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Laser Ablation as Focal Therapy for Prostate Cancer

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Abstract

Purpose of Review—Focal laser ablation is an emerging treatment paradigm for prostate cancer that aims to successfully eradicate disease while also reducing the risk of side effects compared to whole-gland therapies.

Recent Findings—Preclinical and phase I clinical trials for low-risk prostate cancer have shown that focal laser ablation produces accurate, predictable, and reproducible ablation zones with negligible injury to surrounding tissues. Because focal laser ablation is magnetic resonance-compatible, the procedure can be monitored with real-time feedback to optimize targeted treatment of cancerous foci and minimize quality-of-life side effects. The oncologic efficacy of magnetic resonance imaging-guided focal laser ablation is currently being evaluated in ongoing phase II clinical trials.

Summary—Focal laser ablation is a safe and feasible therapy for low-risk prostate cancer, and the oncologic efficacy of this treatment modality is currently under investigation in phase II clinical trials at several institutions.

Introduction

Prostate cancer remains the most frequently diagnosed cancer among men in the United States and the second leading cause of cancer-related death in this population. Since its clinical introduction 25 years ago, the prostate-specific antigen (PSA) blood test has emerged as a widespread screening method for prostate cancer. Coupled with the digital rectal examination, PSA screening has improved early detection, with most cases being identified in a clinically localized stage with a five-year relative survival rate approaching 100% [1]. Furthermore, early detection by PSA screening in conjunction with new and improving treatment options has led to an approximately 40% decrease in age-adjusted prostate cancer-specific mortality in the United States over the past 25 years [2].

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However, prostate cancer has also become increasingly entwined with overdetection and overtreatment, which are defined as diagnoses and interventions, respectively, for cancers that will never become clinically evident or significant during the natural lifespan of a patient. According to the American Cancer Society, approximately 240,000 cases of prostate cancer will be diagnosed in the United States in 2013, yet only 29,000 deaths are attributed to the disease [1]. Furthermore, it has been estimated that 12-37 cancers need to be detected by PSA screening to prevent one prostate cancer-specific death at over ten years of follow-up [3, 4].

Multiple strategies are utilized to mitigate overdiagnosis and overtreatment of prostate cancer. PSA screening guidelines have recently been updated by the American Urological Association with the goal of preserving the benefits of screening and minimizing its potentially harmful impact [2]. Novel screening tests (e.g. the Prostate Health Index and the 4K Score) and gene-based evaluations of cancers (e.g. Prolaris and Oncotype DX) are emerging modalities intending to identify intermediate or high-grade cancers and limit the diagnosis and treatment of low-grade cancers.

Yet, there remain a significant number of prostate cancers diagnosed each year that are treated aggressively with surgery or radiation despite having low-risk features. Approximately half of all men who underwent surgery in the European Randomized Study for Screening Prostate Cancer (ERSPC) trial were found to have cancers that met criteria for clinically indolent disease (< 0.5 cm^3 tumor volume, organ confined, and Gleason score 6) [5]. While most men diagnosed with prostate cancer will pursue one of several surgical or radiation treatment options, which boast high rates of successful disease eradication, existing forms of whole-gland therapy carry meaningful risks of urinary, sexual, and bowel-related morbidity, even under the direction of experienced caregivers. As such, the emphasis of curative therapy has now shifted toward quality of life after treatment and pursuit of therapy for men likely to reap an oncologic benefit.

Among the alternatives to whole-gland therapy for prostate cancer are active surveillance and focal therapy. Active surveillance (AS) is a strategy whereby prostate cancer is maximally characterized at diagnosis utilizing available diagnostic tools. Those patients with low-risk cancer are identified using specific but widely variable criteria, and their cancer is then re-evaluated on a regular basis, with the intention of preventing overtreatment of low-risk disease. When properly applied to men with low-risk prostate cancer, AS has a greater than 97% ten-year metastasis-free and cancer-specific survival [2, 6].

