A Review of Focal Therapy Techniques in Prostate Cancer: Clinical Results for High-Intensity Focused Ultrasound and Focal Cryoablation

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The advancement of focal therapy technology for the treatment of prostate cancer (PCa) is emerging as an option for a middle ground between radical therapies and active surveillance for individuals identified with localized, low-grade PCa. Two promising techniques are high-intensity focused ultrasound (HIFU) and focal cryoablation. Both focal cryoablation and HIFU show promise, but additional prospective trials are necessary before any definitive conclusions can be made on either method's viability.
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Since the accepted use of prostate-specific antigen (PSA) as a screening tool for prostate cancer (PCa), the incidence of PCa has greatly increased. PCa incidence in the United States has risen 26%, but is encouragingly accompanied by a 75% decrease in patients presenting with metastases and a 30% decrease in mortality rates.[1] The new means of screening have also caused an increase in overdetections, or cancers found that would have been clinically insignificant over the patient's lifetime. It is estimated that annual PSA examinations could result in an overdetection rate as high as 50%.[2] Overdetection raises a new dilemma for the overtreatment of formerly undetectable cancers and the subsequent impact on the patient's quality of life (QoL). Overdetection can affect QoL through the

psychologic distress of a cancer diagnosis, and the possible loss of continence and sexual function that comes from definitive management.

PCa can be definitively managed with whole-gland treatment. Radical prostatectomy and radiation therapy demonstrated low cancer-specific mortality rates of 4% to 7% at 15 years and 3% to 6% at 10 years, respectively.[3-5] However, both treatment methods have shown a negative effect on patient QoL with significant morbidities impacting urinary, sexual, and bowel function. As a response to high overdetection rates and the side effects of whole-gland treatment, the strategy of active surveillance (AS) was designed. AS allows for longer observation times with the hope of avoiding unnecessary intervention and the accompanying morbidities. Although this strategy sought to reduce the QoL concerns of whole-gland therapy, it has been demonstrated to increase patient anxiety.[6,7]

Out of this tenuous balance between AS and whole-gland surgery/radiation has emerged a possible answer in focal therapy. The goal of focal therapy is to destroy local cancer lesions while minimizing damage to healthy surrounding tissue. Seeking to be an optimal treatment strategy, focal therapy gives an active treatment option to those not comfortable with surveillance while not exposing them to the potential morbidity profile of whole-gland therapy. It is also an encouraging treatment option because it does not preclude retreatment or whole-gland treatment if the cancer should recur. The most prominent question that remains is whether focal therapy achieves similar cancer control to whole-gland procedures.[8] It is also unclear whether focal treatment can be a true answer for PCa due to the multifocal nature of the disease. Other concerns exist about the ability of our current imaging and biopsy technologies to allow for a true definition of loci of cancer within the prostate, and how to best monitor patients after focal therapy.[9]

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Two main technologies have been used for focal therapy. Cryoablation has gained popularity as a focal treatment option with the increased precision of the third-generation argon-helium gas platforms.[10] This technology is based on the ability to cause the destruction of the cellular membrane through initial freezing and subsequent freeze-thaw cycles. High-intensity focused ultrasound (HIFU) is an alternative to cryoablation that delivers ultrasound waves causing an increase in temperature in target areas resulting in necrosis.[11] In addition, a third technology—laser-induced interstitial thermotherapy—is beginning to be investigated for use in focal therapy.[12]

Both HIFU and cryoablation began as promising alternative methods to whole-gland therapy, with the technologies only recently being adapted for use in focal therapy. Both methods have shown positive results for cancer control when used as a whole-gland treatment. Jones and colleagues studied 1198 patients undergoing whole-gland cryoablation with a mean follow-up of 24.4 months and demonstrated a 5-year biochemical disease-free survival (bDFS) of 77% based on the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria.[13] Murat and associates had 463 patients with a mean follow-up of 23 months undergo whole-gland HIFU and showed a 4-year bDFS of 65% by ASTRO criteria.[14] Both methods demonstrated similar morbidity profiles to other whole-gland options, begging the question whether these technologies could improve sexual, urinary, and bowel outcomes if used as focal therapy.

