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# Early experience in MRI-guided therapies of prostate cancer: HIFU, laser and photodynamic treatment

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**Abstract**

Prostate cancer screening has resulted in earlier diagnosis with lower-grade disease, leading to over-detection and over-treatment in a significant number of patients. Current whole-gland radical treatments are associated with significant rates of morbidity. The high prevalence of low-risk disease together with an inability to accurately identify those men harboring more aggressive cancers has led to tremendous research in low-morbidity focal therapies for prostate cancer. This review summarizes the early experiences with focal therapy with emphasis on early applications of laser, high-intensity focuses ultrasound, and photodynamic approaches.

**Keywords:** *Prostate cancer; Focal therapy; Magnetic resonance imaging; Laser; High-intensity focused ultrasound; Photodynamic therapy.*

## Introduction

Prostate cancer is the most common malignancy among men and the second leading cause of cancer death in the United States[1]. Prostate cancer screening with prostate-specific antigen (PSA) has led to earlier diagnosis with more lower-grade, organ-confined disease[2], leading to over-detection and over-treatment of prostate cancer by at least 30%[3]. It is estimated that the 15-year mortality from low-grade, screen-detected prostate cancer in men aged 55–74 years at diagnosis would be 1%, with an absolute survival benefit of curative treatment of less than 1%[4].

Whole-gland therapies for prostate cancer include radical prostatectomy, external beam radiation therapy (EBRT), brachytherapy as well as several newer techniques discussed in detail later. Radical prostatectomy has been shown to reduce disease-specific mortality in both the Scandinavian trial[5] and the European Randomized Study of Screening for Prostate Cancer (ERSPC)[6]. However, whole-gland treatments will have negative quality-of-life implications[7], with rates of sexual, urinary and rectal dysfunction of 79%, 16% and 29%, respectively[8].

Active surveillance is one method of reducing the number of men harmed by prostate cancer treatment while still offering the potential for cure in those with progressive disease. Appropriate selection includes men with low-risk, localized cancer. While mortality with active surveillance is low, the window of single modality treatment opportunity is potentially lost in some patients[9]. Active surveillance has its limitations and it is estimated that only 8% of eligible patients elect to undergo it[10].

The high prevalence of low-risk disease combined with the inability to reliably predict more aggressive cancers in individual men has resulted in tremendous interest in low-morbidity focal therapies. This review focuses on the early experiences with high-intensity focused ultrasound (HIFU), laser and photodynamic approaches to focal therapy. Cryotherapy, although currently being

used in prostate cancer therapy, is not discussed in this review.

## Multifocality

Focal therapy is controversial as prostate cancer is multifocal in approximately 70–80% of patients[11,12]. However, it is the largest tumor focus (index tumor) that is presumed to be the main factor for tumor progression and prognosis[13]. In a study of 486 patients with prostate cancer treated with radical prostatectomy[12], the index tumor ranged in volume from 0.01 to 29.39 $cm^3$, but was on average significantly larger than any secondary tumors (4.16 versus 0.63 $cm^3$). In another study of 100 consecutive prostatectomy patients and 270 separate tumor foci, there was no case in which a secondary focus had a higher Gleason score than the index lesion of the specimen[14]. Only 2 secondary lesions were found to extend extracapsularly although in one of these patients, the index lesion also extended beyond the capsule. No secondary foci were found to invade the seminal vesicles. With knowledge that outcomes are determined by the aggressiveness of one or more dominant lesions, focal therapies are now being considered.

To ensure a patient is eligible for focal therapy, transperineal mapping or saturation biopsies under transrectal ultrasound (TRUS) guidance is used to detect cancers missed or underestimated by previous transrectal biopsies. This involves obtaining 40–160 separate biopsy cores under general anesthesia[15]. However, with an increasing recognition of magnetic resonance imaging (MRI) as a powerful tool for localization in prostate cancer, more MRI-guided biopsies are being performed routinely.

## The role of MRI

A number of modalities exist that enable localized prostate ablation. These include those that destroy cells through thermal mechanisms (by laser, HIFU, and cryotherapy), localized radiation (brachytherapy), as well as photodynamic therapy. These ablative techniques can be applied to the whole gland or to focal regions via image guidance to minimize damage to normal surrounding tissue.

For focal therapy to be viable, accurate imaging is required for detection, real-time monitoring of the ablation, and assessment of ablation extent[16,17]. TRUS, while well-suited for routine biopsy, has never been accurate in detecting cancer on its own[18] with a sensitivity of 70–80% for detecting cancer after a single biopsy[19].

