Focal Ablation of Prostate Cancer

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The challenge to the urology community is to reduce the risks of screening and treatment by reducing the number of men undergoing unnecessary biopsy and whole-gland curative treatment of low-risk disease. There is compelling evidence that focal ablation of prostate cancer is truly minimally invasive and offers major functional advantages over whole-gland treatment.

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KEY WORDS

Focal ablation • Prostate cancer screening • Prostate cancer treatment • High-intensity focused ultrasound • Irreversible electroporation • Vascular-targeted photodynamic therapy

Prior to the era of prostate-specific antigen (PSA) screening, at the time of diagnosis most prostate cancers were locally advanced or metastatic. The most common treatment for prostate cancer was androgen deprivation achieved via medical or surgical castration. The rare man diagnosed with a prostate nodule confined to the gland underwent radical prostatectomy (RP) or radiation therapy (RT) with the intent of curing the disease. In fact, between 1951 and 1963, Hugh Jewitt, MD, the preeminent prostate cancer surgeon at the Johns Hopkins Hospital, performed only 53 RPs.[1] Prostatectomy provided durable cancer control for most men with these "early" prostate cancers.[2] The clinical challenge was to develop a screening strategy that could identify a greater proportion of men with localized prostate cancer amenable to cure. The only cases managed by active surveillance (AS) in the pre–PSA screening era were men with stage A1 prostate cancer (low-grade and low-volume disease) diagnosed at the time of transurethral resection of the prostate.[3]

In the 1980s, there were several advances that contributed to the widespread acceptance of PSA screening. A major disincentive for detecting early disease was the significant morbidity associated with both RP and RT. The description of the anatomic nerve-sparing radical prostatectomy[4] and more precise delivery of radiation therapy[5] greatly reduced the morbidity of whole-gland curative interventions. Around this time, both transrectal ultrasonography (TRUS)[6] and serum PSA[7,8] were being independently explored as tools for early detection of prostate cancer. Ultimately, PSA testing became the primary screening tool for identifying men at risk for harboring prostate cancer. Diagnostic confirmation ultimately relied upon TRUS-guided biopsy (SB). Due to the limitations of TRUS, biopsy approaches evolved into systematic, random sampling.[9]

The primary drawback of PSA screening and TRUS-guided biopsy is their poor specificity for disease detection, leading to high rates of unnecessary biopsy.[7,8] In addition, a high proportion of men diagnosed with low-risk disease underwent invasive curative intervention leading to "unnecessary" treatment.[10] Another limitation of PSA screening was demonstrated by the Prostate Cancer Prevention Trial, which reported that 15% of men with a PSA <4 ng/mL and a normal digital rectal examination (DRE) had prostate biopsies positive for cancer, but only 3% of these cases were intermediate or high grade.[11]

Despite the dramatic reduction in prostate cancer mortality attributed primarily to PSA screening,[12] in 2012 the United States Preventive Services Task Force (USPSTF) recommended against PSA screening, arguing that the harms of screening due to "unnecessary" biopsy and treatment outweighed its benefits.[13] The USPSTF modified their recommendation in 2018 because the risks and benefits of PSA screening was judged to be equivocal for men between the ages of 55 to 69 due to the adoption of AS for low-risk disease. The USPSTF did not change their recommendation against PSA screening for men 70 years and older.[14]

The challenge to the urology community is to reduce the risks of screening and treatment by reducing the number of men undergoing unnecessary biopsy and whole-gland curative treatment of low-risk disease.

Advances in Screening and Detection of Prostate Cancer

There is increasing evidence that men with low-risk Gleason Grade Group (GGG) 1 disease do not require immediate intervention because these cancers rarely metastasize.[15] Unfortunately, half of GGG 1 cancers detected by SB are found to harbor GGG >1 at the time of RP, a consequence of the inadequate organ sampling using this technique.[16] The challenge is to adopt screening and detection strategies for prostate cancer that minimize detection of GGG 1 disease and maximize detection of GGG 2-5 disease. Although there are many different definitions of significant disease, this review considers any GGG 2-5 in a biopsy core to represent significant disease. Some studies consider high volume GGG 1 in a single biopsy core to represent significant disease. Because the goal is to detect actionable disease, criteria designed to differentiate clinically significant versus insignificant disease must include not only factors predicting aggressiveness of the disease but also life expectancy.

There is now compelling evidence that measuring different forms of PSA in the blood [Prostate Health Index (PHI; Beckman Coulter, Brea, CA) and the 4Kscore Test (OPKO Health, Inc, Miami, FL)] or molecular biomarkers in the blood or urine [ExoDx Prostate (IntelliScore); Exosome Diagnostics, Inc., Waltham MA), SelectMDx for Prostate Cancer (MDxHealth, Irvine, CA)] can decrease biopsy rates by about 30% with a concomitant decrease in the detection rates of low-risk disease with minimal impact on detection rates of GGG 2-5 disease.[17,18] These tools should be adopted by the urology community to address the lack of PSA specificity for detecting significant, actionable disease.

Multiparametric MRI (mpMRI) has also been shown to reliably identify GGG 2 or greater disease. In the PROMIS trial, all men underwent mpMRI and 5-mm transperineal saturation biopsy (TPSB).[19] This unique study design provided the opportunity to characterize prostate cancer without performing RP in a cohort of candidates undergoing prostate biopsy. The negative predictive value of mpMRI for significant disease was 90%, if only men with Prostate Imaging Reporting and Data System (PI-RADS; American College of Radiology) score >2 are selected for prostate biopsy. The implication of the PROMIS study was that approximately 30% of candidates for prostate biopsy with PI-RADS 1 and 2 lesions can avoid prostate biopsy with minimal adverse impact on detecting significant disease. One caveat is that not all significant prostate cancers would be detected by MRI-targeted biopsy with or without SB.

