MR Imaging–Guided Focal Therapies of Prostate Cancer

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KEYWORDS

• Cryotherapy • Laser ablation • HIFU • High-intensity focused ultrasound • MR imaging guidance • Multiparametric MR imaging

KEY POINTS

- A greater number of small-volume, low-risk, and intermediate-risk prostate cancers are being detected.
- Multiparametric MR imaging serves as a valuable method of assessing the prostate gland for cancer in patients with high clinical suspicion of malignancy.
- Once detected, a suspected cancerous lesion in the prostate gland can be subsequently targeted for focal therapy using MR imaging for guidance.
- Early data relating to the use of MR imaging–guided focal therapies, including cryotherapy, high-intensity focused ultrasound, and focal laser ablation, have been promising.

BACKGROUND

Prostate cancer is a major cause of death among men, preceded only by lung cancer in the United States.[1] There has been an increase in the number of prostate cancer cases, localized and low-grade tumors in particular, leading to an interest in the development of alternative treatment methods with fewer complications.[2] The growing number of cases of prostate cancer diagnosed can be attributed in part to a greater reliance on prostate-specific antigen (PSA) as a harbinger of malignancy as well as the adoption of an overall lower clinical threshold for the performance of prostate tissue sampling.[2] Although the US Preventive Services Task Force (USPSTF) advised against the use of PSA as a screening mechanism for certain patients, that is, men of 70 years of age or older, the USPSTF recently updated stance recommends that clinicians conduct periodic checks of serum PSA levels in patients between the ages of 55 and 69.[3] Elevated PSA levels and abnormal digital rectal examinations represent the 2 major criteria currently used in the determination of a patient's need for prostate biopsy.

DIAGNOSIS AND TREATMENT OF PROSTATE CANCER

The traditional method of acquiring tissue samples of the prostate in a patient suspected of having cancer is to pursue a 12-core biopsy of the gland using a transrectal sonographic approach.[4] This conventional transrectal ultrasound (TRUS)-guided biopsy, however, has several disadvantages. Among these is the failure of a TRUS biopsy to consistently reach the apex of the prostate or the anterior aspect of the gland.[5] This leads to undersampling of these areas and missing anterior and apical cancers. In addition, there may be difficulty in the reliable detection of prostate cancer using sonography.[6] For these reasons, it is not

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entirely surprising that the rate of false-negative results after a TRUS-guided biopsy is high: up to 47% of patients may have an undetected prostate cancer after sampling.[4] Another problem with random biopsy is the unreliable Gleason score yielded by these biopsies. In approximately 30% of cases, the Gleason score obtained on random biopsy is upgraded on repeat tissue sampling or after prostatectomy.[7,8]

A more reliable method of detecting and diagnosing prostate cancer is multiparametric MR imaging. Prostate cancer has characteristic MR imaging features, including hypointense signal on T2-weighted imaging, low apparent diffusion coefficient (ADC) signal (restricted diffusion), and early arterial enhancement with subsequent washout on dynamic contrast-enhanced imaging.[9] MR imaging has been increasingly used for identification of targets for biopsy, and targeted biopsy is rapidly emerging as an alternative and more superior diagnostic paradigm.[9–11] Depending on the experience level of the radiologist reading the MR imaging examination, the accuracy of detection of prostate cancer can range between 70% and 90%.[9]

Once a suspicious site is identified on multiparametric MR imaging, MR imaging can be used either directly or indirectly to guide future biopsy of the prostate gland. With the direct method, tissue sampling is done in-bore while the patient is positioned within the scanner. When MR imaging is used in an indirect manner to perform a biopsy of the prostate gland, it is most often achieved through the use of an MR imaging/ultrasound fusion computer platform. In this scenario, the patient's earlier diagnostic MR images are able to be fused with real-time sonographic images and serve to guide the trajectory of the core biopsy needle during the procedure. The targeted biopsy paradigm has allowed for a more reliable and accurate mapping of cancer within the prostate gland and improved characterization of cancer aggressiveness at the time of diagnosis.