Focal Therapy Methods

Our focus is to describe, compare, and summarize outcomes of published studies on focal therapy and discuss their findings and limitations.[15] At the time of this review, a total of seven published studies on focal therapy were available in the literature.[16-22] The abstracts obtained from this initial search were reviewed for appropriate content and considered for inclusion in the meta-analysis. Of those seven studies, three were prospective focal cryoablation studies, three were prospective HIFU studies, and one was a retrospective focal cryoablation study. These studies represent a total of 231 patients, 170 undergoing focal cryoablation and 61 receiving HIFU

treatment. The two groups compared favorably with no significant difference in mean preoperative PSA level (6.25 ± 1.4 ng/mL vs 6.65 ± 1.1 ng/mL; $P = .9106$) or mean follow-up time in months (41.8 ± 24.8 months vs 57.0 ± 61.5 months; $P = .1248$) (Table 1).

Candidate Selection

Although candidate selection for the focal therapy clinical trials has been varied, recent studies have developed more rigorous guidelines for patient enrollment.[16-22] The study by Ellis and colleagues enrolled patients with clinical stage T1 through T3 disease and the following subjective inclusion criteria: "(1) relatively young, but unwilling to undergo standard treatment that would risk potency, or (2) older who were uncomfortable with active surveillance."[18] But by 2011, the HIFU study conducted by Ahmed and associates developed guidelines that would objectively use biopsies, imaging, and clinical data (PSA, clinical stage, Gleason score) to determine the unilateral nature of the disease and patient eligibility.[22] In 2010, a consensus panel at the Second International Workshop on Focal Therapy and Imaging in Prostate Cancer set forth recommendations for candidate selection.[23] The guidelines from the panel indicated that focal therapy should be performed on patients with unilateral low-risk cancer (clinical stage ≤ T2a) and > 10 years of life expectancy, but the panel could not reach a consensus on whether focal therapy was appropriate for intermediate-grade patients with a Gleason score of 3 + 4 = 7. None of the trials strictly adhered to the guidelines recommended by the 2010 consensus panel, yet adoption of a single set of enrollment criteria will allow large, multicenter studies to move forward and increase the reliability of future data (Table 2).[16-22]

Biopsy Strategies

Clinical trials of focal therapy have not agreed on a singular biopsy

Table 1
Focal Therapy Type Summary

Type	N	Mean # Pts (Range)	Mean F/U (Range)	Mean Preoperative PSA (ng/mL)	Mean Postoperative PSA (ng/ml)	Mean △PSA (ng/mL)	Negative Bx (%)	Potency Preserved (%)	Continence Preserved (%)
Cryo	4	42.5 (25-60)	41.8 (15.2-70)	6.25 ± 1.2	2.24 ± 0.1	−4.75 ± 1.0	97	80.8	99
HIFU	3	20.3 (12-29)	57.1 (12-127.2)	6.65 ± 1.1	1.52 ± 0.02	−5.13 ± 1.2	85	97	99

bx, biopsy; Cryo, focal cryoablation; F/U, follow-up; HIFU, high-intensity focused ultrasound; N, number of studies; PSA, prostate-specific antigen; Pts, patients.

Table 2
Focal Therapy Selection Criteria

Study	Type	PSA Requirements (Mean ng/mL)	Gleason Score	Clinical Stage	Bx
Bahn et al[16]	Cryo	All (4.95)	All	NR	Initial 6-8 cores, targeted bx after
Lambert et al[17]	Cryo	All (6.00)	6, 7 (3 + 4)	NR	12 core bx
Ellis et al[18]	Cryo	All (7.2)	All	T1 to T3N0M0	NR (Retrospective)
Onik et al[19]	Cryo	All (NR)	All	T1c - T2b	Ultrasound-guided bx
Muto et al[20]	HIFU	All (5.36)	All	T1c to T2N0M0	NR
El Fegoun et al[21]	HIFU	≤ 10 ng/mL (7.3)	≤ 7 (no predominant pattern 4)	≤ T2a	≤ 3 positive bx, only 1 lobe
Ahmed et al[22]	HIFU	≤ 15 ng/mL (7.3)	4 + 3 or less	≤ T2bN0M0	TRUS-guided bx, then TPM

