MRI-Guided Interventions for the Treatment of Prostate Cancer

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OBJECTIVE. The purpose of this article is to evaluate MRI-guided therapies and to investigate their feasibility for focal therapy in prostate cancer patients. Relevant articles were retrieved using the PubMed online search engine.

CONCLUSION. Currently, MRI-guided laser ablation and MRI-guided focused ultrasound are the most promising options for focal treatment of the prostate in patients with prostate cancer. Other techniques—that is, cryosurgery, microwave ablation, and radiofrequency ablation—are, for several and different reasons, less suitable for MRI-guided focal therapy of the prostate.

Prostate cancer is the most frequently diagnosed cancer, accounting for 28% (218,000) of the total number of new cancer cases [1]. Prostate cancer is the second major cause of cancer death in men, responsible for 11% (32,000) of the total number of cancer deaths in men in the United States in 2010 [1]. Because of the widespread use of the prostate-specific antigen (PSA) test and the lowered PSA threshold for biopsy, the number of newly diagnosed prostate cancers has strongly increased [2]. At present, radical treatment—that is, radical prostatectomy or any form of radiotherapy—is not necessary to treat low-grade prostate cancer (Gleason score ≤6). Consensus exists that radical treatment is essential to treat aggressive prostate cancer (Gleason score >6) [3]. However, whole-gland treatment can lead to significant complications, such as incontinence (20% for radical prostatectomy and 5% for radiotherapy) and impotence (64% for radical prostatectomy and 66% for radiotherapy), and can have a substantial impact on quality of life [4]. Consequently, promising techniques such as cryosurgery, high-intensity focused ultrasound, and laser-induced thermal therapy have emerged as feasible minimally invasive focal treatment options. Although most of these techniques are still considered experimental for focal treatment of prostate cancer and have not been approved by the American Urological Association or European Association of Urology and have not been incorporated in national guidelines, most have been approved by the U.S. Food and Drug Administration, European Medicines Agency, or both. Over the past decade these techniques have been applied more and more in the treatment of prostate cancer [5–7]. Imaging guidance is imperative in all these types of treatment and is provided by transrectal ultrasound (3D), CT, or MRI. Of these imaging modalities, MRI—especially multiparametric MRI—is the most sensitive and specific imaging technique for prostate cancer [8].

Focal therapy of prostate cancer has the potential to reduce treatment-related complications such as incontinence and impotence without making concessions to cancer-specific outcome [9]. According to Meiers et al. [10], 13–33% of patients with prostate cancer have a unifocal prostate cancer lesion and would be eligible for focal therapy. Consistent with the “index lesion theory,” even more patients would be suitable [11].

In 2010, a consensus panel of urologic surgeons, radiation oncologists, radiologists, and histopathologists from Europe and North America defined focal therapy of the prostate as follows [12]:

A type of treatment that aims to eradicate known cancer within the prostate and at the same time preserve uninvolved prostatic tissue with the aim of preserving genitourinary function. Despite this definition, different varieties of focal therapy are described in the literature: hemiablation (i.e., treatment of the tumor affected lateralized hemisphere of the prostate),
hockey-stick ablation (i.e., hemiablation of the prostate plus one half of the contralateral hemisphere), and targeted focal therapy (i.e., only the tumor itself is treated).

On one hand, ample discussion exists about how to select the appropriate patient for focal therapy. However, on the other hand, there is almost no discussion about the optimal focal therapy method. The latter must meet numerous requirements: first, to be able to treat a specific area or one lobe of the prostate; second, to accurately shape the ablation zone with no significant effect on the surrounding tissue; third, to be minimally invasive with a low pre- and postoperative complication rate; and, fourth, to be reproducible.

Consequently, the purpose of this article is to evaluate MRI-guided therapies and to investigate their feasibility for focal therapy in prostate cancer patients.

Materials and Methods
A systematic literature search was performed. Relevant articles published before January 1, 2012, in English, German, or Dutch were retrieved using combinations of both medical subject headings and free search terms in the PubMed online search engine (U.S. National Library of Medicine). A combination of the following search terms was used: MRI, MRI-guided, prostate, ablation, radiofrequency, laser, cryosurgery, microwave, brachytherapy, (high-intensity) focused ultrasound, focal, and therapy. The references of retrieved relevant articles were checked for additional valuable articles. Ex vivo, in vitro, and phantom studies were excluded, as well as all studies published before 2000 because equipment and techniques have changed tremendously since that time.