There are several therapy options currently available to patients diagnosed with prostate cancer, including whole-gland treatment, active surveillance, and, the latest approach, focal therapy. The primary aim of focal therapy is to selectively direct treatment to the index or largest in size cancerous prostatic lesion, while in the process avoiding inadvertent damage to critical locoregional anatomic structures. Among these are the neurovascular bundles, the adjacent urethra and urethral sphincter, the urinary bladder, and the rectum. Focally directed and less-invasive treatment approaches are advantageous, particularly in comparison to whole-gland treatment options, such as a radical prostatectomy, where a greater incidence of post-prostatectomy complications, such as impotence and urinary continence, has been encountered.[12,13] In addition to clinical factors and patient and physician preference, other criteria used in the determination of whether an individual with localized prostate cancer is a satisfactory candidate for focal treatment are Gleason score of 6 or 7, a PSA level measuring less than 15 ng/mL, and a clinical stage of T1c to T2a, as defined by an international consensus group.[14]

PROS AND CONS OF FOCAL THERAPY

Focal therapy is an established paradigm in the treatment of several different cancers, including breast, kidney, thyroid, colon, lung, and liver. Its main advantage in the management of prostate cancer is its association with fewer complications while eradicating the cancer. Focal therapy for prostate cancer is a minimally invasive treatment that can be performed under conscious sedation or with spinal anesthesia without the need to admit patients overnight. Patients can return to their normal life immediately after the procedure. Another advantage of focal therapy is that it does not close the door to potential future whole-gland therapies. One of the main disadvantages of focal therapy is the multifocality of prostate cancer. Prostate cancer is multifocal 80% of the time[15] and focal therapy can only address the index lesion, which is typically the focus with the highest Gleason score and with the largest volume.[16] There is growing evidence that the index lesion determines the prognosis of the patient and, therefore, it may be adequate to ablate the index lesion.[17] Nevertheless, the main goal of focal therapy should be to treat patients with intermediate-risk prostate cancer who otherwise would need whole-gland therapy instead of treating patients with low-risk cancer who could benefit from active surveillance.

MR IMAGING–GUIDED FOCAL TREATMENTS

The most commonly used and studied methods of focal therapy for prostate cancer are cryotherapy, high-intensity focused ultrasound (HIFU), and laser ablation. These treatments offer patients alternatives to prostatectomy or radiation therapy and have been found efficacious in treating localized prostate cancer in a comparatively less-invasive manner. Patients undergoing MR imaging–guided tissue-sparing treatments, such as cryotherapy, HIFU, and focal laser ablation, are not entirely spared from the possibility of experiencing adverse side effects, among which are injury to the urethra, nerve damage, and bowel injury. Preventative measures, however, discussed in greater detail later, are taken during the course of all of these treatment procedures and aid in reducing such untoward sequelae.

Cryotherapy

Consisting of a freezing method used to achieve cellular disruption, cryotherapy is an increasingly used treatment method for prostate cancer. Using a transperineal approach, needles are placed in the prostate and the gland is cooled using argon probes.[18] Thermocouples monitor the patient's body temperature and a transurethral Foley catheter is placed in an effort to prevent urinary complications, including urethral sloughing and incontinence. Saline instilled into the perirectal space has a protective effect on the rectum.[18] Additionally, thermosensors are placed at several anatomic sites, among them the external anal sphincter, the prostate apex, and the neurovascular bundles.[19]

Cryotherapy causes cell apoptosis through the formation of ice crystals at the target site. As a result of the directed cold temperatures, there are cellular dehydration and destruction.[20] Several treatment variables have been found to contribute to a more successful post-therapy outcome: the lowest temperature reached during treatment (a temperature measuring $<-40°C$ is ideal), the rate at which cooling occurs during the freezing step, the length of time during which the freezing occurs, the velocity at which thawing takes place, the number of freeze-thaw cycles used (more extensive tissue damage is typically seen with the incorporation of a double freeze-thaw cycle), and whether there are enlarged vessels present.[21] During the cooling phase, argon gas is used, and helium gas is used in the thawing phase.[19]

Use of multiparametric MR imaging for guidance when performing cryotherapy has proved more beneficial than using the traditional method of TRUS imaging.[2,20] In the latter case, real-time evaluation during treatment may be impeded by the reflection of sound waves adjacent to the ultrasound probe, leading to an inaccurate assessment of the zone of treatment. Additionally, the ice ball formed during cryotherapy is better visualized on MR imaging than on sonography. Typical findings on follow-up MR imaging after cryotherapy include the appearance of hypovascularity and focal signal void at the site of treatment. See **Fig. 1** for an example of a postprocedural MR imaging appearance of the prostate after cryotherapy of a discrete cancerous lesion.

