Focal Therapy for Prostate Cancer: Recent Advances and Future Directions

Alex Wang,* Luke P. O'Connor,* Nitin K. Yerram, MD, Naveen Nandanan, MD, Michael Ahdoot, MD, Amir H. Lebastchi, MD, Sandeep Gurram, MD, Heather Chalfin, MD, and Peter A. Pinto, MD

*Co–first authors.

The authors are affiliated with the Urologic Oncology Branch of the National Cancer Institute at the National Institutes of Health in Bethesda, Maryland. Mr Wang and Mr O'Connor are research scholars, Drs Yerram, Ahdoot, Lebastchi, Gurram, and Chalfin are clinical fellows, Dr Nandanan is a resident surgeon, and Dr Pinto is an investigator and head of the prostate cancer section.

Corresponding author:
Nitin K. Yerram, MD
Urologic Oncology Branch
National Cancer Institute
Building 10, Room 1-5940W
Bethesda, MD 20892
Tel: (240) 858-3700
E-mail: yerramnk@nih.gov

Keywords
Focal laser ablation, high-intensity focused ultrasound, irreversible electroporation, photodynamic therapy, prostate cancer

Abstract: Prostate cancer is the most frequently diagnosed cancer in men after skin cancer. Owing to the rising popularity of prostate-specific antigen screening, large numbers of patients are receiving a diagnosis of prostate cancer and undergoing whole-gland treatment. Some patients with a diagnosis of low-risk, localized disease may not benefit from whole-gland treatment, however, given its known morbidity. In response to advances in prostate imaging and evidence suggesting that the prognosis in prostate cancer is related to the index lesion, many patients have begun to opt for focal therapy, which targets a lesion rather than the entire prostate. This "middle ground" of therapy, between active surveillance and whole-gland treatment, is appealing to patients because the risk for side effects is believed to be lower with focal therapy than with whole-gland treatment. This review discusses the oncologic rationale for focal therapy in localized prostate cancer, examines the major therapy modalities, and addresses future directions.

Introduction

Prostate cancer, which is estimated to have caused more than 31,000 deaths in 2019, is one of the leading causes of cancer death in the United States. Since the late 1980s and early 1990s, urologists have succeeded in increasing the detection rates of prostate cancer while decreasing the number of prostate cancer deaths.[1] However, with the rising use of prostate-specific antigen (PSA) screening, the whole-gland treatment of prostate cancer with radical prostatectomy (RP) has been undertaken more frequently in patients who have low-risk disease.[2] Despite advances in active research and the optimization of techniques, whole-gland treatment carries a considerable risk for morbidities that include erectile dysfunction and incontinence.[3,4] These complications can have a significant effect on patients' quality of life and lead to additional spending on potentially futile treatments to address them. Given the recent push to reduce the overtreatment of prostate cancer, a concerted effort has been made to explore novel methods of managing this disease. Although genomics has helped to identify patients in whom treatment can be delayed,[5,6] a push also has

been made to seek more options for those patients who require definitive management.

An estimated 174,650 new cases of prostate cancer were diagnosed in 2019.[7] Half of men with newly diagnosed prostate cancer have low-risk disease that pathologists rate as Gleason grade group 1 (GG1). These patients can be safely monitored with active surveillance. The active surveillance approach has been in use for almost 2 decades. Although patients initially reacted with some disfavor,[8] active surveillance has since gained in popularity. The advantage of active surveillance was demonstrated in a prospective cohort study by Klotz and colleagues, in which patients had few sexual, urinary, and intestinal side effects at short- and mid-term follow-up.[9] Active surveillance comes with its own set of disadvantages, however. Patients who undergo active surveillance require frequent follow-up visits with their doctor for procedures that include blood tests, magnetic resonance imaging (MRI), and prostate biopsies. This approach can lead to problems with adherence, psychological distress, and economic strain. Additionally, patients undergoing active surveillance are at increased risk for urinary tract infections or even fatal urosepsis due to prostate biopsies.[9]

Oncologic Rationale and Use of Magnetic Resonance Imaging

Given the disadvantages of whole-gland treatment and active surveillance, the question arose of whether we could develop a middle ground, in which we would treat the prostate cancer affecting only a small portion of the gland and at the same time monitor the rest of the gland for potential cancers. Considerable evidence suggests that in most cases of metastatic prostate cancer, a single precursor cell is responsible for driving the cancer to metastasize.[5,6] In addition, Stamey and colleagues showed that although prostate cancers are often multifocal, the pathologic characteristics of the largest lesion (the index lesion) are often the best predictor of the course of the disease and prognosis.[10] Focal therapy is based on the single precursor cell model as well as on the concept of the index lesion; its use as a way to focus treatment on the index lesion in the hope of eliminating the potentially lethal single precursor cell has recently been advocated as a reasonable treatment option for selected patients.

One of the main advancements that has made focal therapy not only more widely known but also within grasp is multiparametric magnetic resonance imaging (MP-MRI), which has improved tumor localization and biopsy guidance.[11,12] MP-MRI typically consists of 3 components: T1-weighted imaging with dynamic contrast enhancement, T2-weighted imaging, and diffusion-weighted imaging with phased array coils.[13] Multiple studies evaluating the effectiveness of MP-MRI have revealed a sensitivity as high as 100%, a specificity as high as 74%, and an 86% accuracy rate for detecting high-grade prostate cancers.[14-16] The use of MP-MRI as a 3-dimensional modeling technique makes is possible to determine the location of prostate cancer foci within the gland, which can be instrumental in obliterating lesions. However, MP-MRI has limitations in that it often underestimates the size of prostate cancer lesions, particularly in the case of cancers with a relatively low Gleason score.[17,18] Furthermore, evidence exists to suggest that although the negative predictive value of MP-MRI ranges from 63% to 98%, making it possible to rule out clinically significant prostate cancer, imaging limitations can result in the incomplete ablation of lesions missed on imaging and/or systematic biopsy.[12] In addition, because prostate cancer is often a multifocal disease, unanswered questions remain regarding how many lesions can be safely ablated with focal therapy and whether focal therapy can be used in patients with clinically significant disease (Gleason score ≥8).[19]