All studies were scored: In each study, data about the study population, sample size, ablation technique, adverse events, and MRI methods were documented.

Results
Cryosurgery
In cryosurgery, tumor tissue is ablated by freezing. Cryosurgery was acknowledged as an established treatment option for men with newly diagnosed or recurrent organ-confined prostate cancer by the American Urological Association in 2008 [13]. Cryosurgery is usually performed under transrectal ultrasound guidance with a transperineal approach; however, cryosurgery can also be performed under CT or MRI guidance [14, 15].

In prostate cryosurgery, the patient is placed in the lithotomy position. A template under imaging guidance, transperineally inserted into the prostate. Because of the Joule-Thompson effect, the argon gas within the needle cools to –186°C and causes the formation of ice at the tip of the probe and gelation of the surrounding tissue. The thawing process can be active (with helium gas) or passive [16]. Correct needle positioning is essential to freeze as much of the tumor as possible and to avoid damaging the surrounding tissues to prevent complications.

To date, only limited data about MRI-guided cryosurgery study of the prostate are available (Table 1). The first results were reported after two canine studies were performed using an open 0.5-T MR system [17, 18]. The two groups of investigators concluded that MRI-guided cryosurgery is technically feasible. However, van den Bosch et al. [18] concluded that the volume of the ice ball does not match the volume of tissue necrosis [18]. As a consequence, attention should be paid to the size and location of the lesion that needs to be ablated and a safety margin of a few millimeters should be applied. Another disadvantage is that the cryoneedles cause an image artifact that is more pronounced on a T1-weighted sequence than on a T2-weighted sequence.

Laser Ablation Treatment
Laser ablation, sometimes also referred to as laser-induced thermal therapy, is a relatively new technique that was originally developed to treat brain tumors [20]. During this therapy, a laser fiber is positioned in the tumor under imaging guidance (ultrasound or MRI). When the position of the fiber is correct, a laser light with a wavelength of 980 nm is delivered through the fiber and

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Type</th>
<th>No. of Subjects</th>
<th>MR Field Strength and Configuration</th>
<th>Treatment Method</th>
</tr>
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<tbody>
<tr>
<td>Reisiger et al. [19]</td>
<td>2011</td>
<td>Patient</td>
<td>12</td>
<td>1.5 T, wide bore</td>
<td>Transperineal</td>
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<td>Tsoumakidou et al. [4]</td>
<td>2011</td>
<td>Patient</td>
<td>9</td>
<td>1.5 T, wide bore</td>
<td>Transperineal</td>
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<td>Josan et al. [17]</td>
<td>2009</td>
<td>Canine</td>
<td>13</td>
<td>0.5 T, open bore</td>
<td>Percutaneous</td>
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<tr>
<td>van den Bosch et al. [18]</td>
<td>2009</td>
<td>Canine</td>
<td>6</td>
<td>0.5 T, open bore</td>
<td>Percutaneous</td>
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*Presented at the 2011 annual meeting of the Cardiovascular and Interventional Radiological Society of Europe.*
the temperature of the tissue around the tip of the fiber increases. When the temperature of the tissue reaches more than 60°C, the tissue is irreversibly damaged and destroyed. The total ablation process takes up to 3 minutes. The laser fiber is placed inside a cooling catheter throughout the ablation to prevent carbonization of the adjacent tissue and to increase laser light penetration depth.

Studies reporting on MRI-guided prostate laser ablation are scarce because it is a considerably new technique (Table 2). Stafford et al. [21] and Peters et al. [22] were the first to report on MRI-guided laser ablation in prostates, although both groups reported the results of animal studies. The most important conclusion was that the damage predicted with MR temperature mapping correlated with the damage seen on 3D TI-weighted contrast-enhanced images, with a slope near unity and excellent correlation \( r^2 = 0.94 \) [21]. Complication rates were not reported because the animals were sacrificed immediately after the procedure.