Research investigations have shown promising results for the treatment of focal prostate cancer with cryotherapy. Among 73 recipients of hemigland cryotherapy in a study led by Bahn and colleagues,[21] only a single patient developed ipsilateral recurrent cancer; in addition, none of the patients who received treatment developed post-therapy urinary incontinence. Another investigation directed by Onik and colleagues[22] found that 45 of 48 patients treated with locoregional cryoablation demonstrated stable PSA values and no evidence of cancer post-treatment. Although there remains a need for additional randomized clinical trials comparing cryotherapy to other regional therapies, early findings support cryotherapy as a promising treatment method for individuals with focal prostatic malignancy.

High-Intensity Focused Ultrasound

Using high-frequency sonographic waves, HIFU can successfully treat a cancerous focus in the prostate gland. A patient undergoing HIFU treatment receives either general or spinal anesthesia for the procedure. A spherical ultrasound transducer is used and the energy from the resultant ultrasound waves is applied to the region of interest in the prostate gland.[23,24] In this manner,

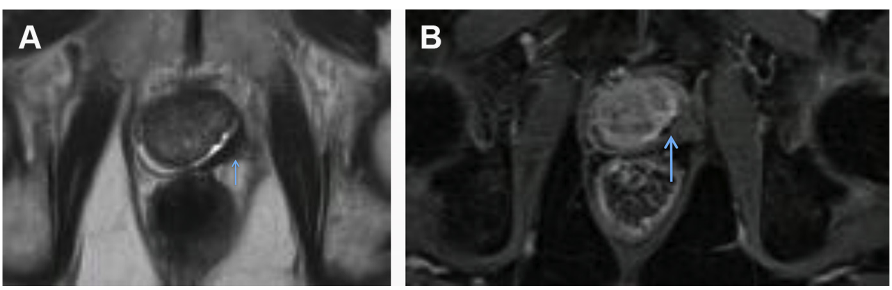

Fig. 1. Cryotherapy. Post-cryotherapy MR imaging of a 72-year-old man with a history of a left midgland peripheral zone prostate adenocarcinoma demonstrates asymmetric focal volume loss at the site of treatment. (*A*) T2-weighted imaging shows ill-defined or amorphous dark signal in the area of treatment in the left midgland. (*B*) Postcontrast imaging of the prostate gland in the axial plane at the midgland level demonstrates thin linear hypointense signal (*arrow*) at the treatment site without evidence of focal nodular enhancement.

coagulative necrosis and cell death are achieved at the site of the cancer. Heat is applied to the cancerous focus for a few seconds (typically 3 seconds), and this is followed by a cooling period of approximately 6 seconds.[24] After HIFU therapy, there are corresponding expected signal changes on MR imaging and the zone of treatment may appear cystic with correlating increased T2 signal intensity and regional hypovascularity on contrast-enhanced imaging. See **Figs. 2** and **3** for examples depicting MR imaging findings related to HIFU treatment of regional prostate cancer.

In a study led by Ahmed and colleagues,[25] HIFU was delivered to a group of individuals with histories of low-risk and intermediate-risk prostate cancers. Up to 95% of the patients who were studied reported preserved urinary incontinence after 1 year. Persistent cancer, however, was seen in more than 20% of the men who were rebiopsied.[25] In addition, although 31 of the 35 patients assessed stated that erectile function for intercourse was overall acceptable, the scores associated with orgasmic function and overall erectile satisfaction were significantly below baseline.[25] Continued follow-up is necessary to better understand long-term treatment outcomes after HIFU therapy.[25,26]

Focal Laser Ablation

Another increasingly used MR imaging–directed method of treating regional prostate cancer is laser ablation. Focal laser therapy consists of the delivery of thermal energy or high-energy photons to the region of interest. Tumor necrosis ensues as a result of this method of rapid heating. The soft tissues of the prostate gland are relatively hypovascular and this in conjunction with its inherent optical absorption rate makes prostatic tissue particularly responsive to laser ablation.[27] At the