Multiparametric MR combining T2-weighted, diffusion-weighted, and contrast-enhanced dynamic imaging provides the highest accuracy in localization and staging of prostate cancer[20–23], while demonstrating quantitative differences between normal and malignant tissue margins[24]. Through diagnosis, MR findings can guide focal treatment options. If a tumor is found to be remote from critical structures (such as the neurovascular bundle or urethra), more readily available ultrasound-guided focal therapy can be used. If a tumor is in close proximity to a critical structure or is in the anterior gland, a region relatively inaccessible by TRUS, MR-guided ablation with real-time thermometry may be of value. As MR-guided therapy can be time consuming, costly, and impractical in many centers, accurately identifying those patients who require it is essential.

Most focal therapies rely on temperature change to induce cellular death through various mechanisms. This temperature change can be monitored by the insertion of thermosensors into the ablated area. However, MR thermometry offers this capability non-invasively and in real time. Several studies have showed that using MR thermometry to monitor spatial temperature distribution within the prostate during transurethral HIFU allows for desired spatial heating to within 1°C[25]. In addition, Staruch and colleagues have recently used MR thermometry temperature control during focused ultrasound hyperthermia for triggering the local release of anticancer drugs within the prostate[26].

Larson et al.[27] found a strong correlation between MRI and histopathologic findings following focal therapy ($r = 0.92$) as did Lindner and colleagues[17] during a phase I trial of focal laser ablation followed by radical prostatectomy ($r = 0.95$). The role of serial imaging following ablative prostate cancer treatment has yet to be established.

## Thermally based ablation

### *Laser-induced thermal therapy*

Laser-induced thermal therapy is a percutaneous tumor ablation technique using small, high-power laser diode systems placed interstitially into the tumor to rapidly heat tissue (Fig. 1)[28].

A 2010 feasibility study by Raz and colleagues[29] showed that MR could be used to guide focal laser ablation in prostate cancer. Two patients with single-focus prostate cancer identified on pre-treatment 1.5-T multiparametric MRI were included. Both were treated with focal laser ablation using a 980-nm diode laser (Visualase Inc, Houston, TX, USA), with optical fibers inserted through a perineal template. Intraoperative MRI was performed using an endorectal coil and surface phased array. Axial T2 fast spin-echo sequences were combined with diffusion-weighted imaging for intraoperative tumor localization. Optical fibers were positioned under MRI guidance using an axial 2D FIESTA (Fast Imaging Employing Steady State Acquisition; GE Healthcare, Waukesha, Wisconsin, USA) sequence and customized positional planning software. Accumulated thermal damage was monitored in real time using MR thermometry software (Visualase, Inc, Houston, TX, USA) and the