Raz et al. [23] treated two patients with MRI-guided transperineal focal laser ablation at 1.5 T. Real-time MRI guidance was used during targeting of the tumor with the laser fiber and to control tissue temperature during the ablation. Patients were discharged 3 hours after treatment. No adverse events were found in the 1 month of follow-up. Woodrum et al. [24] described MRI-guided focal laser ablation at 3-T field strength; however, their study was a feasibility study performed using cadaveric prostates [24]. The same group also treated a patient with local recurrence of prostate cancer after a radical prostatectomy at 3-T field strength [25]. Early follow-up showed no posttreatment incontinence, rectal wall injury, or other complications [25]. In both studies, investigators concluded that MRI-guided laser ablation on a 3-T system is uniquely suited and is a promising technique for accurate focal targeting of prostate cancer because of the inherent high spatial and temporal resolution of MRI [24, 25].

One of the key features of laser ablation is that the fibers used during laser ablation cause no distortion of the electromagnetic field, so no image artifacts exist in the region of interest [26]. In addition, the treatment time is quite short and the ablation zone is sharply defined compared with other ablation techniques [21, 27].

**Focused Ultrasound**

Compared with the aforementioned techniques, focused ultrasound is the only real noninvasive ablation technique. A transducer directs a high-intensity ultrasound beam to converge and focus at a certain point in the tissue with this technique. The energy of the ultrasound waves is sufficient to heat up the tissue and to surpass the thermal dose threshold obligatory for coagulative necrosis in a few seconds. When the transducer consists of multiple piezoelectric elements, greater flexibility in targeting and shaping of the focal spot can be reached [28].

For prostate cancer, the transducer can be applied in various ways: transrectal [29, 30], which is the most applied method; transurethral [31, 32]; extracorporeal, with the transducer placed against the perineum [33]; and interstitial [34], with the transducer inserted transperineally, which is no longer noninvasive.

Experience in MRI-guided focused ultrasound has been gained in the treatment of uterine fibroids [35, 36]. Gradually the treatment area is now being extended to other organs and tissues such as breast, liver, and bone [37–39].

To date, only a few studies have been published about MRI-guided focused ultrasound of the prostate; however, most were performed using dogs (Table 3). McDannold et al. [30] performed the only study of focused ultrasound treatment under 3-T MRI guidance on four dogs using a transrectal probe. They concluded that MRI-guided focused ultrasound is feasible in the prostate. However, prostate movement was an important issue. Other results described in these animal studies were the small transition zones of 0.4–2.0 mm present between ablated tissue and viable tissue [30, 32, 40].

Siddiqui et al. [32] treated five patients with clinically proven prostate cancer (PSA < 15 ng/mL, T1c or T2a, and Gleason score ≤ 7 [3 + 4]) using transurethral MRI-guided focused ultrasound immediately before radical prostatectomy. Approximately 30% of the prostate volume was ablated to examine the technical feasibility of the technique. The treatment was well tolerated by patients and no complications were seen during or after surgery [32]. Overlapping results of the same research group were reported by Chopra et al. [40].

A substantial limitation of MRI-guided focused ultrasound is the extensive ablation time (= 2–2.5 hours, with incidental peaks to > 6 hours [41]), which makes this technique more suitable for focal therapy than for whole-gland therapy. Another disadvantage is that the focal spot loses its correct position in relation to the tumor if the patient moves or if there is any movement of the tumor within the body during treatment.

Besides thermal ablation, focused ultrasound has another promising clinical application: targeted drug delivery. The drug—for example, a chemotherapeutic agent—can be encapsulated and can be systematically administered to the body. The release of the drug can be locally activated by heat from or mechanical oscillation of the focused ultrasound waves [42].

**Radiofrequency Ablation**

During radiofrequency ablation (RFA), a needle electrode needs to be inserted into the tumor tissue. This electrode produces electromagnetic waves with a maximal frequency of 30 MHz. The waves cause friction within the tissue that raises the temperature and causes cell death [43].

Terraz et al. [44] performed MRI-guided RFA of 16 small liver malignancies in 10 patients. All patients were treated successfully,
Selecting the microwave applicator as the treatment option is necessary due to the limited experiences with MRI-guided RFA. Ares et al. [51] used HDR brachytherapy as an extra boost for only a partial volume of the prostate after external beam radiation therapy (EBRT) in 77 patients. In addition, ares et al. [51] used HDR brachytherapy as an extra boost for only a partial volume of the prostate after external beam radiation therapy (EBRT) in 77 patients. In one study, the median size decrease of the prostate after HDR brachytherapy was 43% [52]. Ares et al. [51] used HDR brachytherapy as an extra boost for only a partial volume of the prostate after external beam radiation therapy (EBRT) in 77 patients. In another study, the median size decrease of the prostate after HDR brachytherapy was 43% [52].