Current Practices

Focal Laser Ablation

Focal laser ablation (FLA) has recently gained popularity as a focal therapy option for the treatment of localized prostate cancer. During FLA, a small laser fiber is inserted into the tumor via a transperineal or transrectal approach.[20] Thermal energy discharged through the laser fiber rapidly heats the lesion, creating a homogenous, spherical area of coagulative necrosis with well-defined borders (Table 1).[21] Although the extent of tissue destruction depends on the temperature and duration of the treatment, it has been shown that irreversible cell damage and protein denaturation occur at approximately 60°C.[22]

Although many recent studies have assessed the efficacy of FLA, most are from a single institution with a small cohort.[23-26] In a phase 2 study by Eggener and colleagues, 27 men who had MRI-visible prostate lesions underwent FLA (Table 2).[24] At 12-month follow-up, 11% of the men had cancer in the ablation zone and 30% of the men had cancer outside the ablation zone. In a current FLA study, Feller and colleagues are using a transrectal approach with an MRI-compatible system to monitor energy deposition and coagulation necrosis. Outcomes for 98 patients with 138 cancer foci were released in 2018. The patients in whom biopsy was repeated had a 23% rate of recurrence in the treatment region at 6 months and a 45% mean decrease in the PSA level at 12 months.[27] Another large, single-institution FLA study included 120 patients with low- to intermediate-risk prostate cancer.[28] At 12 months after treatment with FLA, only 20 patients (17%) underwent

Table 1. Mechanisms of Various Types of Focal Therapy

Modality	Mechanism of Treatment
Focal laser ablation	Thermal energy discharged through a laser fiber causes coagulative necrosis.
High-intensity focused ultrasound	Repeated bursts of ultrasound energy cause coagulative necrosis.
Irreversible electroporation	Electrodes fire short pulses of direct current electricity in treatment zone, creating irreversible holes in the cell membrane and eventual apoptosis.
Photodynamic therapy	Photosensitizers collect in malignant cells, become activated by visible light, and release energy that forms reactive oxygen species to cause cellular damage and death.
Cryotherapy	Repeated cycles of rapid freezing and slow thawing induce cellular rupture and death.

additional oncologic treatment when a suspicious result on follow-up MRI was confirmed with biopsy.[28]

With regard to potential side effects of treatment, FLA is one of the safest focal therapy modalities. Among the patients in the study by Eggener and colleagues, both the International Prostate Symptom Score (IPSS) and the Sexual Health Inventory for Men (SHIM) score returned to baseline within 12 months after treatment.[24] The other 2 studies previously mentioned showed similar results; no significant difference in sexual or urinary function was observed at 12-month follow-up as indicated by the patients' IPSS or SHIM score[27] and patient-submitted surveys.[28]

Given its lack of morbidity, FLA is currently one of the safer focal therapy modalities. Other advantages of FLA include that it can be performed under local anesthesia and that MRI/ultrasound fusion can be used for guidance.[25] The major disadvantages of FLA lie in its technical difficulty, lack of prostate-specific procedure platforms, and lack of long-term follow-up data.[23] Although current studies have shown the procedure to provide oncologic control with minimal side effects, further long-term data are required to establish FLA as an effective modality for the treatment of prostate cancer.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) was initially designed as a minimally invasive alternative to surgery for whole-gland treatment but has recently been explored as a focal therapy option.[29] During this procedure, an ultrasound probe is placed in the rectum, and the prostate volume is measured without any compression. Transverse images are created, and the physician then maps out the treatment zones to target cancerous tissue while preserving the bladder neck, apex, and lateral margins and the urethra.[30] Multiple bursts of ultrasound energy are then targeted at the tumor with the goal of reaching a temperature of 100°C in the treatment area. A cooling period follows that helps preserve the surrounding benign tissue.[30]

Transrectal HIFU is currently being used as a minimally invasive technique for the treatment of localized prostate cancer. The treatment process involves the delivery of high-intensity ultrasound energy from the rectum to coagulate prostate tissue. Studies have shown that transrectal HIFU is associated with shorter recovery times compared with surgery[31]; in addition, long-term clinical follow-up of patients who received transrectal HIFU shows its feasibility and efficacy in the treatment of localized prostate cancer, with reports of a lower incidence of comorbidities and acceptable control of the disease.[31-34] In addition to the need to propagate sound waves in the rectal wall, which is a sensitive structure, a major limitation of transrectal HIFU is the inability to measure the temperature distribution during treatment. Accurate measurement of the temperature distribution during treatment is crucial for more precisely localizing the treatment area and not causing unnecessary cell death.

Guillaumier and colleagues conducted the largest HIFU clinical trial known to date, accruing 625 consecutive patients over a 10-year span.[35] Before HIFU, 166 patients had GG1 disease, 327 patients GG2, 86 patients GG3, and 11 patients GG4 or higher. The median follow-up after treatment was 56 months (interquartile range [IQR], 35-70) and included PSA measurement, MP-MRI, and biopsy. The study's primary endpoint was failure-free survival following HIFU treatment, which was defined as freedom from radical or systemic therapy, metastases, and cancer-specific mortality.[35] At 5-year follow-up, the failure-free survival, metastasis-free survival, and cancer-specific survival rates were 88% (95% CI, 85%-91%), 98% (95% CI, 97%-99%), and 100%, respectively.[35] Although this study showed incredibly promising results, it was criticized for its weak follow-up.[36] Because only 222 of the 625 men initially enrolled underwent biopsy after treatment, the authors did not capture the true failure-free survival rate or rate of recurrence for all patients in the study.[35,36]

In a pooled analysis of 7 studies, Albisinni and colleagues investigated HIFU for either focal therapy or hemiablation.[37] Overall, 366 patients were included in the analysis, who had a mean age of 67 years (95% CI, 66-69), mean PSA level of 6.4 ng/mL (5.5-7.4), and mean follow-up of 26 months.[23-30,38] Inclusion criteria for