We use both the 4Kscore Test and mpMRI for selecting men with an elevated PSA for prostate biopsy, recognizing that other PSA-based or molecular biomarkers provide equivalent clinical information (Figure 1). For older men with low risk of harboring significant (or actionable) disease based on PSA, PSA velocity, PSA density (PSAD), and family history, no additional testing is obtained if the 4Kscore Test shows low (<10%) risk of significant disease. For example, biopsy would be deferred in a 70-year-old man with a 60-cc benign prostate, a PSA of 5.1 ng/mL, no family history of prostate cancer, and a 4Kscore Test result of 5%. Conversely, for men with a very high risk of prostate cancer based on PSA, PSA velocity, PSAD, and family history, a biomarker is not necessary to justify the indication for biopsy. All these men undergo mpMRI, which provides additional information to guide their biopsy. A clinical example of high risk of significant disease would be a 54-year-old man with a progressively rising PSA, PSADT

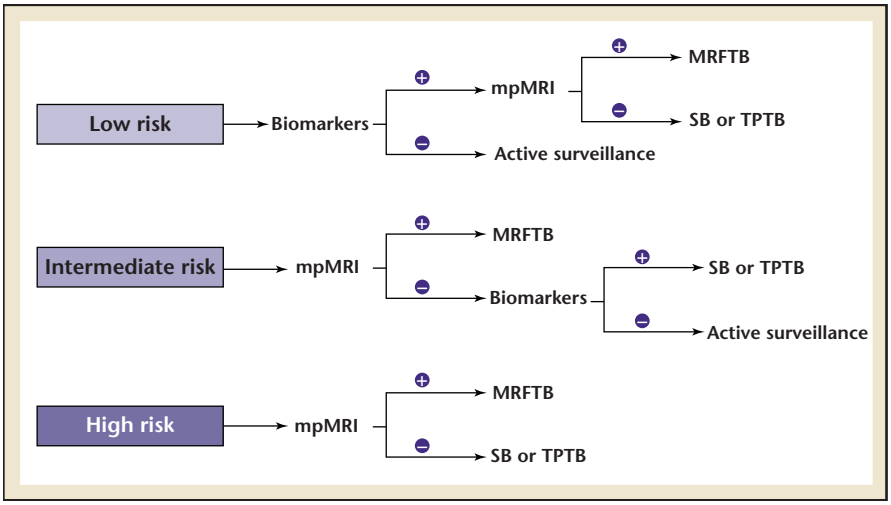

Figure 1. Diagnostic pathway for men with an elevated prostate-specific antigen (PSA) levels. Risk levels are based on age, race, family history, PSA, PSA velocity, and PSA density. Biomarker positivity represents a 10% risk of aggressive significant cancer. Multiparametric MRI (mpMRI) positivity indicates PI-RADS ≥3. Active surveillance includes follow-up PSA, digital rectal examination, and, when indicated, mpMRI. MRFTB, MRI fusion target biopsy; SB, TRUS-guided biopsy; TPTB, transperineal template biopsy; TRUS, transrectal ultrasonography.

of 2 years, a prominent family history, and a 30-cc gland. For men with intermediate risk of harboring significant disease based on PSA, PSA velocity, PSAD and family history, both a 4Kscore Test and mpMRI will influence the decision to proceed with biopsy. If an mpMRI demonstrates a PI-RADS >2 lesion or the risk of significant disease based on the 4Kscore Test is over 10%, a prostate biopsy is performed. A clinical example would be a 60-year-old man with two progressive rises in PSA, a PSA of 5.0 ng/mL, no family history, and a prostate volume of 40 cc. These criteria for identifying candidates for prostate biopsy should be influenced by life expectancy.

An SB has the possibility of identifying significant cancer, detecting insignificant cancer, or missing a significant cancer. NYU Urology has an extensive experience performing MRI fusion target biopsy (MRFTB) to optimize detection of significant disease.[20] We use the Artemis platform (Eigen, Grass Valley, CA) to co-register the MRI and US images. In our experience, MRFTB increases the detection rate of significant disease while concomitantly decreasing the detection of insignificant disease relative to SB.[20,21] The PRECISION study randomized men with elevated PSA to a MRI-targeted biopsy versus SB and reported that MRI-targeted biopsy increased the detection rate of significant cancer by 13% and decreased the detection rate of insignificant cancer by 12%, thereby providing compelling evidence for adoption of MRI as a reflex test prior to prostate biopsy in biopsy-naive men.[22] In this study, only PI-RADS 3-5 lesions were biopsied and these favorable detection rates were achieved while decreasing the overall biopsy rate by 30%.

Is there a role for SB in the era of MRFTB? Bryk and colleagues[23] showed that the SB from the side of the MRI lesion increases detection rate of significant cancer presumably due to limitations and errors associated with MRI-US fusion co-registration and needle-based biopsy. We therefore recommend performing SB ipsilateral to the MRI lesion. SB contralateral to the MRI lesion will simply increase the overall detection rate of low-risk disease and should be avoided unless findings of low-risk disease would influence treatment decisions.

The ability of MRI to localize the site(s) of significant disease was a pivotal step in advancing focal ablation (FA) as a treatment strategy for prostate cancer.

Is there a Role for Focal Ablation of Prostate Cancer?

One of the unique characteristics of prostate cancer is the spectrum of the disease as it relates to disease aggressiveness, age range of those affected, and treatment priorities. The age range in a large personal series of approximately 5000 RP performed by one of the authors of this review (HL) is 36 to 81 years. The risk and extent of disease ranges from men with a single biopsy core with 1-mm GGG 1 cancer to all biopsies showing GGG 4 and 5 disease. The priority of some men is to cure the disease whereas others are motivated to preserve quality of life. It is reasonable to propose that the optimal management of prostate cancer should include AS, whole-gland treatment, and an alternative offering potential for oncological control with preservation of quality of life. We believe this option is FA of prostate cancer.

FA includes any ablative treatment that partially destroys the prostate gland. The extent of ablation can include only the MRI lesion, the MRI lesion plus a margin, hemi-ablation, or sub-total ablation. The optimal extent of ablation has yet to be established. Recent studies suggest that the MRI lesion underestimates the extent of disease and therefore the extent of ablation should include an approximately 10-mm margin to ensure

complete ablation of the MRI-detected cancer.[24] In smaller glands, there is little difference between lesion +10-mm margin and a hemi-ablation. Depending on the extent of the cancer, it may be necessary to treat portions of both lobes. It is reasonable to speculate that increasing the extent of ablation will have some adverse effects on sexual outcomes with reciprocal benefit on oncological outcomes.