bx, biopsy; Cryo, focal cryoablation; HIFU, high-intensity focused ultrasound; NR, not reported; PSA, prostate-specific antigen; TPM, transperineal prostate mapping; TRUS, transrectal ultrasound.

strategy. Onik and colleagues and Ahmed and coauthors performed template transperineal-mapping biopsies to confirm unilateral disease.[19,22] Other studies performed as few as eight core biopsies or did not describe their biopsy strategies rigorously enough to determine how many cores were taken.[16-18,20,21] Conventional 12-core sextant biopsy appears inadequate for determination of unilateral low-grade, focal PCa.[24,25] It is now advised to follow the more comprehensive procedure of transperineal template-guided mapping biopsy, or transrectal/transperineal multicore saturation biopsy. Taking more biopsy cores on a defined grid gives physicians more confidence in the unilateral nature, locality, grade, and stage of the PCa. Importantly, the more extensive biopsy does not seem to have an impact on QoL.[26]

Ablation Strategies

Although all of the examined studies are considered focal therapy for PCa, the definition of *focal* and amount of prostate tissue destroyed differs in each study.[16-22] Only Onik and colleagues can claim true focal ablation, with the freezing of only one center of disease within the prostate.[19] Other studies have chosen a more cautious approach, destroying 75% of the prostate in what is called a "posterior hockey-stick" ablation.[18,20] This method of performing a hemiablation and then destroying the posterior of the contralateral side is favored due to the possibility of unfound PCa existing in the contralateral side of the prostate. This still leaves 25% of the original prostate intact with the hope that the remaining tissue will mitigate possible morbidities of whole-gland ablation. The other four studies performed hemiablation.[16,17,21,22] Whereas the term *focal* suggests a single target, in many studies this is not the case and as such a more fitting title would be *subtotal ablation*.

Clinical Application

Comparing the cancer control and complication rates of the focal cryoablation studies with the HIFU studies is difficult because of the use of varied inclusion criteria, ablation templates, bDFS criteria, and follow-up times. Noting the potential limits and the descriptive nature of the statistics, the data available show that there is no significant difference in the △PSA between the focal cryoablation group and the HIFU group (4.75 ± 1.0 ng/mL vs 5.13 ± 1.1 ng/mL; $P = .9046$). Focal cryoablation demonstrated a statistically significant higher negative biopsy rate (97% vs 85%; $P = .0249$). The HIFU group had a significantly higher rate of potency preservation (97% vs 80.8%; $P = .0008$), whereas there was no significant difference in continence rate. Of note, it is distressing that only two studies included standardized patient reported QoL data and as such there was no viable comparison of International Prostate Symptom Score or Sexual Health Inventory for Men scores between the two groups (Table 3).

In 2006, Bahn and colleagues released the first small-size series investigating focal therapy with focal cryoablation.[16] They were able to demonstrate the feasibility of focal therapy with strong oncologic outcomes and a low comorbidity profile. The disease of the candidates was not adequately described, relying on low core (6-8) biopsy and color Doppler scans with no criteria regarding PSA, clinical stage, or Gleason score. Performing a hemiablation, the mean follow-up time was 70 months with a bDFS of 92.9% by ASTRO criteria. In addition to a strong bDFS, 88.9% retained potency preserved and 100% retained continence.