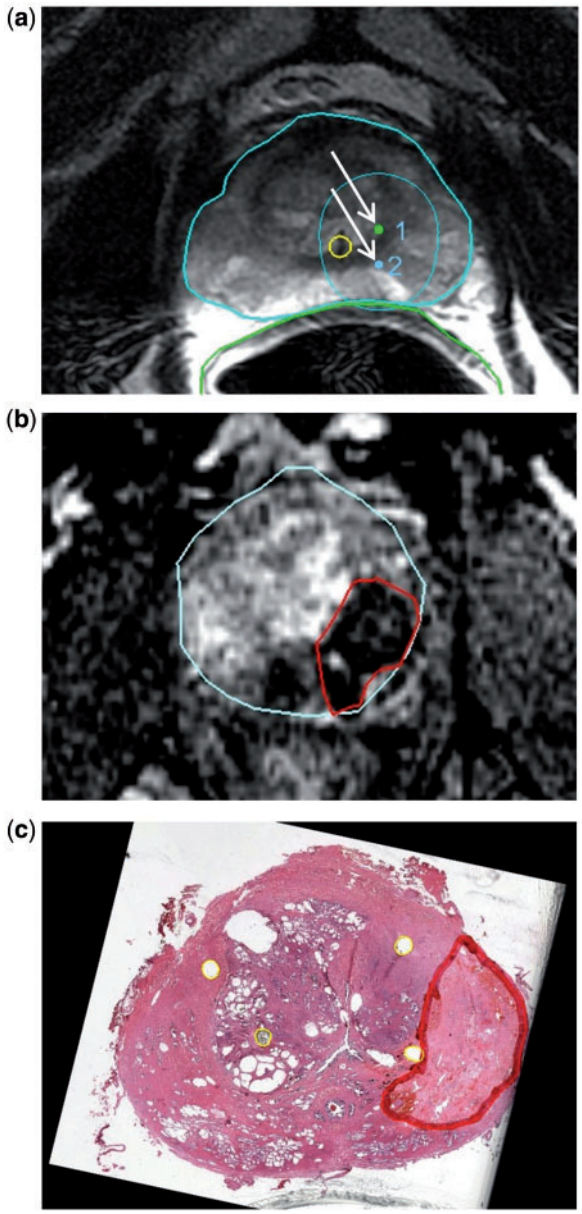


***Figure 1*** **MR scans done just prior to and 7 days after focal laser therapy. (a) T2-weighted image shows the whole prostate (outer turquoise line), desired treatment area (inner light green line), and treatment plan (best fiber placement scheme, white lines). Yellow circle indicates urethra. Green line indicates rectum. (b) Post-treatment dynamic contrast-enhanced MRI shows devascularized tissue. (c) Corresponding pathologic slice with focal necrosis. Red line indicates tumor outline.**

size of the ablation was calculated using a verified method. Temperature and ablation maps were superimposed onto anatomic images and later confirmed by immediate post-treatment contrast-enhanced MRI as areas of non-enhancement. No adverse events were noted.

In another test of feasibility and safety, Lindner et al.[30] performed MR-planned, ultrasound-guided laser ablation in 12 patients with biopsy-proven low-risk prostate cancer identified on multiparametric MRI using an endorectal coil combined with a surface phased array. Target ablation was monitored using interstitially placed thermal sensors and real-time contrast-enhanced ultrasound. There were no perioperative complications and minimal morbidity with no negative effects on potency or continence. Post-operative day 7 contrast-enhanced MRI was completed to assess perfusion. The treatment created a single hypovascularized zone in all patients averaging 2.2 $cm^3$ (range 0.3–4.0), 12 times larger than the average tumor volume. The overall median overlap between pre-treatment and post-treatment MRI was 53%, although substantially higher at 81% in the last 4 patients. Follow-up core biopsy was completed at 6 months and 67% of patients were free of tumor in the targeted area while 50% were free of disease. In a follow-up study using MR-planned, ultrasound-guided laser ablation followed by radical prostatectomy in 4 patients, no viable tumor was found on whole-mount histopathology[17].

## *HIFU*

In HIFU, an alternating voltage is placed across a piezoelectric material creating focused ultrasound pressure waves that can destroy a region of interest[31]. HIFU can be delivered to the whole gland or to a focal region, both under ultrasound or MR guidance.

A growing number of medical associations including those of France, Italy, and the United Kingdom have approved 2 commercial ultrasound-guided HIFU systems for the primary and/or salvage whole-gland treatment of prostate cancer: Ablatherm HIFU (Edap-Technomed, Lyon, France) and Sonablate 500 (Focus Surgery,

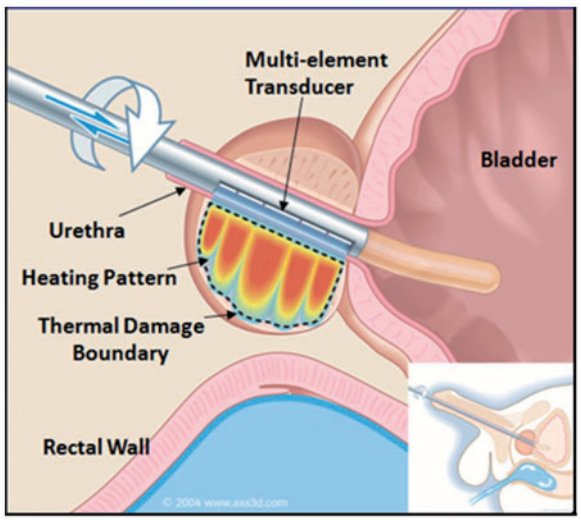


***Figure 2*** **Conceptual diagram of MRI-compatible transurethral ultrasound therapy device developed by Chopra et al.[35] Multiple collimated HIFU beams on a rotational positioning system create localized heating within the prostate gland.**

Indianapolis, IN, USA). At the time of writing, these ultrasound-based systems are not approved in the United States. Neither system involves MR technology.