Focal Ablation of Prostate Cancer: What You Must Believe

Untreated GGG 1 Does Not Pose Oncologic Risk

MRI fails to detect low-volume, low-risk disease.[25,26] Therefore, the selection of candidates for FA based on MRI will leave untreated GGG 1 disease. Adoption of FA assumes untreated low-risk disease poses no immediate oncological risk (Table 1). This concept mirrors the justification of AS for GGG 1 disease.[27] In fact, the USPSTF justified changing its recommendation against PSA screening because the urology community was adopting AS for GGG 1 disease.[14]

MRI Identifies the Index Lesion

Most prostate cancers managed by RP are multi-focal.[28] However, the aggressiveness of prostate cancer is typically defined by a single-index tumor characterized by the highest GGG and pathological stage.[29] MRI reliably identifies the index cancer in more than 85% to 95% of those men undergoing RP.[30,31]

MRI/MRFTB/SB Rarely Misses Significant Disease

The selection of candidates for FA should include a high-quality, multi-parametric MRI (mpMRI), MR-targeted biopsy of the MRI lesion confirming cancer, and contralateral SB showing GGG ≤1 disease. We identified 59 men who fulfilled our selection criteria for FA who underwent RP at our institution.[32] MRI, MRFTB, and SB were performed on all candidates prior to RP. The surgical specimens were step sectioned and all cancers were identified and mapped. The presence of any Gleason pattern 4 disease outside two hypothetical ablation zones was ascertained. If these men underwent FA with a planned ablation template of MR lesion +10-mm margin or hemi-ablation, the likelihood of leaving any contralateral Gleason pattern 4 disease was 23% and 19%, respectively. The linear length of Gleason pattern 4 was always less than 1 mm. Therefore, only very low volume Gleason pattern 4 would have been untreated in both FA templates. Some experts have advocated AS for selected cases of Gleason pattern 4 disease.[33,34] Our study demonstrates that all men undergoing FA must be followed for pre-existing and developing significant disease that may manifest outside the ablation zone.

We Can Deliver Ablative Energy to Predefined Targets

Oncological control following FA has not been adequately investigated and represents a significant limitation when counseling men considering this treatment. There are many energy sources investigated for FA of the prostate. Most in-field biopsies following FA show no significant cancer within a year of treatment, suggesting ablative energy is being effectively delivered to a designated target.[35,36] Whether untreated disease within or beyond the ablation zone will become life threatening over time requires further investigation.

Quality of Life Is an Important Endpoint

There are many experts who have reported excellent functional outcomes following RP. The veracity of these exceptional outcomes is subject to some uncertainty due to study design and reporting bias. Over 2000 men undergoing RP by a single surgeon (HL) signed informed consent to participate in a prospective outcomes study conducted at NYU Langone Health System. Men completed quality-of-life questionnaires at baseline and predefined time points following RP. The operating surgeon was not involved in data acquisition, entry, or retrieval. Urinary continence, defined as using one or fewer protective pads in 24 hours at 3 and 24 months, was 80% and 97%, respectively.[37] Potency was restored in approximately 60% of men undergoing bilateral nerve-sparing surgery. Post-prostatectomy potency was defined as an erection adequate for penetration half the time intercourse was initiated with or without prior administration

TABLE 1

Focal Ablation of Prostate Cancer—What You Must Believe

- Untreated GGG 1 is of no immediate risk
- MRI identifies the index lesion
- MRI/MRFTB/SB rarely fails to detect significant disease
- Ablative energy can be reliably delivered to pre-defined targets
- Preserving quality of life is a high priority for men with localized prostate cancer

GGG, Gleason grade group; MRFTB, MRI fusion target biopsy; SB, TRUS-guided biopsy.

of a phosphodiesterase inhibitor.[38] The return of erectile function was dependent on age, whether a nerve-sparing surgery was performed, pre-operative erectile function, and history of diabetes. However, simply reporting erectile dysfunction ignores climacturia,[39] shortening of the penis,[40] or penile curvature,[40,41] which are issues rarely discussed when counseling men about sexual dysfunction following RP. It is likely that some men will choose a treatment for their prostate cancer that has lower intermediate- or long-term oncological control compared with RP but never causes incontinence and has only a modest and transient effect on erectile function.

It is important to provide realistic expectations for men considering RP. Although RP is the best curative option for localized prostate cancer, disease recurrence does occur. Epstein and colleagues[42] reported that the 5-year probability of biochemical recurrence following RP for men with biopsy GGG 1, 2, 3, 4, and 5 is approximately 4%, 12%, 37%, 52%, and 74%, respectively. Furthermore, RP is not without risk of long-term erectile and urinary morbidity. Haglind and colleagues[43] reported on functional outcomes 1 year following over 2000 open and robotic RP performed in Sweden. The rates of incontinence defined by using two or more pads a day was 20% and 21% following open and robotic RP, respectively. The likelihood of an International Index of Erectile Function (IIEF) score decreasing to <17 was 81% and 77% following open and robotic RP, respectively. Barry and colleagues[44] reported similar results based on pre-operative and post-operative survey of RPs performed in the US Medicare population. Donovan and colleagues[45] recently reported on patient-reported quality-of-life measures to compare functional outcomes between AS, RP, and RT cohorts as part of the ProtecT trial. As expected, men randomized to RP had greater compromise of urinary and erectile function as compared with AS or RT at all time points but had less bowel-related morbidity than the RT cohort.

Selecting Candidates for Focal Ablation

There is no consensus how to optimally stratify men with localized prostate cancer to RP, RT, FA, or AS. A consensus statement recommends that all candidates for FA should undergo an MRI, MRFTB, and SB.[46,47] An alternative would be to perform transperineal saturation biopsy to map the disease. We offer FA to men with a single MRI lesion without gross extracapsular extension who have high-volume GGG 1 or any volume GGG 2-3 and very select cases of GGG 4. Generally, we do not exclude cases with low-volume contralateral GGG 4 (Table 2).

An example of an ideal candidate for FA would be a 68-year-old man who has a 40-cc prostate with a benign DRE and GGG 2 following MRFTB of a single PI-RADS 4 lesion with a negative contralateral SB and an MRI showing no evidence of extracapsular extension or extension of the MRI lesion to the very distal apex (Table 2). In addition, preserving erectile function should be a high priority.

