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Image Guidance in the Focal Treatment of Prostate Cancer

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Abstract

Purpose of Review—The advent of PSA screening has led to a 7-fold increase in the incidence of prostate cancer (PCa) without a resultant decrease in mortality rate. This has led to the belief that urologists are over-detecting and over-treating the clinically insignificant disease. To maintain the delicate balance between high cancer cure rate and overtreatment, which could potentially lead to unnecessary morbidities, focal therapy (FT) has emerged as the reasonable “middle ground.” In this article, we present the conceptual basis and the challenges of FT, while emphasizing the critical role of imaging in focal treatment of prostate cancer.

Recent Findings—Multiple phase I trials have demonstrated the feasibility, short-term efficacy, and safety of FT. Fundamental to the success of these trials and the ultimate acceptance of FT is the integral role of imaging in optimal patient selection. Among the different imaging modalities, only ultrasound and multiparametric MRI (mpMRI) are intimately involved in the detection, diagnosis, staging, and treatment of PCa. Each modality has its own unique advantages and shortcomings. Recent advances in enhanced ultrasound modalities (EUSMs), functional MRIs, and biopsy platforms have taken FT one step closer to becoming the standard of care.

Summary—Although early results of phase I FT trials are encouraging, long-term oncological outcomes remain to be elucidated. Incorporation of these technological advances into large prospective trials is needed to establish FT as an important asset in the urologist’s armamentarium against prostate cancer.

Keywords

multiparametric MRI; focal therapy; enhanced ultrasound modalities; prostate cancer

Introduction

Prostate cancer, the leading non-cutaneous cancer in US men, is responsible for more than 30,000 deaths and 240,000 new cases per year.[1] Accompanying this disease is a significant economic burden costing billions of dollars per year.[2] According to the Surveillance, Epidemiology, and End Results (SEER) database, the advent of PSA screening in 1987 has shifted the entire detection paradigm toward earlier diagnosis of localized disease, resulting

in roughly 7-fold increase in incidence compared to the pre-PSA era. While incidence remains persistently elevated, cancer specific mortality rate remains unchanged at roughly 5%. In fact, the Scandinavian Prostate Cancer Trial demonstrated only modest increase in survival for patients who underwent radical prostatectomy compared with those who elected no primary therapy.[3] This has led to the belief that urologists are over-detecting and over-treating the clinically insignificant disease.

Current whole gland therapies such as radical prostatectomy and radiation offer the best oncological efficacy in exchange for well-documented morbidities. To maintain the delicate balance between high cancer cure rate and overtreatment, strategies such as active surveillance (AS) have been conceived. While the notion of AS is attractive, many patients are often reluctant in forgoing their treatment; thus limiting this in practice. Additionally, up to one-third of patients on AS will still require some form of treatment.[4] As a result, FT arises as a complementary adjunct that may achieve the desired oncological control with minimal morbidity.

To date, there are 7 phase I FT trials in the literature, with the majority employing cryotherapy as the ablative energy source (Table 1).[5–12] Instrumental to their successes is optimal patient selection for which image guidance plays a critical role in cancer detection, localization, staging, and treatment. In this article, we present the conceptual basis and challenges of FT while emphasizing the evolving critical role of imaging in the focal treatment of prostate cancer.

Conceptual Basis and Hurdles of Focal Therapy

Conceptually, focal therapy involves the selective destruction of prostate cancer foci while leaving the rest of the gland intact with the intention of avoiding the urinary and sexual side effects that frequently plague whole gland therapies. In its strictest interpretation, FT strives to achieve cancer cure; however, it could also be considered as a method for cancer control or as a component of multimodal approach for high risk patients.[13] Until recently, FT has been more of a concept rather than a reality due to several conceptual hurdles, such as the multifocal nature of PCa, the lack of a reliably accurate imaging modality in characterizing the cancerous lesions, and the lack of a precise platform that allows for targeted biopsy of suspicious lesions for proper staging. The success of FT rests with optimal patient selection, which demands overcoming these obstacles.