Table 2. Key Clinical Studies for Various Types of Focal Therapy

Study	Modality	No. of Patients	Outcomes	Side Effects
Eggener et al[24]	FLA	27	11% in-field, 30% out-of-field recurrence at 12-mo biopsy	No difference in IPSS or SHIM scores
Walser et al[28]	FLA	120	17% treated following 12-mo biopsy	No difference in sexual or urinary function
Guillaumier et al[35]	HIFU	625	88% failure-free survival at 5-y follow-up	Pad-free continence achieved in 98%; erectile function data not available
Albisinni et al[37] (pooled analysis)	HIFU	366	87% negative biopsy rate at 12-mo follow-up	Continence rate 96%, potency rate 74%
van den Bos et al[42]	IRE	63	16% in-field recurrence, 24% whole-gland recurrence at 6-mo follow-up	Decrease in erectile function (from median QoL score of 66 at baseline to 54 at 6-month follow-up)
Blazevski et al[43]	IRE	123	9.8% in-field recurrence, 12.7% out-of-field recurrence at 12-mo follow-up	Decrease in erectile function reported in 24% of patients
Moore et al[47]	PDT	68	75% cancer-free in treated lobe within 18 mo of treatment	No difference between IPSS scores or IIEF-5 scores at baseline and those at 6 mo after treatment
Gill et al[49]	PDT	413	24% of treated patients received radical therapy after 4 y of follow-up	Not reported
Mendez et al[54] (COLD registry study)	Cryo-therapy	317	14.5% (8/55) positive biopsy rate with median follow-up time of 58.3 mo	Incontinence rate 0%; 68.8% of men with recovery of erectile function at 24-mo follow-up
Shah et al[56] (COLD registry study)	Cryo-therapy	122	90.5% failure-free survival at 3-y follow-up	Incontinence rate 0%; 83.9% of men with decrease in erectile function at most recent follow-up

COLD, Cryo On-Line Data; FLA, focal laser ablation; HIFU, high-intensity focused ultrasound; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; IRE, irreversible electroporation; mo, month(s); PDT, photodynamic therapy; QoL, quality of life; SHIM, Sexual Health Inventory for Men; y, year(s).

the Gleason score varied among the studies, with 3 studies including up to Gleason 7 (3+4), 3 studies including up to Gleason 7 (4+3), and 1 study having no limitation on the Gleason score. The negative biopsy rate for clinically significant cancer at 1 year after treatment was 87% (95% CI, 79%-96%), and the salvage treatment–free survival rate was 92% (95% CI, 85%-98%).[37] In a more recent study, 75 patients underwent MRI and transperineal template saturation biopsy before focal ablation with HIFU.[39] The median age of the patients was 67 years (IQR, 60-71), and the median PSA level was 5.87 ng/mL (IQR, 4.65-7.44). Before focal therapy, 5 patients had low-risk cancer (6.7%) and 70 patients had intermediate-risk cancer (93.3%). Of the men who underwent biopsy at 6 months after treatment, 41% (95% CI, 30.3-53.0) had clinically significant prostate cancer, with a median number of sample cores of 44 (IQR, 36-44).

A recent study by Bass and colleagues assessed the outcomes of partial/focal ablation in 150 patients with intermediate- or high-risk prostate cancer.[40] Of the 87 patients who underwent confirmatory biopsy following HIFU, 37 (42.5%) were found to have GG2 disease or higher. Overall, 37 patients (24.6%) ended up receiving salvage therapy following HIFU. Although these oncologic outcomes were not strong for this high-risk cohort, the authors argue that whole-gland treatment was avoided in 81% of patients.

Although HIFU has the advantage that ultrasound is used to facilitate real-time visualization of the prostate during treatment, it does have drawbacks. The procedure requires general anesthesia and prostate volumes of less than 40 mL.[30] In addition, the treatment of anterior lesions can be nearly impossible owing to the inability of the platform to ablate tissue at a depth greater than

4 cm.[30] Although rectal fistulas have been described as a possible complication of whole-gland treatment, they are extremely rare when HIFU is used for focal therapy (0%-1%).[38] Studies have shown excellent continence rates (94.9%-98%) in patients treated with HIFU, but the rates of potency have not been as high.[35,37,39,40] The study by Albisinni and colleagues showed a potency rate of 74%, whereas the study by Mortezavi and colleagues showed preservation of erectile function after treatment in only 69% of patients.[37,39] Bass and colleagues had slightly higher results of preserved erectile function, with 86.5% of patients having no change following treatment.[40] Although the results of these studies are encouraging, future research needs to focus on preserving erectile function following HIFU as well as on continuing to collect long-term follow-up data.

Irreversible Electroporation

Another focal therapy modality that is currently being explored is irreversible electroporation (IRE). In this procedure, electrodes are placed in the prostate transperineally under ultrasound or MRI guidance, and then short pulses of direct current electricity are fired into the treatment zone. This procedure limits tissue damage outside the treatment zone while irreversible holes are created in the membranes of the cancer cells, thus leading to apoptosis.[41]

A study by van den Bos and colleagues included 63 patients who underwent IRE for Gleason 6 or any-sum Gleason 7 disease.[42] After a minimum follow-up of 6 months, the authors reported in-field and whole-gland recurrence rates of 16% (7/45 patients) and 24% (11/45 patients), respectively.[42] Another study, by Blazevski and colleagues, showed similar results in their cohort of 123 patients, of whom 112 (91%) had intermediate-risk prostate cancer and 11 (9%) had low-risk prostate cancer according to the National Comprehensive Cancer Network (NCCN) risk classification system.[43] With a minimum follow-up of 12 months, the in-field, out-of-field, and overall recurrence rates were 9.8% (10/102), 12.7% (13/102), and 77.5% (79/102), respectively.[43] At 3-year follow-up, the failure-free survival rate (defined as freedom from whole-gland or systemic treatment or metastasis/death) was 96.75%, with 18 patients eventually requiring salvage treatment.[43] A more recent study, by Collettini and colleagues, included 30 men with low- to intermediate-risk prostate cancer who underwent IRE.[44] At 6-month follow-up, 5 of 28 patients (17.9%) who underwent biopsy after treatment were found to have in-field residual disease. An additional 2 patients with no evidence of disease at 6 months were eventually found to have new out-of-field disease after biochemical relapse. Overall, 1 of 30 patients (3.3%) required a second IRE procedure, and 4 of 30 patients (13.3%) required RP.