We have performed more than 250 FA for localized prostate cancer. One case involved a 61-year-old white man who presented with PSA of 11.1 ng/mL in 2016 (up from 6.4 ng/mL in 2012). He was found to have a 1-cm left-sided nodule on DRE. His IEFF and International Prostate Symptom Score (IPSS) scores were 25 and 1, respectively. mpMRI showed a 10 × 8 mm PI-RADS 3 lesion at the left anterior base transition zone (Figure 2 A-C) and calculated prostate volume of 44 cm^3. MRFTB yielded 2 cores of GGG 1 cancer at the lesion. SB yielded 1 core 0.5-mm GGG 1 disease at the right medial base. OncotypeDx® (Genomic Health, Inc., Redwood City, CA) from the MRI target biopsy predicted 57% risk of aggressive disease. After discussing all treatment options including AS, RP, RT, and FA, HIFU focal ablation +10-mm margin was performed in 2016. At 6 months post-treatment, PSA was 2.6 ng/mL and mpMRI showed 11 × 11 mm non-enhancing ablation cavity in left anterior transition zone (Figure 2D) and 12 × 9 mm PI-RADS 2 lesion at the right anterior base central zone (Figure 2E). MRFTB of the ablation zone yielded 6 benign cores, MRFTB of PI-RADS 2 lesion yielded 4 benign cores, and SB yielded 2 benign cores obtained from the right medial base. Six months post-ablation, the IIEF an IPSS scores were of 25 and 1, respectively.

TABLE 2

Optimal Candidates for Focal Ablation of Prostate Cancer

- Benign DRE
- Prostate volume <60 cm^3
- Single PI-RADS lesion w/o extracapsular extension
- No extreme apical extent of MRI lesion
- MRFTB GGG ≥2 or high volume GGG 1
- Contralateral SB negative of GGG 1

DRE, digital rectal examination; GGG, Gleason grade group; MRFTB, MRI fusion target biopsy; SB, TRUS-guided biopsy.

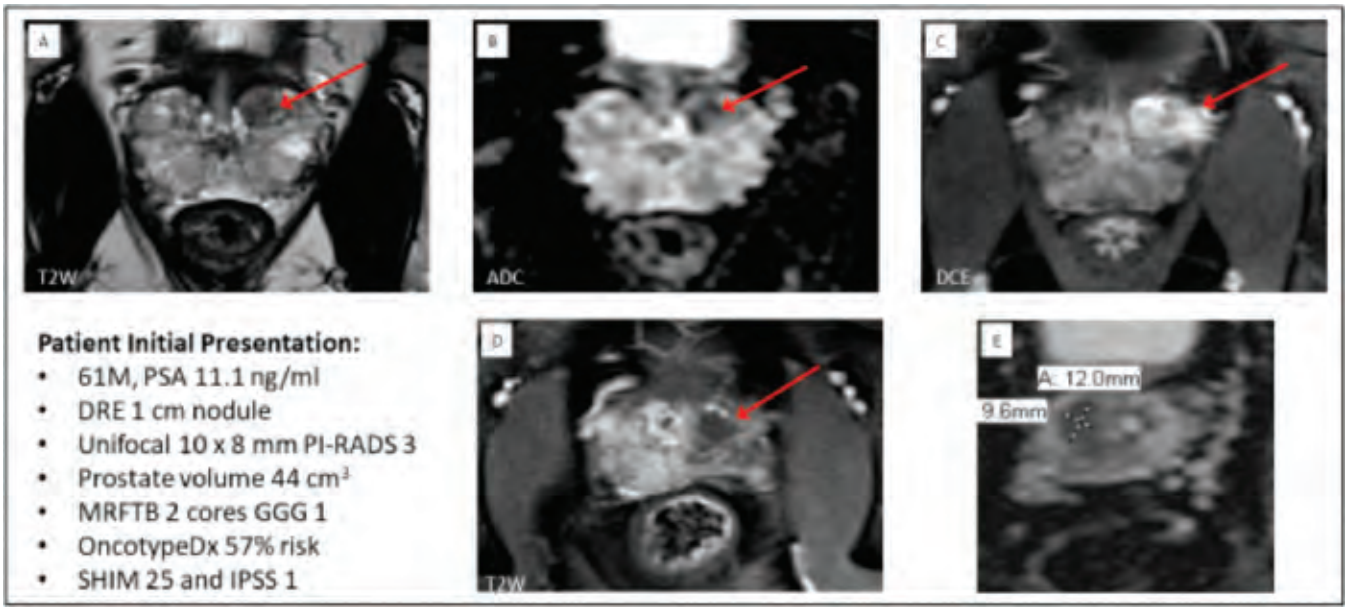

Figure 2. (A) T2-weighted image showing low signal intensity MRI lesion. (B) Low signal intensity of diffusion-weighted imaging. (C) Rapid uptake of contrast on dynamic contrast enhancement imaging. (D) Absent uptake of contrast following focal high-intensity focused ultrasound (HIFU) ablation of the MRI lesion with a 5-mm margin. (E) PI-RADS 2 lesion observed on post-ablation multiparametric MRI that was negative for cancer following MRI fusion target biopsy (MRFTB). DRE, digital rectal examination; GGG, Gleason grade group; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; SHIM, Sexual Health Inventory for Men.

As another example, we consented to perform FA on a very healthy, sexually active 79-year-old man with a 40-cc benign prostate and a PI-RADS 5 showing slight ECE at the base and MRFTB showing GGG 4 disease. He refused radiation therapy with androgen deprivation therapy and is now without evidence of disease based on biopsy, PSA kinetics, and MRI 18 months post-treatment.

We believe there is a reasonable probability that men with long life expectancies will develop significant disease in the ablative field or in untreated prostate over time. In these cases, AS, repeat FT, RP, and RT will be potential salvage treatments. Many men will also seriously consider FA even if disease recurs providing survival is not adversely impacted.

Ablative Energy Sources

The ideal ablative technology achieves confluent tissue destruction in a well-defined treatment volume while limiting impact to tissue outside of the treatment zone. Currently there are multiple ablative energy sources for FA of prostate cancer (Table 3).[36] The energy sources can be categorized as thermal or non-thermal energies.