While it is true that prostate cancer is a multifocal disease, proponents of FT have pointed out that not all lesions are equal in their inherent propensity to progress and metastasize. Some authors have hypothesized the existence of a dominant “index” lesion that is responsible for cancer progression and metastasis. Since the goal of treatment should be to at least eradicate all clinically significant disease, targeted treatment of an “index” lesion may be a viable solution to the multifocality of PCa.[14;15] Similarly to breast cancer where lumpectomy provides a “middle ground” between cancer control and morbidity, FT could be likened to as the “male lumpectomy.”[16] Although the exact natural history of prostate cancer is still being investigated, multiple studies have correlated cancer volume of 0.5cm^3 to disease progression.[15;17] Whereas, the index lesion could represent 80% of the total

tumor volume and account for 90% of extraprostatic extension, secondary lesions typically have a smaller mean cancer volume of 0.3cm³. [18;19] A systematic review and meta-analysis by Harden et al. found that clinically insignificant tumors generally were less than 3mm in length, had a single positive core on biopsy, and did not demonstrate primary Gleason 4 or 5 on biopsy. [20] Armed with this information, urologists could selectively apply FT to lesions $\leq$ 5mm while electing to observe smaller, clinically insignificant tumors. This strategy not only satisfies the desire for oncological control but also allows for a greater understanding of the natural history of these clinically insignificant lesions.

In the past, imaging has played a significant role only in the staging process. Today, it has injected itself into all aspects of the management of prostate cancer. Advances in state-of-the-art prostate imaging, such as enhanced ultrasound modalities (EUSM) and multiparametric MRI (mpMRI), represent big milestones in bringing FT one step closer to standard clinical practice. Traditional grey-scale ultrasound (GSUS) has low spatial resolution due to its inherent speckled pattern. Coupling this with the heterogeneous nature of the prostate has resulted in low predictive value, especially in detecting and delineating isoechoic lesions. [21] The development of EUSMs, such as color Doppler (CDUS), contrast-enhanced (CEUS), and sonoelastography (EUS), has significantly augmented the sensitivity of GSUS in visualizing cancer foci. [22–28] While encouraging, many of these EUSMs remain to be extensively tested.

Research into different MRI techniques has resulted in the development of multiple functional MR modalities, such as spectroscopy, diffusion-weighted, and dynamic contrast-enhanced. The ability to detect, locate, and characterize PCa radiographically has great clinical implications in the diagnostic algorithm. Whereas the sensitivity and specificity for cancer detection using a standard T2-weighted sequence alone ranged from 27–100% and 32–99%, respectively, a combination of the above modalities results in a significant improvement in positive predictive values. [29–33] Using the novel patient-specific MRI-based prostate molds to correlate whole-mount histologic sections to axial MRI images, Turkbey et al. was able to reliably validate this with high accuracy. [33]

Better detection demands better localization. The development of a novel platform that superimposes pre-biopsy mpMR imaging with real-time transrectal ultrasound (mpMRI/US fusion) to allow for targeted biopsy has demonstrated superior cancer detection rate of 54.4%, compared to 27–40.3% for standard random biopsy (FIG 1). [34] Hadaschik et al. also reported a detection rate of 59.4% for his cohort of 106 patients who underwent stereotactic perineal prostate biopsies with mpMRI/US fusion guidance. [35;36] Additionally, the fusion platform allows for potential tracking and re-sampling of each biopsy core. Though this platform has its own limitations, the findings from these studies highlight the potential value of the fusion biopsy platform in properly staging and assessing patient risk.

Ultrasound Guidance in Focal Therapy of Prostate Cancer

Pioneered by Watanabe et al. in the early 1970s, the diagnostic application of transrectal ultrasound (TRUS) has revolutionized the field of urology. Comparing to the crude method

of digitally-directed prostate biopsy, a TRUS-guided approach is safer, more reliable, and highly accurate. In fact, Watanabe et al. reported the diagnostic accuracy of the novel platform to be more than 80%.[37] Since then, several studies have demonstrated the superior yield of biopsy-proven cancer using the TRUS-guided platform compared to the digitally-directed approach. As a result, TRUS-guided biopsy has become the “gold standard” in the diagnosis of prostate cancer.