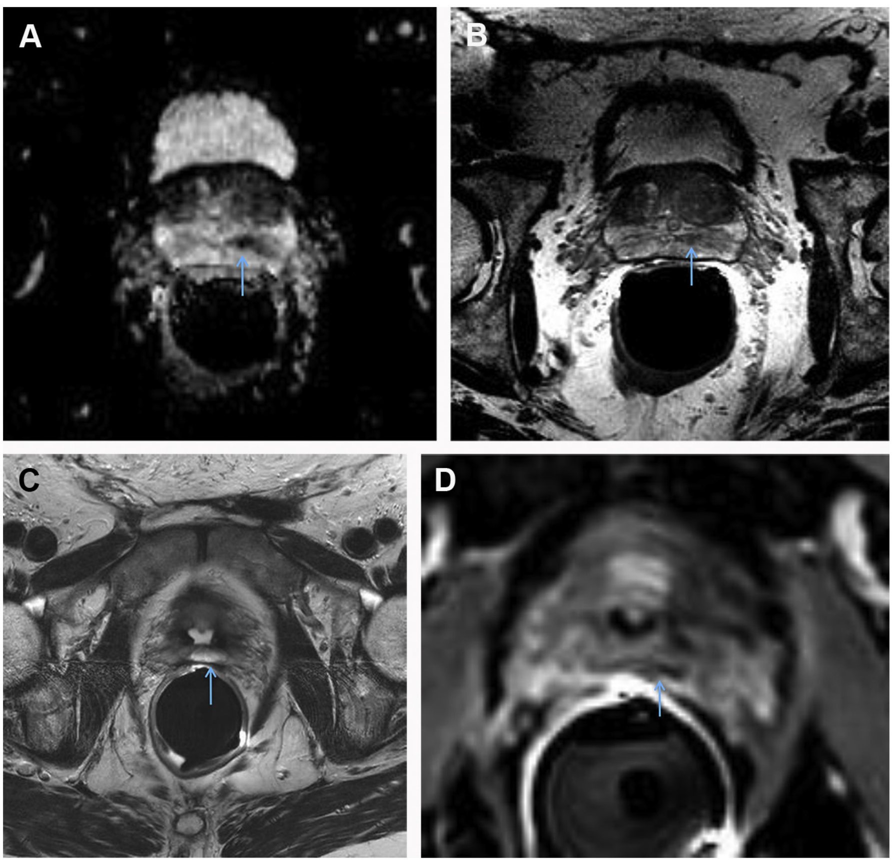

Fig. 2. HIFU treatment. MR imaging of a 61-year-old patient pre-HIFU and post-HIFU treatment of a left-sided Gleason 6 prostate cancer located in the peripheral zone of the medial left midgland/base (*arrows*). (*A*) The peripheral zone cancerous focus in the left midgland/base demonstrates low ADC signal on pretherapy imaging. (*B*) The lesion shows corresponding T2 hypointense signal. (*C*) After HIFU therapy, focal cystic change is seen in the medial left midgland/base, including at site of preexisting cancerous lesion. (*D*) On post-treatment contrast-enhanced MR imaging, there is localized nonenhancement in the region of the patient's original left-sided prostate cancer.