Cryoablation

The ablative technology most extensively studied is cryoablation. Cryoablation is a thermal ablation technique that utilizes US-guided transperineal cryoprobes to create adjustable zones of rapid cooling. Temperatures within the ablation zone can reach below −70°C. Cell death reliably occurs at temperatures of −40°C and is often achieved at temperatures at or below −20°C.[46] US is used to provide real-time assessment on the progress of the ablation zone as the leading edge of ice formation, which is 0°C, is clearly demarcated as a hyperechoic boundary. In addition, strategically placed thermocouple probes allow confirmation that cell-kill temperatures are achieved at the edges of the desired treatment margin. The treatment zone can be carefully controlled to minimize impact upon critical neighboring structures such as the rectum, external sphincter, and the neurovascular bundles. Additionally, a urethral warming catheter is inserted during the procedure to minimize treatment effects upon the prostatic urethra and sphincter.

Commercial cryoablation systems currently available on the market include Endocare® Cryocare® System (HealthTronics, Inc., Austin, TX) and Galil Medical cryoablation systems (Galil Medical Ltd., Arden Hills, MN).

The advantages of cryoablation include the reliability of the confluent treatment zone, accurate real-time monitoring, and the ability to treat larger volumes of tissue. Cryoablation is subject to fewer limitations by prostate gland size and offers an excellent treatment choice for anterior tumors. Depending upon the size and number of cryoprobes utilized, cryoablation produces significant thermal dispersion and is thus more likely to affect surrounding structures and result in potential impact on neurovascular bundles.

TABLE 3

Summary of Ablative Energy Sources With Description of Cellular Destruction Mechanism

Ablative Energy Source	Mechanism of Cellular Destruction
Cryoablation	Rapid cooling ➔ cellular edema, apoptosis, coagulative necrosis
HIFU	Focused ultrasound energy ➔ acoustic cavitation/cellular rupture, coagulative necrosis
Irreversible electroporation	Delivery of electrical currents ➔ membrane nanopores, cellular destabilization and cell death
Vascular-targeted photodynamic therapy	Light-activated generation of reactive oxygen species ➔ microvascular thrombosis
Radiofrequency ablation	Conduction of electromagnetic energy ➔ thermal energy, coagulative necrosis
Laser ablation	Focused laser energy ➔ photothermal energy, coagulative necrosis

HIFU, high-intensity focused ultrasound.

Additionally, tumor location in the posterior midline, distal apex, or near the bladder neck and prostatic urethra pose technical challenges for successful cryoablation.

High-intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is a unique thermal ablative technology that creates tissue destruction without intra-prostatic probes. Using a specialized TRUS probe, HIFU achieves tissue destruction via concentration of an extreme ultrasound frequency to a focused point within the gland. The target tissue absorbs this US signal and is destroyed through a combination of hyperthermia and cavitation (mechanical disruption).[47] HIFU systems achieve tissue destruction in overlapping ellipsoids across multiple focal points. Treatment zones can be carefully planned to avoid critical structures such as the urethra, apex, and neurovascular bundles.

Several HIFU systems are currently available on the US market, including Sonablate® HIFU (SonaCare Medical, Inc., Charlotte, NC) and Ablatherm® HIFU and Focal One® (EDAP TMS, Vaulx-en-Velin, France). HIFU ablation offers an excellent side-effect profile by focusing the thermal effects of tissue destruction to a very small volume. The thermal dose for each treatment zone can be monitored and modified based on ultrasound changes in the focal zone, observed near field changes, and whether the automated tissue control monitoring (TCM) indicates adequate sonographic evidence of energy deposition at the target zone. HIFU is ideally utilized for posteromedial lesions in smaller glands where preservation of potency is a high priority. This technology also employs MRI-US fusion for treatment planning and may deliver energy more precisely than intra-prostatic probes.

HIFU ablation is limited by gland volume (<50-cc gland, <3.5-4 cm in anterior-posterior dimension) and contraindicated when significant intra-prostatic calcifications are present in the targeted tissue. HIFU ablation across urethral tissue may result in urethral morbidity such as tissue sloughing and stricture. Some users of the EDAP platform utilize a pre-treatment TURP to decrease urethral morbidity.[48]

Irreversible Electroporation

Irreversible electroporation (IRE) is a needle-based non-thermal tissue ablation technique. IRE achieves cell kill by developing a short, intense electrical field pulses across tissue using specialized needles. The electrical field changes result in development of nanopores in the cellular membranes, ultimately leading to cellular destabilization and cell death through apoptosis.[48] As a non-thermal ablation technique, IRE results in minimal

tissue impact outside of the ablation zone. Theoretically, structures within the ablation zone are not subjected to thermal destruction. Thus, IRE offers potential for ablation of tumors around critical structures such as the urethra, prostatic apex and bladder neck. Data regarding IRE efficacy remain limited and issues regarding confluency of tissue ablation warrant further exploration.[49,50]

Vascular Targeted Photodynamic Therapy

Vascular targeted photodynamic therapy (VTP) combines mechanical and chemical treatment to achieve non-thermal tissue ablation. VTP uses laser activation of a photosensitizing compound (TOOKAD® Soluble, Steba Biotech S.A.) to generate free radicals and microvascular thrombosis[51,52] within the treatment zone. Laser activation is achieved through transperineal interstitial prostate laser fibers. VTP treatment zones can be carefully contoured and result in minimal thermal dispersion, offering potential advantage in side-effect profile. Treatment across the prostate capsule may be limited, as well as across intraprostatic calcifications. The treatment is further subject to the limitation involving injection of a photosensitizer and achieving treatment confluency.[53]

Radiofrequency Ablation

Radiofrequency ablation (RFA) allows for precise delivery of ablative energy to the prostate.[54] Using the Encage™ device (Trod Medical, St Petersburg, FL), a corkscrew cage is manipulated into the prostate under TRUS guidance. Operating on the Faraday principle, thermal ablation is achieved through RFA-induced hyperthermia within the boundaries of the treatment device. The challenge is optimal placement of the radiofrequency cage and contouring cage placement to the configuration of an intended ablation template.

Laser Ablation

Laser energy without activating a photosensitizer has been investigated to ablate prostate cancer.[55] These diode lasers produce thermally induced coagulative necrosis. The laser fibers are placed trans-rectally under MRI guidance. The primary limitation of laser ablation is creating a confluent lesion because only one laser fiber is used at a time because of the high cost of the individual fibers. Another limitation is patient comfort because they are lying prone in the MRI galley at times for over 2 hours.