Lambert and associates released clinical trial data of unilateral cryoablation of unilateral lesions in 25 patients with a mean follow-up of 28 months.[17] This study underlines the contralateral nature of PCa and the promising oncologic outcomes of retreatment with focal cryoablation. Lambert and colleagues conducted a retrospective study that monitored Gleason 6 or 7 (3 + 4) patients who had not previously received hormonal therapy or radiotherapy, with cancer confirmed to one lobe and tumor volume representing < 10% in a 12-core biopsy. Patients had a bDFS of 88%, with two patients demonstrating cancer on the contralateral side who were retreated to focal cryoablation and considered disease free. Continence was preserved in 100% of patients and potency was preserved in 70.4%.

In an effort to address the contralateral nature of PCa, Ellis and colleagues performed a trial series using a posterior hockey-stick cryoablation template.[18] This study had the most vague candidate selection criteria and no biopsy mapping and as such demonstrated a high percentage of failure with contralateral lesions. Candidates were enrolled with a clinical stage between T1 to T3N0M0 and if (1) they were relatively young and unwilling to risk potency, or (2) they were older and uncomfortable with AS. The bDFS determined by PSA nadir was 88% in a study of 60 patients with a mean follow-up time of 15.2 months. Fourteen patients had positive biopsies for PCa after the procedure, 13 of which were present on the untreated side. Potency was maintained in 70.6% of patients after penile rehabilitation and continence was maintained in 96.3%.

In contrast to the Ellis and colleagues' hockey-stick template, Onik and associates performed a 54-patient series with true focal cryoablation of a unifocal lesion.[19] Although Onik and associates had loose enrollment criteria, the effort of using an ultrasound-guided biopsy to confirm

Table 3
Focal Therapy Cancer Control and Complication Rates

Study	Type	N	Mean F/U (mo)	bDFS % (Criteria)	Negative Biopsy (%)	Potency Preserved (%)	Continence Preserved (%)
Bahn et al[16]	Cryo	31	70	92.9 (ASTRO)	96	88.9	100
Lambert et al[17]	Cryo	25	28	88 (PSA nadir)	96 Untreated lobe: 2 positive bx	70.8	100
Ellis et al[18]	Cryo	60	15.2	80.4 (ASTRO)	98.3 Untreated lobe: 13 positive bx	70.6	96.3
Onik et al[19]	Cryo	54	54	100 (ASTRO)	97.9	90	100
Muto et al[20]	HIFU	29	32	83.3 − low risk 53.6 − moderate risk (3 consecutive PSA increases)	76.5	NR	100
El Fegoun et al[21]	HIFU	12	37	90 at 5 years 38 at 10 years (recurrence-free survival)	91	100	100
Ahmed et al[22]	HIFU	20	36.7	89.5 (absence of cancer)	88.9	95	95

ASTRO, American Society for Therapeutic Radiology and Oncology; bDFS, biochemical disease-free survival; bx, biopsy; Cryo, focal cryoablation; F/U, follow-up; HIFU, high-intensity focused ultrasound; N, number of patients; PSA, prostate specific antigen.

unilateral cancer and a longer follow-up showed the potential success of true unifocal therapy and raised questions about the amount of prostate tissue that actually needs to be removed to obtain cancer control. Candidates were selected when an ultrasound-guided biopsy showed unilateral cancer and maintenance of potency/continence was important to the patient. With a mean follow-up of 4.5 years, the study showed 95% bDFS by ASTRO criteria, potency preservation in 90% of patients, and continence preservation in 100% of patients.

In 2008, Muto and colleagues published the first series using HIFU as a focal treatment of PCa with 29 patients.[20] This study served as the proof of concept for focal HIFU with acceptable cancer control, but unclear potency results demanded more studies. The study used a similar posterior hockey-stick approach as Ellis and associates in a patient population aged > 60 years, clinical stage between T1c and T2N0M0, and with a biopsy and MRI indicating localized disease. Patients of low-risk demonstrated a bDFS of 83.3% and patients of moderate risk had a bDFS of 53.6% as defined by three consecutive PSA increases. Potency results were not reported and continence was preserved in 100% of patients.