The major drawback of IRE is the reported decrease in erectile function following treatment. The patients in the study of Collettini and colleagues did not report a statistically significant decrease in sexual function after treatment.[44] The patients in the study of van den Bos and colleagues reported a slight decrease in sexual function (median score, 66 at baseline vs 54 at 6 months; $P<.001$) on quality-of-life questionnaires,[42] and 13 of 53 patients (24%) in the study of Blazevski and colleagues reported a decrease in erectile function.[43] Although these results need to be validated with further research, future efforts should be directed at increasing the rates of potency following IRE.

Photodynamic Therapy

In addition to the modalities previously mentioned, photodynamic therapy (PDT) is a focal therapy option for patients with localized prostate cancer. PDT depends on 3 main components: a photosensitizer, visible light, and oxygen.[45] The photosensitizer is a chemical compound that collects primarily in malignant cells. These compounds are activated by visible light and release energy that is transferred to oxygen molecules, thus creating reactive oxygen species. The accumulation of reactive oxygen species in cancerous tissue results in cellular damage and death.[45,46]

Several clinical trials have assessed the efficacy and safety of PDT as a focal therapy. Moore and colleagues conducted a phase 2 trial in which 38 patients underwent PDT, and 20 of these patients (53%) had a negative biopsy result at 6-month follow-up.[47] In another phase 2 trial, which included 68 patients who underwent PDT, 51 of the patients (75%) were considered to have had successful ablation, defined as absence of cancer in the treated lobe at follow-up.[48] The follow-up period was short, however, with more than 90% of patients assessed for cancer via biopsy within 18 months after treatment. Of those patients whose disease failed to respond to initial treatment with PDT, 14 went on to receive definitive therapy for their prostate cancer (surgery, radiation, or HIFU).[48] In 2018, Gill and colleagues published their results from the phase 3 PCM301 trial (Efficacy and Safety Study of TOOKAD® Soluble for Localised Prostate Cancer Compared to Active Surveillance), which randomly assigned 413 men with low-risk prostate cancer to treatment with either PDT (207) or active surveillance (206).[49] According to biopsy results obtained at 24-month follow-up, 50% of the patients who received ablation remained cancer-free in the entire prostate, compared with 14% of patients who underwent active surveillance (absolute risk difference, 36%; 95% CI, 28%-44%). Among the men with positive biopsy results anywhere in the prostate, Gleason 7 disease was found in 16% of those in the PDT arm

compared with 41% of those in the active surveillance arm. A search for in-field recurrence revealed Gleason 7 disease in the treatment zone in 10% of all the positive biopsy specimens of those who received PDT and Gleason 7 disease in the treatment zone in 34% of all positive biopsy specimens of those who underwent active surveillance.[49] After 4 years of follow-up, 24% of the patients treated with PDT went on to receive radical therapy vs 53% of those randomly assigned to active surveillance (hazard ratio, 0.31; 95% CI, 0.21-0.46).[49]

With regard to sexual and urinary outcomes, PDT is a relatively safe focal therapy option. At 2 years before their most recent update, Azzouzi and colleagues published results from the same clinical trial that included follow-up data on sexual and urinary function.[50] The authors reported no difference between patients in the PDT group and those the active surveillance group in regard to the IPSS or the 5-item version of the International Index of Erectile Function (IIEF-5). Similarly, the study by Moore and colleagues reported no change in the IPSS or the IIEF-5 between baseline and 6 months after treatment.[47] Although these initial results are encouraging, longer follow-up is required to determine the long-term efficacy of PDT, as well as the effect of PDT on sexual and urinary function.

Cryotherapy

Although cryotherapy was originally developed for whole-gland treatment, it has recently been adopted as a focal therapy option.[51] Cryotherapy is different from the other focal therapy modalities previously listed in that it does not use thermal energy to destroy malignant cells. Cancers are instead treated by rapidly freezing and slowly thawing the target area in repetitive cycles, inducing cellular rupture and death.[52] Needles are placed into the prostate via a transperineal approach, and the tumor is cooled to a target temperature of –40°C.[53] Monitoring probes are placed at the urethral sphincter, at the prostatic apex, and adjacent to the neurovascular bundles to ensure thermal control. The use of a urethral warming device and the injection of saline solution into the interprostatorectal space provide additional thermal protection for the urethra and rectum, respectively.[53]

Mendez and colleagues conducted a study in which they used the Cryo On-Line Data (COLD) Registry to match 317 men who underwent focal cryotherapy with 317 men who underwent whole-gland ablation with cryotherapy.[54] After a median follow-up of 58.3 months, 14.5% of the 55 men who underwent biopsy after focal cryotherapy had a positive result, compared with 11.6% of the 95 men who underwent biopsy after whole-gland ablation. In an additional study using the COLD registry, Tay and colleagues analyzed 166 matched pairs of men who underwent focal cryotherapy or whole-gland ablation. After 5 years of follow-up, the focal cryotherapy cohort had a biochemical progression-free survival rate of 70.5%.[55] A more recent study, by Shah and colleagues, included 122 consecutive patients who underwent focal cryotherapy.[56] At 3-year follow-up, the overall, NCCN intermediate-risk, and NCCN high-risk failure-free survival rates, with failure defined as conversion to radical, whole-gland, or systemic therapy or metastasis/death, were 90.5% (95% CI, 84.2%-97.3%), 93.3% (95% CI, 86.8%-100%), and 84.7% (95% CI, 71.4%-100%), respectively.[56] Although results from this study showed promising oncologic control, the authors were criticized for not excluding high-risk patients on androgen deprivation therapy (ADT).[57] The authors acknowledged that ADT could influence focal therapy outcomes by reducing tumor volume and neovasculature, but further studies will need to be conducted to assess the effect of neoadjuvant hormonal therapy on focal therapy outcomes.[58]

While cryotherapy has been shown to have oncologic outcomes similar to those of the other modalities previously listed, the rates of erectile dysfunction have been higher. Although 100% of the focal therapy cohort in the study of Mendez and colleagues remained continent at 24 months following cryotherapy, only 68.8% of 160 men had recovery of erection.[54] In the study of Tay and colleagues, patients had a 12-month continence rate of 95.1%, but the 12-month effective intercourse rate was only 46.8%.[55] Likewise, patients in the study of Shah and colleagues had an excellent incontinence rate (0%), but the erectile dysfunction rate was worse (16.1%).[56] Although the oncologic outcomes of focal cryotherapy are encouraging, further refinement is required to reduce the high rates of erectile dysfunction associated with this modality.