With its relative ease of use, reasonable sensitivity, low operating cost, portability, and widespread availability, it is not surprising that TRUS has become the basis for many early focal therapy trials. In 2002, Onik et al. published a pilot FT trial involving cryo-hemiablation in 9 patients with unilateral localized disease, with the primary objective of determining the potency rate after unilateral nerve sparing. TRUS assisted in the injection of saline into the Denonvilliers fascia to increase the “safety zone” between the prostate and rectum, guided the cryoprobes in place, and monitored ice ball formation. At a mean follow up of 36 months, all patients had stable PSAs, 6 out of 9 patients had negative repeat biopsies, and 7 out of 9 patients had maintained their potency.[5] In his updated series of 48 patients with a mean follow up of 4.5 years, 94% had stable PSAs per ASTRO criteria, 90% of those who were potent preoperatively had preserved their potency, and none had residual disease among the 24 patients who had routine biopsies. No patients experienced significant morbidities such as urinary incontinence or rectal fistula.[10] This study highlighted the crucial role of ultrasound in providing intra-operative guidance as well as demonstrated the feasibility and efficacy of FT in controlling tumor burden without compromising potency.

Following this initial trial, Lambert et al. reported similar results in a retrospective review of 25 patients with low volume, cT1c Gleason 7 (3+4) cancer who underwent cryo-hemiablation. All patients underwent standard random TRUS biopsy for diagnosis and lateralization of the disease. The procedure was performed under TRUS guidance. At a median follow up of 28 months, the biochemical disease free survival was 88% using the definition of PSA nadir + 2. Three patients who were found to have disease recurrence in either ipsilateral or contralateral sides to the surgery subsequently underwent repeat cryoablation and were rendered biochemically disease free. All patients remained continent, but only 71% of those who were potent preoperatively were able maintain their potency.[8] In another study of 60 patients with cT1c-T2cN0M0 disease who underwent “hockey-stick” cryo-hemiablation, Ellis et al. reported that 80% remained biochemically disease-free at a mean follow up of 15 months. The diagnostic, qualification, and treatment processes were similar to those utilized in the preceding trial. While continence and potency rates were similar, persistent disease was found in 14 out of 35 patients who underwent post-treatment biopsy, yielding a 23% rate for the entire group or 40% of those who were re-biopsied.[7] Using high intensity focused ultrasound (HIFU) as the ablative energy source, Muto et al. treated 29 patients with unilateral localized disease. These patients were included based on their extended TRUS biopsy and pelvic MRI. The 2-year biochemical disease free survival rates were 83.3% and 53.6% for low and intermediate risk groups, respectively. While 25/28 (89%) had a 6-month post-HIFU negative biopsy, only 13/17 (76%) achieved similar results at their 12 month biopsy.[9] These studies exposed the inherent flaw of standard random TRUS biopsy in understaging prostate cancer and emphasized the importance of optimal patient selection.

The development of multiple EUSMs serves to combat the Achilles' heel of GSUS in detecting small, isoechoic foci in heterogeneous prostates. Based on the principle that cancerous lesions are densely packed and have increased vascularity, CDUS aims to enhance the visualization of these lesions by detecting regions of hypervascularity. Early studies have suggested that CDUS may improve the radiographic sensitivity of GSUS.[38;39] In his study of 31 men with clinically organ-confined prostate cancer who underwent cryo-hemablation, Bahn et al. utilized CDUS to thoroughly examine the prostate, target suspicious lesions, and lateralize the cancer. At a mean follow up of 70 months, 92% (26/28) achieved biochemical disease-free status using the ASTRO definition, 96% (24/25) of those who underwent repeat biopsy had negative results, and 89% (24/27) had maintained their potency despite some requiring phosphodiesterase-5 inhibitors initiation.[6] The result from this study demonstrated the importance of continuing research commitment to improve our diagnostic modality.