Ablative Energies Available in the United States

Cryoablation is the only energy that is approved in the United States for ablation of prostate cancer. It is not approved for focal ablation of prostate cancer. HIFU using Ablatherm, Focus One, or Sonablate is approved for destruction of prostate tissue but not prostate cancer specifically. IRE and RF are approved only for tissue destruction. VTP is not approved in the United States.

Outcomes Following FA

All energy sources used for FA of prostate cancer are designed to be out-patient procedures performed under sedation with a prostate block or general anesthesia. The requirement for general anesthesia appears to be at the discretion of the surgeon rather than inherent properties of the energy sources. An exception to this is IRE, which requires a paralytic agent to prevent muscle contractions from electrical pulses.

At NYU Langone, we have performed cryoablation, HIFU, RF, and VTP under general anesthesia. Our patients prefer general anesthesia and as surgeons we prefer complete lack of movement. Independent of energy source, patients leave the outpatient facility about 2 hours after the procedure with an indwelling Foley catheter. Depending on the volume of tissue ablation, baseline prostate volume, and underlying voiding history, a voiding trial is scheduled 3 to 5 days following the procedure. Unsuccessful trials of voiding are atypical. Men typically return to employment following catheter removal. In over 250 FA cases performed at our institution, only 1 patient developed any significant incontinence. It is rare for any patient to use protective pads after catheter removal. Because preserving sexual function is a high priority for most men, they must be counseled that seminal volume may diminish. Although we have observed transient erectile dysfunction, baseline potency is often restored within 6 months. Some men will benefit from PDE-5 inhibitors to expedite restoration of erectile function.

Valerio and colleagues[36] reported on a comprehensive literature review of FA in 2017. In most studies, there was modest improvement in lower urinary tract symptoms (LUTS), extremely rare cases of incontinence, and very modest changes in erectile function. The consensus is that MRI lesions can be effectively ablated with virtually no adverse impact on functional outcomes.

The major limitation of FA is whether these excellent functional outcomes are achieved with good oncological control. The literature provides an abundance of biopsy-based oncological outcomes within the first year of FA.[36] There is a paucity of studies reporting intermediate and long-term oncological

control following FA. An additional major limitation of the FA literature is the lack of standardization of the assessment of oncological control. For example, in many reported studies, not all men underwent pre-ablation MRI with MR-guided biopsy. Some studies enrolled primarily GGG 1 whereas others included GGG 2 or 3. Many of the reported multi-center randomized or large single center studies performed MRI and in-field prostate biopsy between 6 to 12 months following FA. There was no standardization of how many in-field cores were performed. The ability to detect untreated prostate cancer will undoubtedly be dependent on core sampling. Many studies do not perform reflex biopsies after 6 months and rely on changes in PSA or MRI to trigger a for-cause biopsy. At this point, the literature provides compelling evidence that FA of prostate cancer is truly minimally invasive with excellent functional outcomes. Rigorous oncological outcomes are lacking and ultimately must be reported to define the role of FA for men with prostate cancer.

Clinical Studies

The role of FA in the management of localized prostate cancer will ultimately be defined by prospective multi-center trials using standardized enrollment criteria, validated quality-of-life questionnaires, and oncological outcomes based on serum PSA levels, MRI, and both in- and out-of-field biopsies. Our experience with focal laser ablation (FLA) underscores the importance of in-field prostate biopsy beyond 1 year of FA.[56,57] We previously reported 96% of in-field biopsies 6 months following FA showed no cancer.[56] At 2 years, all of these men underwent PSA and MRI testing.[57] Overall, 10 men with a non-suspicious MRI refused a recommended in-field prostate biopsy. Of the 22 men undergoing in-field prostate biopsy at 2 years, 17 (77%) and 9 (41%) exhibited any cancer or GGG >1 disease, respectively. Of the 8 cases with a suspicious MRI, all underwent in-field biopsy and all exhibited cancer. Of the 14 men with negative MRI, 9 and 3 exhibited any cancer or GGG >1, respectively. There was a trend for men with both a negative MRI and negative in-field prostate biopsy to have a longer PSA doubling time. Our very preliminary conclusion is that significant in-field disease recurrence is unlikely in the presence of a negative MRI and stable PSA. A negative MRI and stable PSA does not exclude GGG 1 disease.

The present review highlights only those contemporary prospective studies enrolling at least 50 subjects. In some studies, disease was not consistently localized using mpMRI coupled with MRFTB or TPSB (Table 4). Functional and oncological outcomes were ascertained using validated quality-of-life questionnaires and in-field biopsy was performed at a designating time point following FA.

Rischman and colleagues[58] reported on 110 subjects enrolled at 10 sites who underwent hemi-ablation using the EDAP Ablatherm

TABLE 4

Representative Focal Ablation Studies

Author	Ablation Energy & Template	Study Population	Timing to In-field Biopsy	In-field Biopsy Results
Rischmann et al[58]	HIFU hemi-ablation	110, multi-center	6-12 mo	CSC: 5/101 (5%) Any cancer: 12/101 (12%)
van Den Bos et al[59]	IRE focal	63, single site	6-12 mo	CSC: 7/45 (16%) Any cancer: not reported
Dickinson et al[60]	HIFU hemi- and focal ablation	111, multi-center	6 mo	CSC: 12/111 (11%) Any cancer: 28/111 (25%)
Ganzer et al[61]	HIFU hemi-ablation	51, multi-center	1 y	CSC: 4/49 (8%) Any cancer: 13/49 (27%)
Gill et al[62]	VTP focal	206, multi-center	1 y and 2 y	CSC: 21/206 (10%) Any cancer: 51/206 (25%)

CSC, clinically significant cancer; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation; VTP, vascular-targeted photodynamic therapy.