Future Directions

Imaging: 7-Tesla MRI

The advent of MP-MRI changed the landscape of focal therapy for localized prostate cancer. However, because of its low negative predictive value and the results of studies showing poor specificity with a high false-positive rate (16%-33%) despite use of the Prostate Imaging Reporting and Data System (PI-RADS) version 2,[59] the use of MP-MRI has remained limited. In traditional MRI, either 1.5 or 3 teslas (T) is typically used to generate images for clinical diagnosis. The 7-T MRI machine (Siemens Healthcare, Erlangen, Germany) more than doubles the magnetic field strength of the 3-T machine. Early studies using 7-T MRI have shown promising diagnostic potential, with unprecedented spatial resolution and a non-enhanced hyperintense vessel signal.[60] A

recent study using 7-T MRI for prostate-specific lesions showed satisfactory to good T2-weighted image quality, and clinically significant central zone and peripheral zone prostate cancers could be detected with the use of an external transmit/receive coil.[61] Although this study used endorectal coils for imaging patients, such coils were not used for ^{1}H signal detection. The addition of a ^{1}H receiver could further enhance the image quality of 7-T MRI. A recent study showed the feasibility of using a ^{31}P trans-receiver and a ^{1}H Rx endorectal coil in combination with an 8-channel trans-receiver external body array coil in MP-MRI at 7 T in patients with prostate cancer in one MRI examination.[62] Another study showed that 7-T MRI can generate high-quality T2-weighted images in less than 2 minutes for each patient.[63]

MRI-Guided Transurethral Ultrasound Ablation

An exciting new modality being introduced to the realm of focal therapy is MRI-guided transurethral ultrasound ablation (TULSA). Unlike HIFU, which is centered on multiple small-volume treatments, TULSA utilizes high-intensity directional ultrasound, which has a distinct pattern of thermal dose and temperature deposition that allows the more accurate monitoring of tissue damage and necrosis. The TULSA procedure involves administering high-intensity ultrasound beams to raise and maintain tissue temperatures above 55°C while also monitoring the temperature distribution and ablation area with MR thermometry.[64,65] The ablated tissue can then be visualized after treatment with contrast-enhanced MRI (CE-MRI) to look for nonperfused volume, which indicates cell death.[66-68] The ablated tissue undergoes acute coagulation necrosis followed by delayed necrosis.[69] The degree of necrosis depends on the total thermal dose received. An early feasibility study using TULSA followed by prostatectomy 3 weeks later showed a significant increase of post-TULSA nonperfused volume, suggesting successful coagulation necrosis of all targeted tissue on histology.[70]

The introduction of live MRI technology has proved to be an important step forward in making it possible to gauge temperature distributions during TULSA procedures. Studies have already shown live MRI technology to be useful in localizing prostate cancer for biopsy[71-74]; one can extrapolate the use of this technology in the ablation of localized disease. MR thermometry provides real-time temperature mapping during treatment and shows the relationships between treatment temperatures and actual thermal tissue damage. These advantages allow more control over the treatment outcome, which makes MR thermometry particularly useful for minimally invasive procedures such as TULSA. In an early study investigating the feasibility of MRI-controlled transurethral ultrasound therapy, it was well tolerated in all of the participants in the study, with a temperature uncertainty of less than 2°C.[75] Longer-term studies have also shown some promise. In the study of Bonekamp and colleagues, at 12 months after their TULSA procedure patients showed a median reduction in viable prostate volume of 88%, with delayed thermal ablation volume (derived from MR thermometry) the most accurate predictor of viable prostate tissue reduction at 12 months.[76] Initial study results have been promising, but longer-term follow-up with prostate biopsy, as well as longer-term evaluations of clinical safety, need to be conducted to evaluate for late toxicity.

Use of Androgen Deprivation Therapy With Focal Therapy

Focal therapy modalities remain promising in the treatment of localized prostate cancer; however, they do not come without their own set of complications. Although short- to medium-interval studies have shown the effectiveness and safety of focal therapy,[77] longer-term studies have revealed areas with room for improvement. Approximately 20% of patients have a positive post-treatment biopsy result after 1 year, and the 10-year re-treatment rate is estimated at 50%.[77,78] One theory posited to explain these focal therapy failures is the possibility of cancer foci that are undetectable owing to the limitations of imaging and biopsy techniques. Another possible explanation is the focal therapy itself. The tumor microenvironment in prostate cancer consists of numerous indirect and direct cellular interactions involving immune cells, mesenchymal stem cells, stromal fibroblasts, and blood vessels.[79,80] Focal therapy–induced inflammation may favor tumorigenesis in the surrounding tissues, either damaging benign tissues and/or favoring the transition of foci of indolent prostate cancer into clinically significant prostate cancer.[80] Not unlike most cancer treatments, focal therapy targets prostate cancer lesions directly, but it does not target the microenvironmental modifications that possibly also should be targeted.

One potential approach to targeting the prostate cancer microenvironment is ADT. With regard to its efficacy, ADT has been shown to increase overall survival in patients with localized intermediate- to high-risk prostate cancer when it is combined with external beam radiation therapy (EBRT) or RP.[81] Jones and colleagues conducted a randomized trial comparing EBRT alone vs EBRT with 4 months of ADT in 1979 patients who had prostate cancer and found improvements in disease-free survival and overall survival at 10 years with the addition of ADT.[82] Regarding the practicality of this approach, some groups have already used short-term ADT for whole-gland HIFU to reduce prostate volume and postoperative

urinary symptoms,[83-85] with no related toxicity. ENHANCE (Evaluation of HIFU Hemiablation and Short Term Androgen Deprivation Therapy Combination to Enhance Prostate Cancer Control) is an open-label, single-arm pilot study to assess the oncologic efficacy and safety, in terms of functional outcomes and morbidity, of HIFU hemiablation with concomitant short-term ADT for the treatment of low- to intermediate-risk localized prostate cancer.[86] Overall, ADT combined with focal therapy is an interesting treatment technique to target not only the tumor itself but also the environment surrounding the tumor. Further studies evaluating long-term efficacy, as well as the side effect profile, are needed before this modality is incorporated into the focal therapy paradigm.