Focal therapy, which is essentially partial gland therapy, specifically targets known areas of cancer in the prostate while attempting to minimize the side effects associated with whole-gland treatment, which may cause damage to critical structures like the urethra, urethral sphincter, erectile nerves, and rectum. The goals of focal therapy for prostate cancer are multifold. This management option relies on optimizing cancer characterization and location at diagnosis and eradicating clinically meaningful cancers to achieve effective oncologic control. Quality of life is concurrently prioritized as focal therapy spares non-cancerous portions of the organ and intends to reduce the risk of urinary, sexual, and bowel-related side effects. Finally, this therapeutic modality allows for retreatment with focal or whole-gland

intent, if needed. As such, focal therapy of the prostate gland endeavors to combine the most appealing elements of whole-gland therapies (i.e. definitive eradication of cancer) and AS (i.e. preservation of quality of life). Given these desirable aims, there has been emerging interest and study of minimally invasive focal therapy for clinically localized prostate cancer.

Focal therapies for cancer are familiar to urologists. Transurethral resection of bladder tumors, partial cystectomies, and partial nephrectomies are focal therapies commonly employed within the field of urology. In comparison, the most widely accepted and best-studied form of focal therapy is lumpectomy for breast cancer. First reported in the 1930s, lumpectomy was not well received or utilized by practitioners for decades. With time, multiple large-scale randomized trials reported equivalence of lumpectomy to radical mastectomy for many women with breast cancer, such that by 2010 approximately 75% of newly diagnosed breast cancers were treated by lumpectomy [7].

While the management of prostate cancer continues to be driven by whole-gland treatment modalities, focal therapy is emerging as an increasingly desirable treatment paradigm for prostate cancer. Focal therapy of the prostate can be administered by several modalities: cryotherapy, high-intensity focused ultrasound, radiotherapy, electroporation, photodynamic therapy, and laser-induced interstitial thermal therapy (LITT or laser ablation). This review article will focus on laser ablation guided by magnetic resonance imaging (MRI) as a focal therapy for prostate cancer. We will consider the current technique for focal laser treatment of the prostate gland as well as supporting evidence for this therapy in existing literature.

Focal Laser Ablation

MRI-guided focal laser ablation (FLA) is a technique currently being evaluated for focal therapy of prostate cancer. Prostate tissue is particularly well suited for laser ablation due to its optical absorption rate and lack of excessive vascularity. As will be discussed in this review, the laser can create accurate, predictable, and reproducible ablation zones and induce minimal changes to the tissues outside the targeted ablation zone. Additionally, because FLA is magnetic resonance (MR)-compatible, it affords a significant imaging advantage over other surgical and ablative techniques that utilize transrectal ultrasound to guide and monitor treatment. MR imaging provides excellent soft tissue contrast and anatomical visualization to facilitate treatment planning and targeting. Additionally, MR-based temperature monitoring allows for real-time feedback during FLA.

Technique

At our institution, all patients are placed on prophylactic antibiotics the night prior to the procedure. Imaging and ablation are performed under monitored conscious sedation. MRI-guided FLA can be performed on a 1.5 or 3 Tesla (T) MR scanner. While some groups have employed a transrectal approach, we utilize a transperineal approach aimed at reducing the risk of rectal wall damage and providing improved access to the apical and anterior portions of the prostate. An MR-compatible transperineal template (Figure 1A) is fixed to an endorectal coil. A high-quality T2-weighted image of the prostate is acquired and subsequently loaded into the software (Visualase, Inc.; Figure 1B) for guiding applicator

placement. Titanium trocars and guide catheters are placed through the appropriate grid hole on the transperineal template and inserted to the target depth reported from the planning software. Next, an imaging plane containing the applicator provides the desired view of critical structures (e.g. urethra, rectum, and prostatic capsule). Multi-planar imaging is used for monitoring, with particular attention to the target tumor and critical surrounding structures. Temperature-sensitive fast radiofrequency-spoiled gradient-recalled echo images are then repeatedly acquired during the ablation procedure to provide real-time temperature information from the tissues of interest.