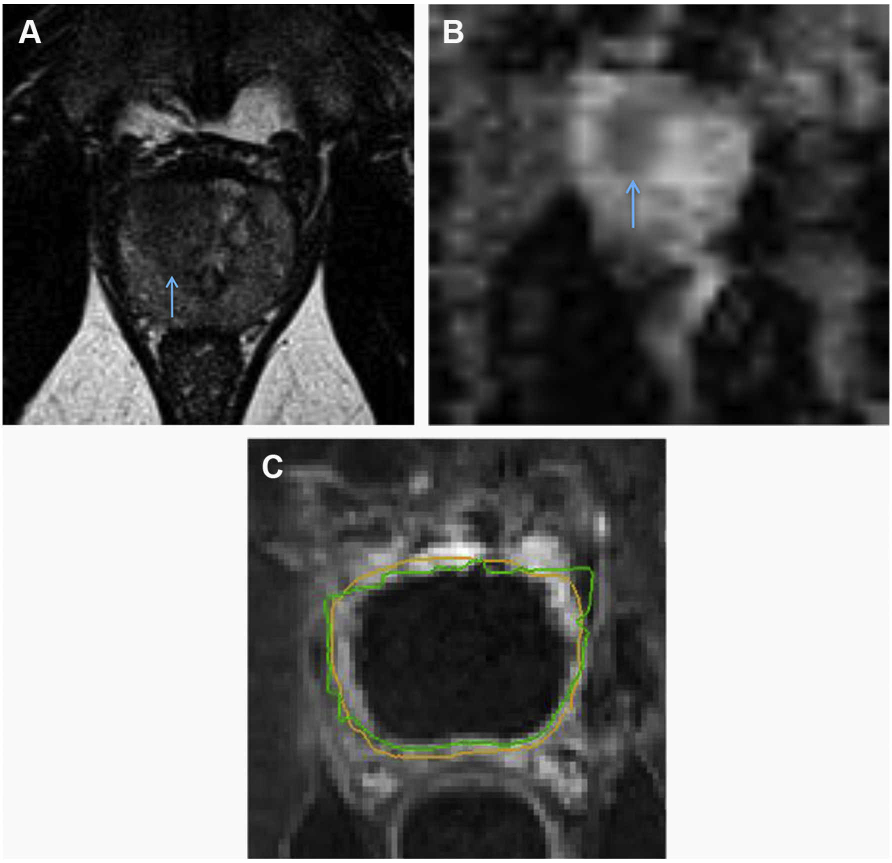

Fig. 3. HIFU treatment. A 56-year-old man with a history of Gleason 3 + 4 prostate cancer and a PSA value of 8.1 ng/mL underwent HIFU therapy for a right-sided transition zone cancer evident on MR imaging (*arrows*). (*A*) A rounded T2 hypointense lesion is identified in the right transition zone of the gland. (*B*) The lesion demonstrates restricted diffusion with corresponding decreased ADC signal visualized. (*C*) Post-treatment dynamic MR imaging after the administration of intravenous contrast shows expected avascularity of the gland. The green/yellow lines are indicative of the region of interest, the prostate gland.

start of the procedure and using MR imaging for guidance, optical fibers are placed in the prostate gland using a transperineal route. The efficacy of locoregional laser treatment is dependent on the depth of photon dispersal and the amount of heat energy distributed. It is helpful to reach a minimum temperature of 60°C to better ensure tumor destruction. Fluoroptic or MR-directed thermometry is used to assess the effects of treatment on the rectum and other critical anatomic structures. In addition to its ability to target a lesion exactly, focal laser ablation has several other benefits, including its ability to assess therapy effects in a real-time fashion and at a low cost. Additionally, laser fibers used in the procedure are MR imaging compatible. There is also no distortion of the electromagnetic field by the optical fibers; thus, image degradation or MR imaging artifacts at the treatment site do not pose a problem.[20] Prefocal and postfocal laser ablation findings on MR imaging are shown in **Fig. 4**.

Several research investigations have demonstrated the clinical efficacy of focal laser ablation in treating regional prostate malignancy. At the University of Chicago, a phase I trial led by Oto and colleagues[28] was conducted in 2013 to evaluate the feasibility of focal laser ablation in the treatment of low-risk prostate cancer; postablation biopsy of the treatment zone demonstrated no evidence of malignancy in 7 of the 9 patients included in the study. In 2016, a phase II trial at the institution also deemed focal laser ablation a safe form of treatment; patients assessed 1 year after therapy were found to have satisfactory morbidity rates and clinical outcomes.[29] Raz and colleagues[30] conducted a feasibility study in 2010 confirming that regional laser ablation is a successful method of treatment of prostate cancer; 2 patients underwent laser ablation treatment with no immediate post-treatment complications seen and no injury to the adjacent rectum or neurovascular bundles identified on MR imaging