Conclusion

Although long-term data are pending, focal therapy is a promising alternative for the treatment of prostate cancer, especially in patients unable to tolerate the morbidity of whole-gland therapy. Advances in imaging have not only led to better diagnostics and clinical staging but also established a solid foundation for focal treatment directed at specific lesions. As the field naturally advances toward the implementation of more minimally invasive techniques, focal therapy may prove to be a useful tool in the arsenal of treatments for localized prostate cancer. However, further research is still required to analyze both long-term oncologic outcomes and effects on patient quality of life before focal therapy can be implemented into the mainstream treatment algorithm.

Disclosures

This research was made possible through the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, Genentech, the American Association for Dental Research, the Colgate-Palmolive Company, and other private donors.

The National Institutes of Health (NIH) has a Cooperative Research and Development Agreement with Philips Electronics. The NIH has intellectual property in the field, including the patent "System, methods, and instrumentation for image guided prostate treatment" (US Patent number 8948845), with inventors/authors who include Dr Pinto. The NIH and Dr Pinto receive royalties from a licensing agreement with Philips/Invivo Corporation. The NIH does not endorse or recommend any commercial products, processes, or services. The views and personal opinions of the authors expressed herein do not necessarily reflect those of the US government, nor do they reflect any official recommendation or opinion of the NIH or National Cancer Institute.

References

1. Cancer stat facts: prostate cancer. National Cancer Institute. https://seer.cancer.gov/statfacts/html/prost.html. Accessed January 9, 2020.
2. Loeb S, Gonzalez CM, Roehl KA, et al. Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. *J Urol*. 2006;175(3 pt 1):902-906.
3. Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol*. 2012;62(3):405-417.
4. Pinsky PF, Parnes HL, Andriole G. Mortality and complications after prostate biopsy in the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial. *BJU Int*. 2014;113(2):254-259.
5. Ahmed HU. The index lesion and the origin of prostate cancer. *N Engl J Med*. 2009;361(17):1704-1706.
6. Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. *Nat Med*. 2009;15(5):559-565.
7. American Cancer Society. Key statistics for prostate cancer. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html. Updated August 1, 2019. Accessed January 9, 2020.
8. Harlan SR, Cooperberg MR, Elkin E, et al. Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: results from CaPSURE. *J Urol*. 2003;170(5):1804-1807.
9. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33(3):272-277.
10. Stamey TA, McNeal JM, Wise AM, Clayton JL. Secondary cancers in the prostate do not determine PSA biochemical failure in untreated men undergoing radical retropubic prostatectomy. *Eur Urol*. 2001;39(suppl 4):22-23.
11. De Visschere PJ, Briganti A, Fütterer JJ, et al. Role of multiparametric magnetic resonance imaging in early detection of prostate cancer. *Insights Imaging*. 2016;7(2):205-214.
12. Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. *Eur Urol*. 2015;68(6):1045-1053.
13. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. *Eur Urol*. 2011;59(4):477-494.
14. Cirillo S, Petracchini M, Della Monica P, et al. Value of endorectal MRI and MRS in patients with elevated prostate-specific antigen levels and previous negative biopsies to localize peripheral zone tumours. *Clin Radiol*. 2008;63(8):871-879.
15. Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? *Eur Urol*. 2006;50(6):1163-1174.
16. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging*. 2007;25(1):146-152.
17. De Visschere PJ, Naesens L, Libbrecht L, et al. What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging? *Eur Radiol*. 2016;26(4):1098-1107.
18. Kamrava M, Chung M, Mesko S, et al. Correlation of quantitative diffusion-weighted and dynamic contrast-enhanced MRI parameters with NCCN risk group, Gleason score, and maximum tumor diameter in prostate cancer. *Pract Radiat Oncol*. 2013;3(2)(suppl 1):S4.
19. Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. *Eur Urol*. 2015;67(3):569-576.
20. Colin P, Mordon S, Nevoux P, et al. Focal laser ablation of prostate cancer: definition, needs, and future. *Adv Urol*. 2012;2012:589160.
21. Stafford RJ, Shetty A, Elliott AM, et al. Magnetic resonance guided, focal laser induced interstitial thermal therapy in a canine prostate model. *J Urol*. 2010;184(4):1514-1520.
22. Ritchie KP, Keller BM, Syed KM, Lepock JR. Hyperthermia (heat shock)-induced protein denaturation in liver, muscle and lens tissue as determined by differential scanning calorimetry. *Int J Hyperthermia*. 1994;10(5):605-618.
23. Ahdoot M, Lebastchi AH, Turkbey B, Wood B, Pinto PA. Contemporary treatments in prostate cancer focal therapy. *Curr Opin Oncol*. 2019;31(3):200-206.
24. Eggener SE, Yousuf A, Watson S, Wang S, Oto A. Phase II evaluation of magnetic resonance imaging guided focal laser ablation of prostate cancer. *J Urol*. 2016;196(6):1670-1675.