In modern medicine, the drive is toward the development and improvement of treatments and techniques that minimize intervention to the patient and hospitalization. MRI-guided interventions provide a minimally invasive approach to cancer therapy that is gaining clinical acceptance. Of the available techniques, we consider MRI-guided focal laser ablation to be the most sophisticated focal therapy treatment option in the prostate. It appears to be fast and feasible because of the sharply defined ablation zone, no distortion of laser fibers, few anticipated adverse events and complications, quick recovery of patients, and possibility to repeat the therapy as often as needed. Furthermore, it is easy to fit in clinical practice. MRI-guided focused ultrasound alone or combined with local drug delivery is a promising technique for focal therapy in the prostate. It has the potential to surpass focal laser ablation as the most sophisticated technique because it is not invasive and is highly accurate given the small focal spot. However, to
achieve this, the relative long treatment time even for small lesions needs to be shortened and the first experiments of patients need to be performed.

HDR brachytherapy can be performed under MRI guidance to give a local boost to the tumor as a supplement to EBRT of the entire prostate. For both types of brachytherapy, MR images can be used to localize the tumor and to monitor the insertion of the catheter and seeds in real time. During the actual therapy, MRI has no surplus value because this cannot be seen on the MR images.

The other techniques—cryosurgery, microwave ablation, and RFA—are, for several and different reasons, less suitable to use for MRI-guided focal therapy of the prostate. According to the first results in patients and animals [17, 18, 30] and earlier results under ultrasound guidance [6, 54–58], MRI-guided cryosurgery of the prostate is feasible even for focal therapy. However, because of the indistinct ablation zone, a safety margin of a few millimeters should be applied. Furthermore, MRI-guided focal cryosurgery can be repeated, is minimally invasive, and has a relative low complication rate.

Microwave ablation and RFA work with electromagnetic waves that can possibly interfere with the radiofrequency signals of the MR system itself [45]. These signals are dependent of the field strength of the magnet, in the range of 0–128 MHz when using a 1.5- or 3-T magnet. This possible interference makes these treatments less suitable for focal therapy because the tissue temperature of the adjacent healthy structures needs to be monitored carefully.

In general, the benefits of performing an intervention under MRI guidance (i.e., the accuracy during needle placement or the possibility of temperature mapping during the procedure) should be considered carefully against the disadvantages. These disadvantages include increased costs, difficult patient selection considering the multifocality of prostate cancer (this also accounts for transrectal ultrasound–guided procedures), limited amount of space during the procedure for the patient and physician, the need for special MR-compatible materials, and the limited time available in MRI scanners. Nevertheless, MR systems are increasingly being adjusted to allow interventional MRI. New systems with shorter and wider bores are being produced to provide more space for the patient and the physician as well.

Another way to overcome the accessibility problem and to speed up the procedure is to perform part of the procedure with the help of an MRI-compatible robot. Several robots for needle placement and LDR seed implantation have been described in the literature and the results of these studies are promising [59–62].

To date, the issue of how to select the appropriate patient for focal therapy has been discussed extensively. Several methods are used for prostate cancer diagnosis and staging: digital rectal examination, PSA test, and transrectal ultrasound–guided prostate biopsy. Nevertheless, these techniques are not accurate enough and fail to reveal a large fraction of clinically significant tumors [63]. Transrectal ultrasound–guided transperineal mapping or saturation biopsies were introduced to avoid missing clinically significant tumors. However, these biopsies have major disadvantages such as the need for anesthetics, patient discomfort, and intensive pathologic processing [64, 65]. Currently, MRI, especially multi-parametric MRI, is the most sensitive and specific imaging technique for prostate cancer [8] and should certainly be used for proper patient selection for focal therapy.

The largest limitation of this review is the sparse amount of data. Unfortunately data published on this subject are limited and most of the studies have a small study group and a short follow-up.

Future steps will be to validate these new procedures in prospective clinical trials with more patients and longer follow-up periods and to compare them with active surveillance and radical therapies in randomized controlled trials.

**Conclusion**

MRI-guided focal therapy of the prostate seems possible with the present techniques; however, the one method is more feasible than another.

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