Despite CDUS's early encouraging results, further studies failed to validate its superior sensitivity over GSUS due to the fact that most small tumors have not developed macroscopic angiogenesis.[40] Utilizing microbubble contrast agents to image vascular perfusion patterns, CEUS appeared to be promising in some early studies. Xie et al. reported the superior sensitivity and specificity of CEUS to be 81.1% and 84.3%, respectively.[26] This finding was consistent with the results of several TRUS biopsy controlled studies with reported CEUS sensitivity ranging from 65–93%.[22–24;27] In his phase I FT trial of 12 patients using a diode laser as the ablative energy source, Lindner et al. creatively employed CEUS to monitor ablative areas, which appeared as well-defined regions of decreased enhancement. Post-treatment MRI confirmed good overlap of necrotic areas with intraoperative CEUS findings.[11]

Capitalizing on the principle that tumors have higher density which results in increased “stiffness,” sonoelastography (EUS) translates “in vivo palpation” of prostatic tumors into visual representations according to their relative level of “stiffness”.[28] This technique has been found to have improved sensitivity upwards of 80%. When combining this with GSUS, Miyagawa et al. reported a high sensitivity of nearly 90% for cancer detection.[41] Furthermore, some authors have suggested that EUS may permit tumor size estimation, potentially allowing for FT monitoring.[42]

These advances seek to reinstate ultrasound's dominance and pivotal role in the diagnosis and management of prostate cancer. Certainly, no single imaging modality is perfect by itself. Perhaps, as the PCa paradigm evolves, improvements in ultrasound will keep up to prevent it from being antiquated.

MR Guidance in Focal Therapy of Prostate Cancer

Recent advances in MRI will eliminate the biggest conceptual hurdle against FT. The ability to accurately characterize suspicious lesions and precisely navigate a biopsy or treatment apparatus to target is crucial in optimal patient selection to ensure good oncological outcome with minimal morbidity. With its superb ability in soft tissue differentiation, mpMRI provides excellent visualization of the prostate and pelvic anatomy. While plain T2-weighted

MRI has low sensitivity for tumor detection, the combination of additional parameters such as diffusion-weighted, spectroscopy, and dynamic contrast enhanced sequences significantly improves its sensitivity and overall positive predictive values.[43]

Although most early focal therapy trials utilized GSUS for detection, localization, and guidance, mpMRI offers some unique advantages over ultrasound. One such advantage is its ability accurately detect temperature changes in real-time – a feature that allows for intraoperative assessment of thermal damage. In our IRB-approved, phase I focal laser ablation (FLA) trial at NIH/NCI, we recruited patients with organ-confined clinical T2a Gleason 7(3+4) in 4 cores or less and screened all patients with mpMRI using a 3.0 Tesla MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands). Standardized MRI acquisition of T2-weighted, axial diffusion-weighted, 3D spectroscopy, and axial dynamic contrast-enhanced sequences was performed by using a combination of a 6-channel cardiac surface coil (SENSE, Philips Healthcare) placed over the pelvis together with an endorectal coil (BPX-30, Medrad, Pittsburgh, Pennsylvania). Two experienced GU radiologists independently evaluated and graded any suspicious lesions based on the number of positive functional MRI modalities (low 2/4, moderate 3/4, or high 4/4). Subsequently, using the mpMRI/US fusion platform, we performed targeted biopsy of these suspicious lesions plus standard 12 core random TRUS biopsy. Once biopsy-proven to be cancerous, treatment of these lesions involved using the FDA-approved Visualase 980nm diode laser system (Visualase, Houston, TX). In-gantry mpMRI was employed to locate the desired tumor, guide laser fiber placement, and confirm optimal placement. MR-thermometry provided precise, real-time assessment of ablative zones (Fig 2). So far, we have treated five patients using this method. Post-treatment mpMRI confirmed good overlap between cancerous lesions and areas of necrosis, in all patients except for one. Although long-term oncological data is still pending, the acute toxicity profile appears to be minimal.

Similarly, in his phase 1 FT trial of 12 patients with localized prostate cancer, Lindner et al. utilized two parameter (T2-weighted and diffusion-weighted) mpMRI to additionally screen for any suspicious lesions within the prostate.[11] Those who were found to have MR-detectable tumors subsequently underwent targeted biopsy. In their study, 3D ultrasound provided guidance for laser fiber placement and CEUS with a microbubble contrast agent was utilized to monitor ablative lesions. At 6 month follow up, six patients were found to have completely negative biopsies, four were found to have residual disease in the treatment areas, and two had disease in the contralateral lobe. No perioperative or significant post-operative morbidities were noted.