25. Natarajan S, Jones TA, Priester AM, et al. Focal laser ablation of prostate cancer: feasibility of magnetic resonance imaging-ultrasound fusion for guidance. *J Urol*. 2017;198(4):839-847.
26. Natarajan S, Raman S, Priester AM, et al. Focal laser ablation of prostate cancer: phase I clinical trial. *J Urol*. 2016;196(1):68-75.
27. Feller J, Greenwood B, Jones W, Toth R. Transrectally delivered, outpatient MRI-guided laser focal therapy of prostate cancer: seven year interim results of NCT #02243033 [AUA abstract MP30-02]. *J Urol*. 2018;199(4)(suppl): e374-e375.
28. Walser E, Nance A, Ynalvez L, et al. Focal laser ablation of prostate cancer: results in 120 patients with low- to intermediate-risk disease. *J Vasc Interv Radiol*. 2019;30(3):401-409.e2.
29. Blana A, Walter B, Rogenhofer S, Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. *Urology*. 2004;63(2):297-300.
30. Barkin J. High intensity focused ultrasound (HIFU). *Can J Urol*. 2011;18(2):5634-5643.
31. Crouzet S, Murat FJ, Pasticier G, Cassier P, Chapelon JY, Gelet A. High intensity focused ultrasound (HIFU) for prostate cancer: current clinical status, outcomes and future perspectives. *Int J Hyperthermia*. 2010;26(8):796-803.
32. Ahmed HU, Moore C, Emberton M. Minimally-invasive technologies in uro-oncology: the role of cryotherapy, HIFU and photodynamic therapy in whole gland and focal therapy of localised prostate cancer. *Surg Oncol*. 2009;18(3): 219-232.
33. Crouzet S, Rebillard X, Chevallier D, et al. Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients. *Eur Urol*. 2010;58(4):559-566.
34. Murat FJ, Poissonnier L, Pasticier G, Gelet A. High-intensity focused ultrasound (HIFU) for prostate cancer. *Cancer Control*. 2007;14(3):244-249.
35. Guillaumier S, Peters M, Arya M, et al. A multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. *Eur Urol*. 2018;74(4):422-429.
36. Taneja SS. Re: a multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. *J Urol*. 2019;201(3):443-444.
37. Albisinni S, Mélot C, Aoun F, et al. Focal treatment for unilateral prostate cancer using high-intensity focal ultrasound: a comprehensive study of pooled data. *J Endourol*. 2018;32(9):797-804.
38. Hübner N, Shariat SF, Remzi M. Focal therapy of prostate cancer. *Curr Opin Urol*. 2018;28(6):550-554.
39. Mortezavi A, Krauter J, Gu A, et al. Extensive histological sampling following focal therapy of clinically significant prostate cancer with high intensity focused ultrasound. *J Urol*. 2019;202(4):717-724.
40. Bass R, Fleshner N, Finelli A, Barkin J, Zhang L, Klotz L. Oncologic and functional outcomes of partial gland ablation with high intensity focused ultrasound for localized prostate cancer. *J Urol*. 2019;201(1):113-119.
41. Onik G, Mikus P, Rubinsky B. Irreversible electroporation: implications for prostate ablation. *Technol Cancer Res Treat*. 2007;6(4):295-300.
42. van den Bos W, Scheltema MJ, Siriwardana AR, et al. Focal irreversible electroporation as primary treatment for localized prostate cancer. *BJU Int*. 2018;121(5):716-724.
43. Blazevski A, Scheltema MJ, Yuen B, et al. Oncological and quality-of-life outcomes following focal irreversible electroporation as primary treatment for localised prostate cancer: a biopsy-monitored prospective cohort [in press]. *Eur Urol Oncol*. 2019. https://doi.org/10.1016/j.euo.2019.04.008.
44. Collettini F, Enders J, Stephan C, et al. Image-guided irreversible electroporation of localized prostate cancer: functional and oncologic outcomes. *Radiology*. 2019;292(1):250-257.
45. Luksiene Z. Photodynamic therapy: mechanism of action and ways to improve the efficiency of treatment. *Medicina (Kaunas)*. 2003;39(12):1137-1150.
46. Dobson J, de Queiroz GF, Golding JP. Photodynamic therapy and diagnosis: principles and comparative aspects. *Vet J*. 2018;233:8-18.
47. Moore CM, Azzouzi AR, Barret E, et al. Determination of optimal drug dose and light dose index to achieve minimally invasive focal ablation of localised prostate cancer using WST11-vascular-targeted photodynamic (VTP) therapy. *BJU Int*. 2015;116(6):888-896.
48. Noweski A, Roosen A, Lebdai S, et al. Medium-term follow-up of vascular-targeted photodynamic therapy of localized prostate cancer using TOOKAD soluble WST-11 (phase II trials). *Eur Urol Focus*. 2019;5(6):1022-1028.
49. Gill IS, Azzouzi AR, Emberton M, et al. Randomized trial of partial gland ablation with vascular targeted phototherapy versus active surveillance for low risk prostate cancer: extended followup and analyses of effectiveness. *J Urol*. 2018;200(4):786-793.
50. Azzouzi AR, Vincendeau S, Barret E, et al; PCM301 Study Group. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol*. 2017;18(2):181-191.
51. Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localized prostate cancer: a phase I/II trial. *J Urol*. 2011;185(4):1246-1254.
52. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology*. 1998;37(3):171-186.
53. Bozzini G, Colin P, Nevoux P, Villers A, Mordon S, Betrouni N. Focal therapy of prostate cancer: energies and procedures. *Urol Oncol*. 2013;31(2):155-167.
54. Mendez MH, Passoni NM, Pow-Sang J, Jones JS, Polascik TJ. Comparison of outcomes between preoperatively potent men treated with focal versus whole gland cryotherapy in a matched population. *J Endourol*. 2015;29(10):1193-1198.
55. Tay KJ, Polascik TJ, Elshafei A, Tsivian E, Jones JS. Propensity score-matched comparison of partial to whole-gland cryotherapy for intermediate-risk prostate cancer: an analysis of the Cryo On-Line Data Registry Data. *J Endourol*. 2017;31(6):564-571.
56. Shah TT, Peters M, Eldred-Evans D, et al. Early-medium-term outcomes of primary focal cryotherapy to treat nonmetastatic clinically significant prostate cancer from a prospective multicentre registry. *Eur Urol*. 2019;76(1):98-105.
57. Shah TT, Peters M, Arya M, Ahmed HU. Reply to Zhipeng Mai's Letter to the Editor re: Taimur T. Shah, Max Peters, David Eldred-Evans, et al. Early-medium-term outcomes of primary focal cryotherapy to treat nonmetastatic clinically significant prostate cancer from a prospective multicentre registry. *Eur Urol*. 2019;76:98-105. *Eur Urol*. 2019;76(3):e63-e64.
58. Mai Z. Re: Taimur T. Shah, Max Peters, David Eldred-Evans, et al. Early-medium-term outcomes of primary focal cryotherapy to treat nonmetastatic clinically significant prostate cancer from a prospective multicentre registry. *Eur Urol*. 2019;76:98-105. *Eur Urol*. 2019;76(3):e61-e62.
59. Mertan FV, Greer MD, Shih JH, et al. Prospective evaluation of the prostate imaging reporting and data system version 2 for prostate cancer detection. *J Urol*. 2016;196(3):690-696.
60. Laader A, Beiderwellen K, Kraff O, et al. 1.5 versus 3 versus 7 Tesla in abdominal MRI: a comparative study. *PLoS One*. 2017;12(11):e0187528.
61. Vos EK, Lagemaat MW, Barentsz JO, et al. Image quality and cancer visibility of T2-weighted magnetic resonance imaging of the prostate at 7 Tesla. *Eur Radiol*. 2014;24(8):1950-1958.
62. Philips BWJ, van Uden MJ, Rietsch SHG, Orzada S, Scheenen TWJ. A multitransmit external body array combined with a ^{1}H and ^{31}P endorectal coil to enable a multiparametric and multimetabolic MRI examination of the prostate at 7T. *Med Phys*. 2019;46(9):3893-3905.
63. Maas MC, Vos EK, Lagemaat MW, et al. Feasibility of T2 -weighted turbo spin echo imaging of the human prostate at 7 tesla. *Magn Reson Med*. 2014;71(5):1711-1719.
64. Chopra R, Tang K, Burtnyk M, et al. Analysis of the spatial and temporal accuracy of heating in the prostate gland using transurethral ultrasound therapy and active MR temperature feedback. *Phys Med Biol*. 2009;54(9):2615-2633.
65. Ishihara Y, Calderon A, Watanabe H, et al. A precise and fast temperature mapping using water proton chemical shift. *Magn Reson Med*. 1995;34(6):814-823.
66. Böni RA, Sulser T, Jochum W, Romanowski B, Debatin JF, Krestin GP. Laser ablation-induced changes in the prostate: findings at endorectal MR imaging with histologic correlation. *Radiology*. 1997;202(1):232-236.
67. Rosset R, Bratan F, Crouzet S, et al. Can pre- and postoperative magnetic resonance imaging predict recurrence-free survival after whole-gland high-intensity focused ablation for prostate cancer? *Eur Radiol*. 2017;27(4):1768-1775.
68. Rouvière O, Lyonnet D, Raudrant A, et al. MRI appearance of prostate following transrectal HIFU ablation of localized cancer. *Eur Urol*. 2001;40(3):265-274.
69. Boyes A, Tang K, Yaffe M, Sugar L, Chopra R, Bronskill M. Prostate tissue analysis immediately following magnetic resonance imaging guided transurethral ultrasound thermal therapy. *J Urol*. 2007;178(3 pt 1):1080-1085.
70. Anttinen M, Mäkelä P, Suomi V, et al. Feasibility of MRI-guided transurethral ultrasound for lesion-targeted ablation of prostate cancer. *Scand J Urol*. 2019;53(5):295-302.
71. Ahmed HU, El-Shater Bosaily A, Brown LC, et al; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389(10071): 815-822.
72. Radtke JP, Kuru TH, Bonekamp D, et al. Further reduction of disqualification rates by additional MRI-targeted biopsy with transperineal saturation biopsy compared with standard 12-core systematic biopsies for the selection of prostate cancer