After confirming the laser tip (Figure 1C) is situated in the desired location, the laser is activated at a power level insufficient to cause thermal injury. This intermediary test step is performed to verify appropriate placement of the applicator and proper operation of thermal imaging. Following this test pulse, laser treatment is initiated. A single ablation is typically 60-120 seconds with the laser at a power level of 6-25 W. Repeated imaging continues for approximately 30-60 seconds after cessation of laser activity in order to visually confirm cooling of the prostate and return to baseline temperature.

The duration of the procedure is largely dictated by the time needed to accurately target the cancerous lesion. The planning software and transperineal template determine proper placement of the titanium trocar and guide catheter, although multiple fine adjustments in all planes are often required to appropriately position these instruments. As a result, procedure time may be prolonged, especially when several foci of cancer are being treated.

In nearly all patients, multiple laser activations are planned. During these compound exposures, the laser applicator can be advanced, retracted, or placed through a new entry port of the transperineal template. At the end of all laser treatments, post-treatment MRI data (including dynamic, diffusion-weighted and contrast-enhanced T1-weighted images) are acquired to determine the effective treatment region. Upon completion of post-treatment imaging, the patient is monitored until they meet standard criteria for discharge. Most patients are discharged on the same day of the procedure or the following day.

Preclinical Trials

A preclinical evaluation of MRI-guided FLA in seven dogs was reported by Stafford and others [8]. A laser applicator was surgically placed in the prostate via laparotomy for two dogs with cancer and by a transperineal approach for five dogs without cancer. Targeted tissue destruction was guided by 1.5 T real-time magnetic resonance temperature imaging (MRTI). FLA was performed using single and compound exposures by a 980 nm diode laser at a power level of 4-14 W and an average exposure time per site of 158 seconds. Eleven ablation zones were generated with a mean width of 13.7 mm (range 11.4-15.5 mm) and a mean length of 19.0 mm (range 12.4-26.7 mm). Histological examination of ablation zones in all dogs was similar, showing a central area of unviable tissue surrounded by a rim of coagulative necrosis. Predictions of thermal damage derived from MRTI correlated strongly with the damage found on post-treatment MR imaging ($r^2 = 0.94$), with the slope of the regression line near unity. These findings demonstrated the efficacy and reproducibility of targeted ablation of the prostate using a transperineal MRI-guided FLA system with real-time guidance.

Colin and others [9] applied MRI-guided FLA to 10 rats with heterotopic Dunning prostate cancers. FLA was performed with a 980 nm diode laser at a power of 5 W for 75 seconds. Following treatment, ellipsoid lesions were visible on MRI, with mean necrosis volume of 0.98 mL (SD 0.05 mL) at 48 hours after FLA. Histological analysis of thermal damage at 48 hours showed evidence of coagulative necrosis within an ellipsoid-shaped lesion similar to that seen on MRI. Mean necrosis volume on MRI at 48 hours after FLA strongly correlated with histological analysis (r = 0.87).

As preclinical studies have shown that FLA-induced histological ablation zones are concordant with MR estimates, this laser therapy may be monitored by real-time feedback (e.g. by real-time MRTI of the ablation zone and surrounding critical structures) with the goals of optimizing accuracy and reducing potential side effects. As such, FLA is typically performed in the MRI gantry. This allows for superior soft tissue contrast resolution in the organization and real-time monitoring of the therapy as well as the modification of the treatment plan, if needed.