Instead of using laser as the ablative energy source, Ahmed et al. utilized high intensity focused ultrasound (HIFU) to treat 20 men with low to intermediate risk unilateral disease. [12] All of these men underwent mpMRI for screening followed by template transperineal mapping biopsies for staging. At a mean follow up of 12 months, 89% (17/19) of patients achieved the trifecta status of continence, sufficient erectile function, and cancer control.

Despite having many distinct advantages over GSUS, mpMRI also poses certain challenges, including its extreme sensitivity to metals and time-consuming image acquisition process. Nevertheless, multiple clinical trials have cemented the crucial role that mpMRI will play in

FT and also suggest that its future clinical applications may be limitless. As a result, interventional MR-guided treatments are gradually gaining acceptance among urologists and patients.

Main Points

- Multiple phase I focal therapy trials demonstrated feasibility, safety, and short-term oncological control.
- Long-term oncological efficacy remains to be answered.
- Enhanced ultrasound modalities augment grey-scale ultrasound sensitivity in cancer detection.
- Multiparametric MRI possesses highest predictive values in tumor detection.
- MRI/US fusion biopsy platform yields superior cancer detection rate compared to TRUS-guided biopsy.

Conclusion

Focal therapy is an evolving paradigm that still requires further investigation. Many obstacles need to be overcome prior to its acceptance as a treatment choice in the urologic community. These preliminary phase I studies demonstrated the feasibility, short-term efficacy, and safety of FT. However, the ultimate question regarding long-term oncological control remains to be answered. The success of FT rests with optimal patient selection which largely depends on the ability of our imaging tools to accurately stage and risk-stratify patients. What has traditionally been lacking in ultrasound can be found in mpMRI. From its superb resolution in characterizing soft tissues and anatomy, its unparalleled ability to accurately guide an ablative apparatus to a target, and its unique capacity to assess temperature changes, mpMRI has become a favorite among proponents of FT. However, recent developments in EUSMs partly serve to bridge the technological gap between the two modalities as well as re-establish its relevance in this field. Incorporation of these technological advances into large prospective trials is needed to establish FT as an important asset in the urologist's armamentarium against prostate cancer.

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Fig 1.
mpMRI/US fusion prostate biopsy (Philips Healthcare, Netherlands).

Fig 2.

A. Pre-operative T2 weighted axial MRI image of a suspicious lesion in the right mid anterior prostate B. Coronal MRI planning image showing laser fiber being placed within the area of suspicion C. Real time MR thermometry monitoring of ablation zone D. Six month post-operative T2 weighted axial MRI with region of hypo-intensity signifying necrosis, corresponding to area of suspicion on pre-operative scan. Regional atrophy is also noted.

Table 1

Phase I focal therapy trials

Authors	Patients (n)	Tumor detection	Treatment modality	Follow up (mths)	Clinical stage	PSA	BDFS	Disease Persistence	Potency	Incontinence
Onik et al.[5]	9	TRUS-guided bx	Cryoablation	36 (mean)	cT2b Gl 8	8	100%	0	78%	0
Bahn et al.[6]	31	TRUS-guided bx	Cryoablation	70 (mean)	cT2 Gl 4+3	4.95	93% [/]	4%	89%	0
Ellis et al.[7]	60	TRUS-guided bx	Cryoablation	15 (mean)	cT1c-cT2c	6.1	80% [/]	23%	71%*	3.60%
Lambert et al.[8]	25	TRUS-guided bx	Cryoablation	28 (median)	cT1c Gl 3+4	6	88%	12%	71%	0
Muto et al.[9]	29	TRUS-guided bx	HIFU	34 (median)	cT1c-cT2a	5.4	83.54,0% [†]	14% [‡]	NR	NR
Onik et al.[10]	48	TRUS-guided bx	Cryoablation	54 (mean)	NR	7.8	92% [/]	8	90%	0
Lindner et al.[11]	12	mpMRI + TRUS-guided bx	Laser Ablation	6	cT1c Gl 3+3	5.7	NR	50%	100%	0
Ahmed et al.[12]	20	TRUS-guided bx	HIFU	12 (mean)	cT2b Gl 4+3	7.3	80%	11%	95%	10%

[/] ASTRO criteria

[‡] after 12 months