or Focal One platform. All men underwent pre-treatment MRI and MRFTBs were performed on all PI-RADS >2 lesions. Eligibility included unilateral GGG <3 and MRI lesions >6 mm that were at least 5 mm from the prostatic apex in the sagittal midline. TURP was performed prior to FA if the prostate volume exceeded 50 cm^3. Overall, 74% of cases were GGG 1. None of the cases were lost to follow-up at 1 year. Of the 110 subjects, 101 (92%) underwent in-field biopsy and SB within 1 year. A clinically significant cancer was defined by any GGG >1, any disease core length >3 mm, or >1 core positive. The clinically significant cancer detection rate in the treated and untreated lobes was 4.9% and 6.9%, respectively. The non-clinically significant cancer detection rate in the treated and untreated lobes was 6.9% and 11.9%, respectively. At 1 year, 97% were pad free and of the 3 subjects using a single pad, none had higher than grade 1 stress urinary incontinence. There was a 3-unit decrease in the mean IPSS compared with baseline. Of the 51 subjects with good erections defined by an IIEF >16, 78% 1 year later had an IIEF >16. An IIEF change from 17 to 15 is clinically insignificant; however, this score change reflects as adverse impact because the value declined to <16. The mean change in IPSS was only a 1.2-unit decrease.

van den Bos and colleagues[59] conducted a single-institution FA trial of IRE for localized prostate cancer. Eligibility for IRE was determined by pre-treatment mpMRI, TRUS-guided template biopsy, or transperineal template-guided mapping biopsy (TTMB) with or without targeted cognitive fusion biopsies of suspicion lesions. Patients with unilateral GGG ≤3 disease were included for IRE. Ideally, the ablation zone was planned to include a 5- to 10-mm margin around the MRI lesion while sparing 5 mm from the neurovascular bundles, rectum, and urethra. T2-weighted MRI was obtained at 1 week to determine extent of the ablation zone and mpMRI was obtained at 6 months to assess in-field disease. Follow-up biopsy was performed at 6 to 12 months and 89% of these biopsies were TTMB. Sixty-three men were included in this study and 45 had undergone follow-up biopsy at the time of analysis. Clinically significant cancer was defined as GGG 1 associated with cancer core length >5 mm or >50% of the core, or any GGG ≥2. Clinically significant cancer in-field and out-of-field detection rates were 16% and 10%, respectively. Of note, in-field clinically significant cancer detection rates were higher in cases with a 5-mm ablation zone margin (4/10) compared to those with a 10-mm margin (3/35) ($P < 0.001$). At 6 months, 44 of 45 men (98%) were pad free; the one man using a single pad was pad free at 1 year. Of men who reported erections sufficient for intercourse at baseline, 8 of 26 (31%) and 3 of 13 (23%) men were unable to achieve penetration at 6 months and 1 year, respectively. There were no significant differences between median baseline and 6-month AUA symptom scores. In addition, bowel function (as determined by the Expanded Prostate Cancer Index Composite) and mental and physical function (as determined by the 12-item short-form health survey) did not significantly differ from baseline to 6-month follow-up.

Dickinson and colleagues[60] reported on three HIFU multicenter protocols employing hemi-ablation (n = 20), focal ablation(s) (n = 42), and ablation of only the index lesion (n = 56). Following mpMRI, and TTMB or SB, eligibility criteria included PSA ≤20 ng/mL and GGG ≤3. Unilateral disease in the hemi-ablation group was based on biopsy alone whereas in the other cohorts, unilateral disease was based on a single biopsy-proven index tumor. The Sonablate 500 platform was used for HIFU delivery. Follow-up MRI was performed between 48 hours and 4 weeks and at 6 months post-HIFU with saturation biopsy of the treated area at 6 months. After 6 months, for-cause biopsies were performed for rising PSA or progression on mpMRI. Clinically significant cancer was defined by detection of Gleason pattern 4 or 5, and/or maximum cancer core length >3 mm. At 6 months, 28 (25.2%) and 12 (10.8%) men had any cancer and significant in-field cancer, respectively. The area under the curve for MRI was superior to PSA for predicting both clinically significant cancer recurrence (0.85 vs 0.71) and any cancer recurrence (0.77 vs 0.65) at 6 months. In both models, the positive predictive power of mpMRI was poor. Urinary continence, defined as pad-free at 1 year, was 84.8% and 85.1% of men maintained erectile function sufficient for intercourse. IPSS scores at 1 year showed statistically significant improvements compared with baseline.

Ganzer and associates[61] conducted a phase 2 multi-center prospective hemi-ablation study using the Ablatherm or Focal One HIFU platforms. Eligibility was limited to subjects with unilateral disease following SB who subsequently underwent mpMRI. A PIRADS ≥4 lesion contralateral to unilateral SB disease was an exclusion criterion. Inclusion criteria were unilateral GGG ≤2, cancer core length ≤5 mm, and PSA ≤10 ng/mL. The study design has been criticized because the majority of candidates had low-risk disease. The anterior/posterior height was restricted to ≤30 mm for Ablatherm or ≤40 mm for Focal One cases. mpMRI with SB with or without

MRFTB (for PI-RADS ≥4 lesions) was performed at up to 1 year. Clinically significant cancer was defined as GGG 2 or GGG 1 with cancer core length >4 mm. Of the 51 enrolled subjects, 48 underwent mpMRI and biopsy at 1 year. Prostate cancer was detected in the treated lobe in 13 of 49 (26.5%) cases, of which 4/49 (8.2%) were clinically significant.

A recent phase 3 multi-center randomized study by Gill and colleagues[62] compared VTP versus active surveillance (AS) in men with low-risk prostate cancer. Eligibility was established following TRUS-guided 12-core SB and included only GGG 1, core length <6 mm and <4 positive cores. Of the 413 men randomized, 206 and 207 were randomized to VTP and AS, respectively. Oncological outcome was based on SB at 1 and 2 years. At 2 years, in-field detection of any cancer in the VTP and AS groups occurred in 51 of 206 (24.8%) and 134 of 207 (65.0%) men, respectively. Detection of GGG >1 in the VTP and AS groups was observed in 21 of 206 (10.2%) and 70 of 206 (34.0%) men, respectively. Sixty-four percent of subjects were followed off-protocol for >4 years. Sixty-one (32%) and 87 (53%) subjects in the AS group converted to radical therapy (RP or RT) by 2 and 4 years, respectively. Thirteen (7%) and 36 (24%) subjects in the VTP group converted to radical therapy by 2 and 4 years, respectively. Increase in GGG >1 and patient preference prompted conversion to radical therapy in 22 (61%) and 10 (28%) in the VTP group compared with 43 (49%) and 19 (22%) in the AS group.

