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Seminar article

Target ablation—Image-guided therapy in prostate cancer[1]

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Abstract

Introduction: Current treatment options for prostate cancer, other than active surveillance, are limited to entire prostate gland destruction through removal (radical prostatectomy), radiation (external beam, brachytherapy, or a combination of both), or thermal ablation (cryoablation, high-intensity focused ultrasound, or radiofrequency). There has been a demand to develop ablative therapies that attempt to reduce treatment burden while retaining cancer control and avoiding the psychological morbidity associated with surveillance.

Materials and methods: We reviewed the literature to concentrate on the practical aspects of focal therapy for Pca with the following key words: photodynamic therapy, HIFU, cryotherapy, focal laser ablation, electroporation, radiofrequency, external beam radiation, organ-sparing approach, focal therapy, prostate cancer. The aim of this article is to review these energy modalities' functional and oncologic results.

Results: Prostatic tumor ablation can be achieved with different energies: freezing effect for cryotherapy, thermal effect using focalized ultrasound for HIFU and using thermal effect of light for FLA and activation of a photosensitizer by light for PDT, among others. Radiofrequency and microwave therapy have been tested in this field and demonstrated their usefulness. Electroporation is currently being developed on preclinical models. External beam radiation with microboost on neoplastic foci is under evaluation. HIFU and cryotherapy require the use of sophisticated and expensive machines. However, series published short term effective with low morbity, reversible therapy.

Conclusion: Several energy modalities are being developed to achieve the trifecta of continence, potency, and oncologic efficiency. Comparison of the different focal approaches is complex owing to important heterogeneity of the trials. In the future, it seems likely that each technique will have its own selective indications.

Keywords: Focal therapy; Prostate cancer; Image fusion; HIFU; Cryotherapy; Photodynamic therapy; Focal laser ablation

Background

Current treatment options for prostate cancer (PCa), other than active surveillance, are limited to entire prostate gland destruction through removal (radical prostatectomy), radiation (external beam, brachytherapy, or a combination of both), or thermal ablation (cryoablation, high-intensity focused ultrasound [HIFU], or radiofrequency). Furthermore, a growing number of small-volume and low-grade cancer foci are diagnosed in young healthy men [1]. As many of these cancers grow slowly and, even if untreated, never progress to symptomatic disease, patients and clinicians face the dilemma of if, when, and how to treat localized PCa.

Focal therapy (FT) is an emerging alternative treatment option for active surveillance for these patients and offers great hopes in terms of cancer control and decreased morbidity for localized PCa. The challenge of therapy modalities is to treat only localized tumors, focusing on tissue preservation, especially near the urethral sphincter and the neurovascular bundles, to minimize the potential morbidity [2–4].

The concept of FT remains controversial because PCa is frequently multifocal. However, some authors showed that in case of multifocal localizations, only the volume of the index lesion itself (i.e., the main lesion) is predictive of progression [5–7]. A threshold volume of 0.5 ml is currently understood as the clinically significant lesion size.

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Table 1
Patient selection criteria for FT

Criteria	Best selection criteria for FT	Comments
Age	No limits	Life expectancy >5 y might be added.
Urinary function	No limits	IPSS to inform about the risk of AUR.
Prostate size	Depends upon modality	In small glands <20 cc (or previous TURP), FT may damage periprostatic striated sphincter.
MRI and MRI-targeted biopsies	Yes (some cancers not seen on MRI could be eligible for FT)	MRI best modality to see index tumor and check if rest of the gland is free of tumor. MRI-targeted biopsies necessary to diagnose 20% of tumors missed by posterior systematic biopsies.
Index tumor, >0.5 cc or 7 mm diameter	Yes	Represents the limit of detection by MRI. Could be 2 index tumors need to be treated.
Tumor grade	Grades 3 or 4	If well circumscribed and located of grade 4 <50% is not a countraindication (4 + 3 or 4 + 4 reserved in phase III FT vs. RP).
Tumor volume	0.5–2 cc	Should be less than two-thirds of a lobe in height and less than half of a lobe in thickness. Otherwise, it should be subtotal therapy.
DRE, T category	Could be T1c or T2 or T3a	DRE could be suspicious or not. Best criteria are location and size on imaging and biopsy results.
PSA	3–10 ng/ml or 10–20 ng/ml in concordance with tumor grade and volume	PSA value should be concordant with tumor size and grade and gland size. If PSA level is close to 20 ng/ml with a kinetics >1 ng/ml/y in case of a 0.5 cc grade 3 + 3 tumor, there is discordance.
Location	Not at the apex	Ablation of lesion plus margin located the apex without sphincter damage has not been validated. Lesion contour at MRI should be >5 mm from apex. Anterior location or close to urethra or bladder neck is not a countraindication.
Multifocality	Yes	Not a countrainduction if clinically unsignificant tumor foci.[a]

AUR = acute urinary retention; DRE = digital rectal examination; IPSS = International Prostate Symptom Score; RP = radical prostatectomy.
[a]Clinically unsignificant tumor foci defined as a cT1c, negative results on DRE, 1 or 2 positive results on biopsies <3 mm grade 3 + 3 (Hardern Criteria), not seen on MRI.

Patient selection

Parameters to select patients for FT include primarily tumor location and size, which are best assessed by magnetic resonance imaging (MRI)–targeted biopsies. MRI is the best modality to see the index tumor and check if the rest of gland is free of tumor. MRI-targeted biopsies help to diagnose 20% of anterior tumors missed by posterior systematic biopsies. Hence, FT modalities should be able to reach the location of the cancer and encompass its contour with a safety margin. Other parameters such as number of positive biopsies and cancer length at systematic biopsies are not accurate enough to be taken as primary parameters. If the tumor is well circumscribed and located, a grade 4 <50% is not a contraindication (4 + 3 or 4 + 4 must be reserved in phase III FT vs. radical prostatectomy). Investigators would then have to begin treating localized cancers with aggressive features, to determine the oncologic efficacy and utility. Prostate-specific antigen (PSA) and tumor grade are parameters that may be part of the selection for FT but should be validated. A list of best selection criteria for FT has been proposed; however, consensus for these criteria is not yet published (Tables 1 and 2). A limitation of including intermediate- and high-risk men is the higher rate of micrometastases and disease progression observed in them, even after radical therapy [8].

Experts must work on these criteria for patient selection and on the surveillance modality too. There is no world consensus to report oncologic outcomes and efficacy: negative results on biopsy, biochemical disease-free survival, and PSA decrease. These criteria based only on PSA are challenged because in FT only the tumor area or the hemiprostate is treated, so prostate gland is spared and it is difficult to determine the progression of hyperplasia in the prostate. The American Society for Radiation Oncology (ASTRO) criteria (3 consecutive increases in PSA levels from nadir) and the Phoenix criteria (nadir PSA +2 ng/dl rise) are often used but have not been validated yet for FT. In summary, a combination of biochemical, histological, and imaging results can be used to evaluate the oncologic control achieved by focal treatment.

Intraprostatic imaging

Several imaging modalities have shown potential to guide focal ablative therapy. These include ultrasound (US; Doppler, contrast enhanced, and tissue-characterization algorithms) and MRI (contrast enhanced and diffusion weighted) but, none have become standards of care to one or more issues with sensitivity, specificity, positive predictive value, negative predictive value, or reproducibility. Pioneering works in the fusion imaging of the prostate used radiotherapy (external beam radiation therapy and brachytherapy) with fusions of computed tomography, MR, US, and fluoroscopy [9,10].