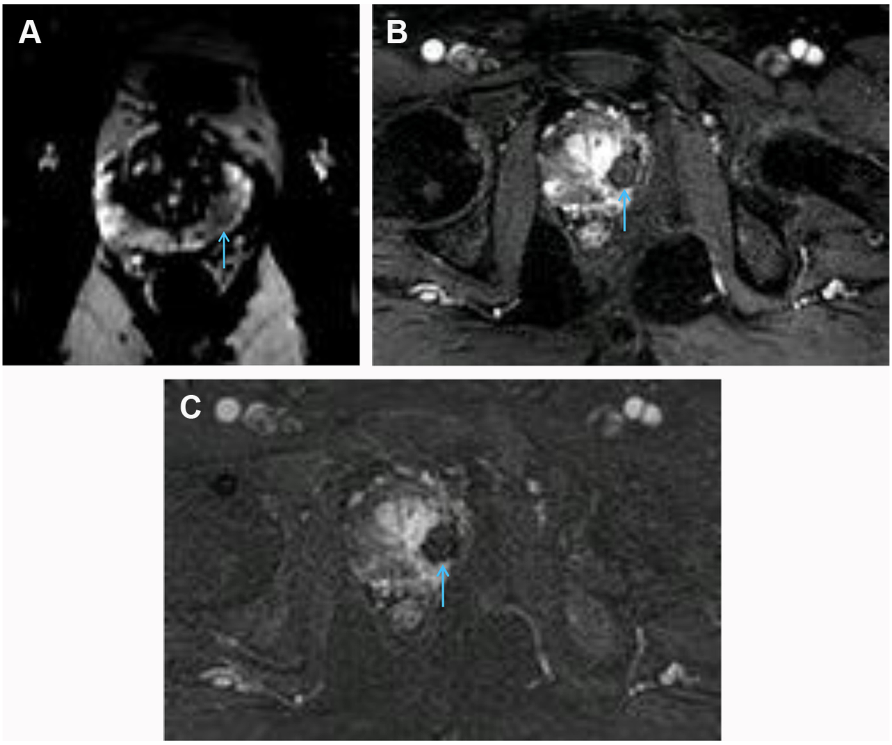

Fig. 4. Focal laser ablation. A 60-year-old patient with Gleason 7 prostate cancer underwent focal laser ablation for a lesion located in the left apex (*arrows*). Prophylactic antibiotics were administered to the patient prior to and after the procedure. Treatment was done using moderate-degree conscious sedation. A laser ablation template was placed on the patient's perineal surface and a lesion on MR imaging suspicious for prostate cancer was successfully localized. After the administration of lidocaine for local anesthetic, MR-compatible needles were directed into the area of the aforementioned lesion. After confirmation of needle location, ablation was performed. (*A*) A T2 hypointense cancerous focus is seen in the peripheral zone of the left apex. (*B*, *C*) After localized laser ablation, regional hypoenhancement is apparent in the left apex/midgland on unsubtracted and subtracted postcontrast imaging sequences, respectively.

performed 2 weeks after the procedure. In a phase I trial directed by Natarajan and colleagues,[31] 8 men were treated with directed laser ablation for intermediate-risk prostate cancer, with 5 of the patients determined cancer-free in the treatment area at their 6-month follow-up evaluation; in addition, the patients' sexual function and urinary habits were essentially preserved. Lindner and colleagues[32] conducted a phase I trial in which 12 patients harboring low-risk prostate cancers underwent focal laser therapy; post-treatment analysis performed after 3 months to 6 months demonstrated that more than half of the patients' rebiopsy results were negative for cancer in the region of treatment, and the primary complaint reported by most patients was simply perineal irritation. Another investigation led by Lepor and colleagues[33] followed 25 men who had undergone focal laser ablation, and no residual prostate cancer was detected in the post-treatment zones on rebiopsy performed 3 months later; an overall decrease in the patients' PSA values was also appreciated.

SUMMARY

Focal therapies, including cryotherapy, HIFU treatment, and regional laser ablation, are viable treatment options for men with intermediate-risk prostate cancer. By directing treatment to the site of interest, the adverse effects of the more traditional radical treatment options, such as prostatectomy or whole-gland brachytherapy and external beam radiation therapy, may be avoided. Fewer post-treatment urinary side effects, for instance, have been reported after locoregional cryotherapy and HIFU.[21,25]

Multiparametric MR imaging is the imaging modality of choice when performing focal therapies for locoregional prostatic tumor due to its accuracy in the initial detection of index lesions and its allowance for real-time monitoring during the course of treatment.[34] Treatment directed to the index lesion, or largest-volume or dominant tumoral focus, has been found to dictate the overall prognosis of the patient's disease process[17] and thus its reliable identification on MR imaging is vital. During the therapy process, the monitoring of temperatures in the adjacent soft tissues can help confirm that appropriate therapeutic levels are being reached. Additionally, real-time temperature checks can aid in avoiding inadvertent damage to nontarget anatomic structures, such as the urethra, urethral sphincter, bladder, and bowel.

Although continued scientific inquiry is required, current data regarding the efficacy of focal therapy options in the treatment of localized, low-risk, and intermediate-risk prostate cancer have been highly encouraging. Positive oncologic outcomes with an accompanying decreased incidence of untoward side effects have been observed. Additional longitudinal studies will help to clarify the long-term effects of focal treatments targeting prostate cancer.

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