patients for active surveillance. *Prostate Cancer Prostatic Dis*. 2016;19(3):283-291.
73. Siddiqui MM, George AK, Rubin R, et al. Efficiency of prostate cancer diagnosis by MR/ultrasound fusion-guided biopsy vs standard extended-sextant biopsy for MR-visible lesions. *J Natl Cancer Inst*. 2016;108(9):djw039.
74. Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. *Eur Urol*. 2015;68(1):8-19.
75. Chopra R, Colquhoun A, Burtnyk M, et al. MR imaging-controlled transurethral ultrasound therapy for conformal treatment of prostate tissue: initial feasibility in humans. *Radiology*. 2012;265(1):303-313.
76. Bonekamp D, Wolf MB, Roethke MC, et al. Twelve-month prostate volume reduction after MRI-guided transurethral ultrasound ablation of the prostate. *Eur Radiol*. 2019;29(1):299-308.
77. Linares-Espinós E, Carneiro A, Martínez-Salamanca JI, et al. New technologies and techniques for prostate cancer focal therapy. *Minerva Urol Nefrol*. 2018;70(3):252-263.
78. Feijoo ER, Sivaraman A, Barret E, et al. Focal high-intensity focused ultrasound targeted hemiablation for unilateral prostate cancer: a prospective evaluation of oncologic and functional outcomes. *Eur Urol*. 2016;69(2):214-220.
79. Giraldo NA, Sanchez-Salas R, Peske JD, et al. The clinical role of the TME in solid cancer. *Br J Cancer*. 2019;120(1):45-53.
80. Tourinho-Barbosa RR, de la Rosette J, Sanchez-Salas R. Prostate cancer multifocality, the index lesion, and the microenvironment. *Curr Opin Urol*. 2018;28(6):499-505.
81. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell*. 2015;162(2):454.
82. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*. 2011;365(2):107-118.
83. Berge V, Dickinson L, McCartan N, et al. Morbidity associated with primary high intensity focused ultrasound and redo high intensity focused ultrasound for localized prostate cancer. *J Urol*. 2014;191(6):1764-1769.
84. Blana A, Murat FJ, Walter B, et al. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. *Eur Urol*. 2008;53(6):1194-1201.
85. Murat FJ, Poissonnier L, Rabilloud M, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. *Eur Urol*. 2009;55(3):640-647.
86. Marra G, Dell'oglio P, Baghdadi M, Cathelineau X, Sanchez-Salas R; EvaluatioN of HIFU Hemiablation and short-term AndrogeN deprivation therapy Combination to Enhance prostate cancer control (ENHANCE) study. Multimodal treatment in focal therapy for localized prostate cancer using concomitant short-term androgen deprivation therapy: the ENHANCE prospective pilot study. *Minerva Urol Nefrol*. 2019;71(5):544-548.