Future Directions

Interest in FA for management of prostate cancer continues to grow among the urologic community. A literature search for publications relating to prostate cancer focal ablation/therapy yielded more than 150 citations indexed by PubMed Central in 2017, which is more than double the number between 2006 and 2016. The literature provides compelling evidence that with technology available today, FA is a minimally invasive treatment with an expedited recovery and causes minimal adverse impact on functional outcomes. There remains a paucity of studies evaluating oncological control beyond 2 years. Because FA will be offered to men with life expectancies of up to 30 years and the natural history of prostate cancer is prolonged, there is no way now to predict if FA will achieve long-term oncological control, and if so, who benefits from this treatment approach. Urologic oncologists, industry representatives, and government officials have established a nationally representative coordinated registry network requiring a standardized framework for investigating prostate cancer FA independent of energy delivery platform.[63] This group is currently developing consensus recommendations regarding criteria for patient selection and assessment of oncologic outcomes. The current recommendation requires follow-up MRI with both in-field and out-of-field biopsy at 1-year post-ablation. Clinically significant disease recurrence is currently defined as GGG ≥2. Longer term follow-up is needed as 1-year outcomes will provide no new insights about the viability of FA as a treatment for prostate cancer.

It is hoped that ongoing and future clinical trials will address many of the limitations of prior FA studies. The INDEX trial (NCT01194648) is a multi-center prospective single-arm focal HIFU (Sonablate 500) study currently ongoing in the United Kingdom.[64] This study seeks to enroll 354 eligible men with GGG ≤3 disease detected on TTMB and/or MRFTB. Initial follow-up includes mpMRI and targeted biopsy at 1 year and mpMRI and TTMB at 3 years. The study design was modified to capture rates of conversion to radical therapy, systemic therapy, metastasis, or death for up to 10 years. As a secondary goal, the INDEX trial will address cost effectiveness of HIFU FA compared with other primary prostate cancer interventions. This trial is scheduled to conclude in 2028.

A multi-center randomized controlled trial (NCT01835977) is currently ongoing with the goal of comparing focal IRE to hemi-ablative IRE in men with unilateral GGG ≤2 disease diagnosed following TTMB and MRI.[65] The investigators hypothesize that focal IRE will better preserve urinary and sexual function without sacrificing oncologic control. At 6 months, subjects will undergo functional and oncological assessment by TTMB and mpMRI. Oncological outcomes will be assessed over 5 years by PSA and mpMRI. Unfortunately, subsequent TTMB is not mandated as part of the study protocol. This study seeks to complete enrollment of 200 subjects by 2019.

Conclusions

Selecting men with an elevated PSA for prostate biopsy by utilizing a combination of molecular markers and mpMRI will greatly reduce the detection of low-risk disease and opportunity for over-treatment. The ability to reliably identify the location of actionable prostate cancer has been enabled by advances in mpMRI and targeted prostate biopsy technology. Despite widespread acceptance of PSA-based screening, some men will be diagnosed with high-risk or high-volume disease and whole-gland treatment with RP or RT with ADT will be indicated. In the modern era of prostate cancer screening and detection, there will

be an increasing proportion of men diagnosed with a single intermediate risk index lesion that may be amenable to organ-sparing strategy. Organ-sparing treatment is an accepted management paradigm for most solid organ malignancies. Today, we have the technology to focally ablate prostate cancer utilizing a host of energy sources. The fact prostate cancer is generally a multifocal disease is no longer a contraindication to FA because the gland can be monitored biochemically and through imaging for disease recurrence. There is compelling evidence that FA of prostate cancer truly is minimally invasive and offers major functional advantages over whole-gland treatment. Treatment that essentially eliminates urinary incontinence, erectile dysfunction, and rectal dysfunction will have tremendous appeal to men diagnosed with "focal" prostate cancer. The challenge today is to identify appropriate candidates for FA, the optimal ablation energy and ablation template, and a cost-effective protocol to monitor for in- and out-of-field oncological control. It is imperative that those urologists who embrace FA recognize the gaps in our knowledge about this treatment. Meticulous technique and follow-up are imperative. Industry and the government must support prospective studies that could provide insights to how to evaluate and optimize oncological control. If done responsibly, FA will emerge as an effective treatment for a select group of men with prostate cancer. If done irresponsibly, men will succumb to disease that otherwise should have been cured by alternative approaches. ■

The challenge today is to identify appropriate candidates for FA, the optimal ablation energy and ablation template, and a cost-effective protocol to monitor for in- and out-of-field oncological control.

If done responsibly, FA will emerge as an effective treatment for a select group of men with prostate cancer. If done irresponsibly, men will succumb to disease that otherwise should have been cured by alternative approaches.

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MAIN POINTS

- Selecting men with an elevated prostate-specific antigen levels for prostate biopsy by utilizing a combination of molecular markers and multiparametric MRI will greatly reduce the detection of low-risk disease and opportunity for over-treatment.
- In the modern era of prostate cancer screening and detection, there will be an increasing proportion of men diagnosed with a single intermediate risk index lesion that may be amenable to organ-sparing strategy. Organ-sparing treatment is an accepted management paradigm for most solid organ malignancies.
- Today, we have the technology to focally ablate prostate cancer utilizing a host of energy sources. The fact prostate cancer is generally a multi-focal disease is no longer a contraindication to focal ablation (FA) because the gland can be monitored biochemically and through imaging for disease recurrence.
- There is compelling evidence that FA of prostate cancer truly is minimally invasive and offers major functional advantages over whole-gland treatment. Treatment that essentially eliminates urinary incontinence, erectile dysfunction, and rectal dysfunction will have tremendous appeal to men diagnosed with "focal" prostate cancer.
- The challenge today is to identify appropriate candidates for FA, the optimal ablation energy and ablation template, and a cost-effective protocol to monitor for in- and out-of-field oncological control.
- It is imperative that those urologists who embrace FA recognize the gaps in our knowledge about this treatment. Meticulous technique and follow-up are imperative. Industry and the government must support prospective studies that could provide insights to how to evaluate and optimize oncological control. If done responsibly, FA will emerge as an effective treatment for a select group of men with prostate cancer. If done irresponsibly, men will succumb to disease that otherwise should have been cured by alternative approaches.

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