Ablatherm combines planning and treatment ultrasound probes allowing for direct visual feedback[31]. Differences between Ablatherm and Sonablate 500 technology mainly concern patient positioning, treatment algorithms, and technical details[32]. Subsequent transurethral resection of the prostate is performed at some centers to reduce gland size and prevent stricture formation[33].

A recent systematic review[34] on ultrasound-based applications of HIFU in prostate cancer identified 34 clinical studies, 29 of which examined HIFU as primary treatment and 5 as salvage treatment for recurrence after radiotherapy. As primary therapy, negative biopsy rates ranged from 35 to 95%. Only 5 studies reported disease-free survival rates that ranged from 55 to 95%. In the studies of HIFU as salvage treatment, negative biopsy rates ranged from 73 to 84%. Overall, the authors concluded that high-quality evidence on the efficacy and safety of whole-gland HIFU in prostate cancer is lacking and could not support its use as an alternative to standard curative treatment options.

Because of the inherent nature of ultrasound-based HIFU therapy, limitations include the potential for small gaps in thermal ablation and the lack of direct real-time visualization of the thermal effect. MR has the potential to improve on this with guidance, focal targets, and improvements in the therapeutic ratio.

The ExAblate® 2000 (InSightec, Tirat Carmel, Israel) is a commercial MRI-based device using an endorectal method for thermal ablation of prostate tumors using HIFU, and is now in multi-center clinical trials. At the time of writing, the device has not been approved for use in prostate cancer, but is approved for treatment of uterine fibroids and painful bony metastases in the United States and Europe. T2-weighted MR images are obtained for intraoperative tumor localization and act as a guide to define the treatment volume. Gradient echo MR thermal images are obtained throughout the treatment, providing real-time feedback of treatment effect. Immediately after the procedure, a contrast-enhanced T1-weighted image is obtained and used to evaluate the non-perfused volume, allowing for pre- and post-treatment overlap assessment.

Another method of MRI-based focal ultrasound ablation under MRI guidance has recently been developed by Chopra and colleagues using a transurethral approach (Fig. 2)[35–37]. Five males with localized prostate cancer underwent the MR-guided procedure prior to prostatectomy. Intraoperative MRI scans were performed using a standard gradient echo sequence. A feedback control algorithm was created to adjust the output power, frequency, and rotation of the ultrasound ablation device based on real-time MR thermometry. Immediate post-treatment scans confirmed the thermal damage pattern, visualized as areas of non-enhancement on contrast-enhanced MRI. Correlation between anatomical, thermal, and histologic images was $\leq 3$ mm. This feasibility study verified that MRI, combined with a motorized piezoelectric actuator, can deliver precise patterns of thermal damage[35]. This technology is currently also being validated through clinical trials and is not approved at the time of writing.

## Photodynamic therapy

Photodynamic therapy (PDT) uses a photosensitizing drug activated by light of a specific wavelength applied by interstitially placed optical fibers. The activated drug produces reactive oxygen species which in turn results in direct cellular damage[38]. In prostate cancer, photosensitizing drugs are given orally or intravenously and later activated by low-energy light transmitted within optical fibers placed directly within the prostate with TRUS and perineal template guidance[39].

Temoporfin (mTHPC, Foscan®), a tissue-based photosensitizer, was the first to be used in a formal clinical study in 14 patients with locally recurrent prostate cancer after radiotherapy[40] where there were reductions in PSA by up to 96% in 10 of 14 patients. Adverse events included recto-urethral fistula in 1 patient, urinary retention in 3 patients and temporary stress incontinence in an additional 2 patients.

There has since been further work using numerous photosensitizers including vascular acting agents such as padoporfin (Tookad® WST-09) and padeliporfin (Tookad® WST-11) which are currently under investigation for use in prostate cancer (Fig. 3)[41]. Reactive oxygen species formed by these agents result in vessel constriction and thrombosis, leading to necrosis. The first clinical trial of WST-09 as salvage therapy was conducted in 25 men with recurrent prostate cancer after failed EBRT[39,42,43]. Non-enhanced T2-weighted and dynamic gadolinium-enhanced T1-weighted MR scans with surface phased-array coil were performed at baseline, 1 week, 4 weeks, and 6 months after PDT.