Patient Selection

There are not widely consistent selection criteria for men being treated with FLA. Generally, patients treated with FLA have low or intermediate-risk prostate cancer (PSA < 15 ng/mL, Gleason score 6-7, and clinical stage T1c-T2a). MR imaging of the prostate is a key step for localizing foci of cancer, determining eligibility for clinical trials, and planning treatment. Most centers require anatomic concordance of the cancerous lesions between the biopsy and MRI. We have found it essential for the urologist to discuss each individual case with an experienced prostate MRI radiologist. At our center, every FLA is performed by a urologist and radiologist. High-volume cancers, as determined by biopsy or MRI, are not ideal for FLA, as maximum ablation zones are approximately 2 cm^3 and repositioning laser applicators can be a time-consuming and arduous process. Attention to the location of the intended ablation zone is essential because certain areas of the prostate gland (e.g. anterior) may be more challenging to access, and proximity of the tumor to critical structures such as the erectile nerves, urethral sphincter, or rectal wall may increase the risk of side effects.

Phase I Clinical Trials

Very early literature on FLA for prostate cancer has shown promising results for the technique as a safe and viable alternative to whole-gland therapies. A case report by Lindner et al. [10] described four patients who underwent FLA one week prior to radical prostatectomy for prostate cancer. A random area of the prostate gland was targeted for ablation and was not specific to the location of the cancerous lesions. On microscopy, ablation zones were found to contain homogenous areas of coagulative necrosis without evidence of viable cells. Specifically, histopathological examination of the prostate specimens showed no cytokeratin 8 staining, a vital stain for prostate cancer, within the ablated areas of the gland. Lindner et al. also found the ablated volume measured on MRI correlated strongly with the ablation volume highlighted by vital staining but not with the volume traced on hematoxylin and eosin (H&E) staining. This supported the previous findings in preclinical trials that MRI can be used to guide FLA procedures and verify ablation following treatment.

A phase I trial of FLA for localized prostate cancer at the University of Toronto [11] treated twelve men with low-risk disease in one conventional sector and a concordant lesion identifiable on MRI. After MRI-based mapping of the prostate gland, a transperineal laser ablation was performed under ultrasound guidance. The median volume of treatment lesions was 2.2 cm^3. Perineal discomfort was the most common postoperative complaint (25% of patients). Utilizing validated quality-of-life questionnaires, no significant changes in urinary or sexual function were identified in the cohort after treatment. On post-treatment biopsy at 3-6 months, of which two cores targeted the ablated zone, four (33%) patients had positive biopsies at the site of ablation. Six (50%) patients had no evidence of disease on biopsy, and two (17%) patients had newly diagnosed contralateral cancers.

Our group similarly ran a phase I trial [12] and demonstrated that MRI-guided FLA is a feasible and safe therapy for clinically low-risk prostate cancer. Our cohort of interest had low-risk disease defined as PSA < 10 ng/mL, stage T1c, and Gleason score ≤ 7 in three cores in one sextant obtained with ultrasound guidance and a concordant lesion on endorectal MRI. Among the nine patients enrolled in the study, the procedure lasted for 2.5-4 hours, with a mean duration of laser ablation of 4.3 minutes. A hypovascular focal defect was identified on immediate postoperative MRI in eight cases. All patients were discharged home on the day of the procedure. Self-resolving perineal dermal abrasion occurred in one patient, while another had transient focal paresthesia of the glans penis. There were no significant changes in urinary and sexual function, as measured by validated quality-of-life questionnaires. MRI-guided biopsy of the ablation zone at 6 months after FLA revealed no cancer in seven patients and Gleason 6 tumors in two patients. On review of the ablation images in the two patients with positive findings, the ablation zone did not completely encompass the lesion site. Due to the small size of the ablation zones, mean PSA level was not significantly different after treatment.

While the results of these phase I trials are promising, they are limited by several factors, including small sample sizes and short follow-up periods. Residual or unrecognized cancer was detected on follow-up biopsy in a small number of patients in our study [12] as well as in the University of Toronto study [11], highlighting the investigational nature of this technique and the potential for omission of clinically meaningful cancers after initial biopsy and imaging. As long-term oncologic and toxicity data for FLA are lacking, there is also a degree of uncertainty regarding the safety and effectiveness of compound exposures and repeat sessions of laser therapy. Finally, it can be argued that many patients with low-risk cancer chosen for these studies may be more successfully managed by active surveillance.

