals, insensitivity to antigrowth signals, resistance to apoptosis, unlimited replicative potential, sustained angiogenesis, and, most importantly, tissue invasion and metastasis.[9] This is borne out with clinical data from large series, which show that true Gleason score 6 (3 + 3) does not have metastatic potential, with lack of lymph node metastases in men with pure Gleason 6 disease on radical prostatectomy specimens[10] and a 0% mortality in 9772 patients 15 years after radical prostatectomy.[11]

Small lesions (<0.5 cm^3) are also common, can be considered incidental, and are unlikely to develop into significant disease. A cystoprostatectomy series performed for bladder cancer demonstrated incidental lesions in 30% of prostates, with multifocality in 60% of these. None of these lesions was grade 4 or 5, and 90% were less than 0.5 cm^3.[5] In a series of patients with radical prostatectomy performed for prostate cancer, the presence of tumors less than 0.5 cm^3 did not contribute to the rate of disease recurrence. The size and grade of the index tumor, however, did correlate significantly with the rate of recurrence.[12] Stamey and colleagues[13] demonstrated that all lesions that may have developed into clinically significant prostate cancer were greater than 0.5 cm^3. This gave rise to the Epstein criteria for clinically insignificant prostate cancer: an organ-confined (pT2) cancer, less than 0.5 cm^3, Gleason score less than or equal to 6, and lacking any Gleason grade 4 or 5 component.[14] A later study has suggested this cutoff may be too stringent. This suggests that a minimum threshold of 1.3 cm^3 can be taken, if stage and grade are taken into account.

Altogether, these data suggest that candidates for focal therapy and any active treatment should be selected with a minimum lesion size of 0.5 cm^3 and a Gleason score of greater than or equal to 7. There are less clear data to support a maximum size for lesions to be ablated, although a significant, functional proportion of tissue must remain for any therapy to be considered focal ablation. Early studies often used hemiablation, although this has been refined in many later studies.[7] An international task force review in 2007 recommended maximum lesion diameter of 12 mm.[15] The same task force also recommended no Gleason 4 or 5 disease should be treated with focal therapy. That recommendation is now 10 years old and may reflect a tentative approach to the early experimental status of ablative technology at that point. University of Chicago Medicine has extended the criteria to Gleason score 6 or 7.[16] This in the authors' opinion is also too conservative because