At 1 week after PDT, MR findings confirmed intraprostatic necrosis on contrast-enhanced T1-weighted images and were a better predictor of 6-month biopsy results negative for cancer than PSA assessment[43]. However, treatment margin irregularities and islands of perfused (spared) tissue were seen and thought to be related to varied tissue response to the light–drug combination. T2-weighted images were less successful at demonstrating regions of necrosis with mixed signal intensity change. In 14 of 22 patients, treatment effects extended into the extraprostatic tissues, and again these were poorly visualized on T2-weighted images. Sixty percent of those who received the minimum effective threshold light dose had no residual disease on 6-month follow-up biopsy. Adverse effects in this series included recto-urethral fistula (2 patients) and intraoperative hypotension (1 patient).

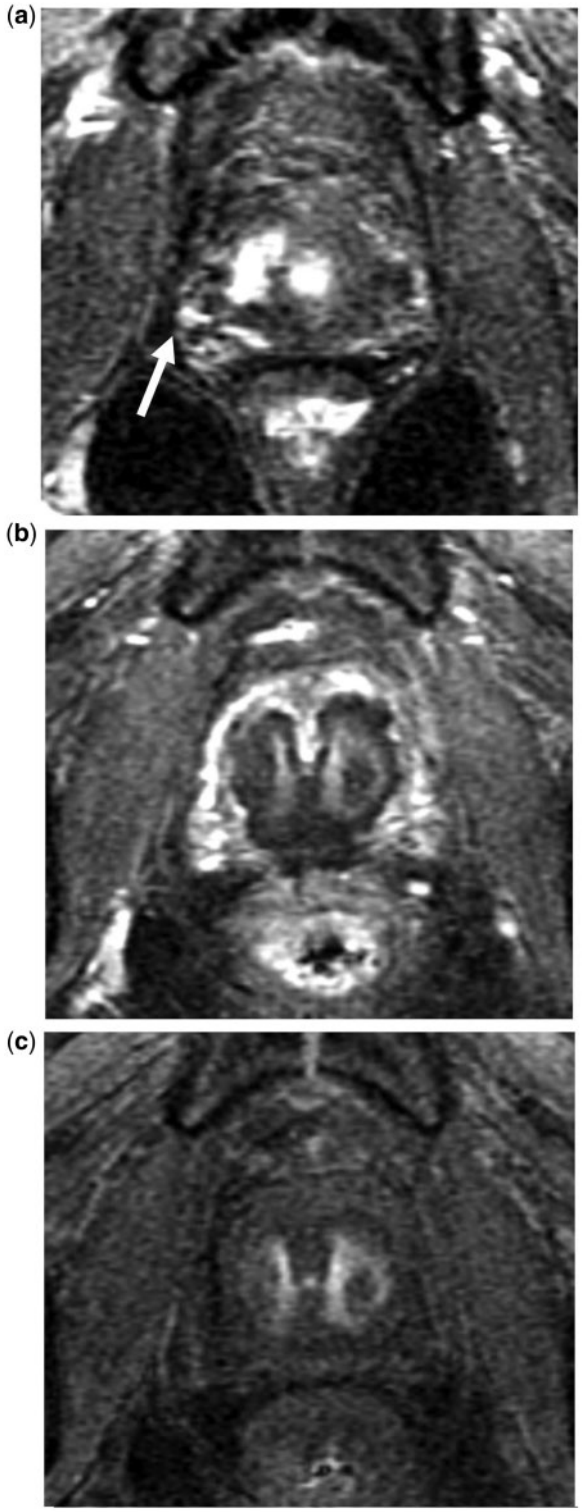


*Figure 3* **Post EBRT recurrent cancer. Baseline image (a) shows early enhancement on dynamic contrast-enhanced MRI (white arrow). Post WST-09 PDT (b, c) showing lack of enhancement at 7 days with hemorrhagic necrosis on pre- and post-contrast images. Patient tumor free at 6 months.**

## Conclusion

Emerging thermal and photodynamic based focal therapeutic modalities are beginning to show promise as a conservative treatment option in low- and intermediate-risk prostate cancer. Imaging will be at the forefront of focal treatment enabling precise detection, monitoring of ablation in real time, and subsequent assessment of the post-ablation prostate. Proving technology to be effective in prostate cancer treatment is a difficult process, and with traditional end points like mortality, may even be impossible. Regulatory issues may require the outcome comparator for focal therapy to be active surveillance as opposed to radical prostatectomy or radiation treatment. Currently we are at the threshold in the application of image-guided ultrasound and MR-based prostatic ablation technology. New interactions between radiologists interpreting prostate MRI and urologists performing treatment and biopsy will need to be defined.

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