Phase II Clinical Trials

At present, there are fewer than ten sites in the United States that offer FLA. As early phase I trials have demonstrated the safety and feasibility of FLA for prostate cancer, the efficacy of this therapeutic modality is being examined in phase II trials at our institution as well as at the University of Toronto and the National Cancer Institute. Our NCI-funded study (NCT01792024) investigates the oncologic efficacy of FLA and the MR sequences and imaging findings that predict successful oncologic treatment; secondary endpoints include safety and quality-of-life measures like urinary and sexual function. In comparison to our

phase I trial [12], the inclusion criteria have been broadened to include intermediate-risk patients (PSA < 15 ng/mL or PSA density < 0.15 ng/mL, stage T1c-T2a, Gleason 7, and 25% positive cores). Additionally, lesions in multiple sites are targeted for ablation following confirmation of anatomic concordance between biopsy and MRI, and follow-up is more rigorous, including biopsy of the ablation zone at 3 months and twelve-core biopsy of the treatment zone at 12 months. The study is active, and recruitment is ongoing.

Conclusion

Focal laser ablation is an emerging paradigm for treatment of low-risk prostate cancer that intends to definitively eradicate clinically meaningful cancers while reducing quality-of-life side effects such as urinary incontinence and erectile dysfunction. This minimally invasive procedure may be performed in an outpatient setting with little need for post-operative pain management as compared to whole-gland therapy. Real-time MR imaging during FLA allows for titration of the ablation zone and temperature monitoring of surrounding critical structures. Furthermore, FLA does not preclude retreatment with focal or whole-gland therapy, if needed. As publicly available data on the oncologic efficacy of this treatment modality are sparse, further experience and long-term follow-up are required to fully understand the potential role of FLA as a viable alternative to active surveillance or conventional whole-gland therapies for prostate cancer.

Acknowledgments

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Papers of particular interest, published within the annual period of review, have been highlighted as: * of special interest.

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Key Points

1. MRI-guided focal laser ablation (FLA) is a safe and feasible therapy for low-risk prostate cancer.

2. Patient selection, proper identification of clinically meaningful cancers, and accurate localization of cancerous lesions are important to the therapeutic success of FLA.

3. Phase II clinical trials of FLA for prostate cancer are ongoing at our institution as well as at the University of Toronto and the National Cancer Institute.
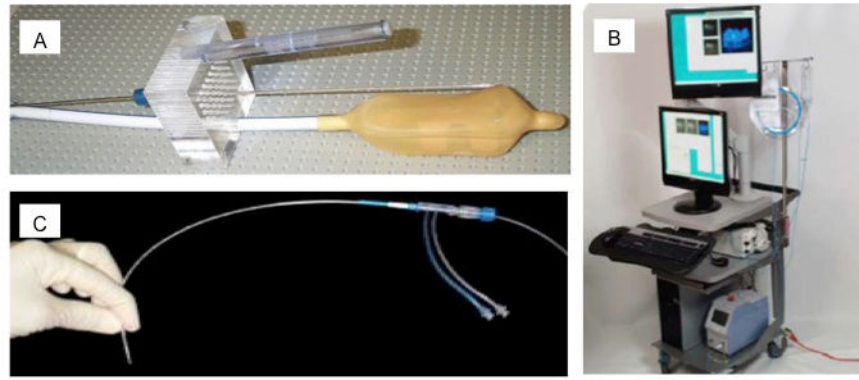
Figure 1.
Instruments used for targeting and treating foci of prostate cancer by MRI-guided focal laser ablation. (A) An MR-compatible transperineal template is fixed to an endorectal coil. (B) A high-quality T2-weighted image of the prostate is acquired and loaded into the software (Visualase, Inc.) for guiding applicator placement. Titanium trocars and guide catheters are placed through the appropriate grid hole on the transperineal template as determined by the planning software. (C) When the laser tip is situated in the desired location, laser treatment is initiated. MRI, magnetic resonance imaging; MR, magnetic resonance.