El Fegoun and coauthors performed a small HIFU series in 12 patients with an average follow-up time of 10.6 years.[21] This study builds on the work of Muto and colleagues by introducing strict enrollment criteria, longer follow-up times, and encouraging morbidity data. Using a hemiablation template, El Fegoun and associates increased the sophistication of selection criteria. Patients were required to have a PSA < 10 ng/mL, ≤ 3 positive biopsies in only one lobe, clinical stage $\leq$ T2a, Gleason score ≤ 7, negative staging, and no history of definitive PCa treatment or hormonal therapy. The patients in this study had a 1-year negative biopsy result rate of 91%, followed by a 5-year bDFS of 66.7%, and a 7-year bDFS of 58.3%. All patients were reported to preserve both continence and potency.

Ahmed and colleagues performed a hemiablative HIFU procedure in 20 patients with a mean follow-up of 12 months.[22] This study is the first to use transrectal ultrasound (TRUS) and

a template transperineal mapping (TPM) system to define unilateral disease, and strict enrollment criteria demonstrated promising cancer control and a low morbidity profile. Candidates must have low to intermediate risk, unilateral disease defined as Gleason score ≤ 4 + 3, PSA ≤ 15 ng/mL, and clinical stage ≤ T2bN0M0. In addition, they must be diagnosed by TRUS-guided biopsies, and then must undergo multiparametric magnetic resonance imaging and TPM biopsies to confirm unilateral disease. Patients had a bDFS of 89.5% as defined by the absence of any cancer; 95% of patients retained potency and 95% of patients retained continence.

Conclusions

Patients with localized, low-risk PCa previously had the uncomfortable choice between AS and whole-gland therapy. The limited data suggest that focal therapy is a possible third option that allows for active cancer management with a lower morbidity profile. HIFU and focal cryoablation both represent promising technologies, but it is still not possible to make any final comment on the advantages of either platform. Studies to date have not been able to effectively determine ideal patient selection and positive pretreatment indicators. Also, it is unclear how many patients present with true unilateral disease that is appropriate for treatment with focal therapy.

Moving forward, it is important that new prospective, multicenter clinical trials follow the lead of El Fegoun and colleagues and Ahmed and associates to develop strict candidate selection criteria, use all imaging/biopsy technology available (namely, TRUS/TPM), and contain clear QoL endpoints using standardized patient-reported data forms. Studies need to prospectively follow patients long term to allow for the possibility of a true recurrence of PCa. In addition, enrollment of more patients is needed to achieve a well-powered study. Only with trials that meet the aforementioned criteria will patients and physicians alike be convinced of the long-term effectiveness and safety of focal therapy. ■

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Main Points

- It is estimated that annual prostate-specific antigen examinations result in overdetection rates as high as 50%, which raises a new dilemma for the overtreatment of formerly undetectable cancers and the subsequent impact on the patient's quality of life (QoL): psychologic distress of a cancer diagnosis and the possible loss of continence and sexual function that comes from definitive management.
- Prostate cancer can be managed with whole-gland treatment. Radical prostatectomy and radiation therapy demonstrate low cancer-specific mortality; however, both methods have shown a negative effect on patient QoL with significant morbidities impacting urinary, sexual, and bowel function.
- Focal therapy has emerged as a treatment option to destroy local cancer lesions while minimizing damage to healthy surrounding tissue, which gives an active treatment option to those not comfortable with surveillance as well as not exposing them to the potential morbidity profile of whole-gland therapy.
- Cryoablation has gained popularity as a focal treatment option which is based on the ability to cause the destruction of the cellular membrane through initial freezing and subsequent freeze-thaw cycles. High-intensity focused ultrasound (HIFU) is an alternative to cryoablation that delivers ultrasound waves that cause an increase in temperature in target areas resulting in necrosis.
- Both cryoablation and HIFU represent promising technologies, but it is not possible at this time to make any final comment on the advantages of either platform. Studies to date have not been able to effectively determine ideal patient selection and positive pretreatment indicators.

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