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RESEARCH ARTICLE

Role of Image-Guided Focal Cryoablation in Localized Prostate Cancer

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ABSTRACT

Prostate cancer is the most common non-cutaneous malignancy in men, with the majority of newly diagnosed clinical scenarios eligible for active surveillance. However, there may be psychological ramifications associated with living with an untreated malignancy. Furthermore, recent reports show long-term progression exceeds 50% even for low-risk disease. Given the morbidity of traditional whole-gland prostate cancer therapies further advancements are necessary to maximize cure and minimize treatment side effects. Advances in multiparametric MRI has enabled a paradigm shift not only in the detection of clinically significant disease, but also toward more specific disease localization. While traditional treatments for prostate cancer involve whole-gland treatment, contemporary MRI technology allows for consideration of focal ablation via various technologies. This review details focal cryoablation for primary and salvage prostate cancer treatments and compares its efficacy to other treatment methods, including brachytherapy, external beam radiation, and high intensity focused ultrasound. The use of focal cryoablation as a primary treatment has shown promising oncologic outcomes, similar to that of whole-gland cryoablation, but with better functional outcomes. Focal cryotherapy as a salvage treatment has mixed results regarding efficacy and warrants further study. When compared to other focal treatments, cryotherapy leads to similar, or better, oncologic control outcomes. In addition, the review details the considerations for adjunct therapies and future applications to enhance the precision accuracy of current focal cryoablation techniques.

Introduction

Prostate cancer is the most common non-cutaneous malignancy in men, with >288,000 cases predicted to be diagnosed in 2023 in the United States.[1] Although the majority of newly-diagnosed men pursue active surveillance, recent data suggests progression rates up to 60% by 10 years follow-up even for well-selected men with National Comprehensive Cancer Network® (NCCN®) very-low and low risk disease.[2-3] Furthermore, active surveillance has been associated with the psychological ramifications of an in-situ untreated malignancy.[4] More concerning are reports of increased prostate cancer specific mortality (HR 1.66, 95% CI 1.15-2.39) and metastatic disease (HR 1.34, 95% CI 1.15-1.57) after roughly 10 years median follow-up in the propensity-matched retrospective cohort study of low-risk patients by Timilshina et al.[2] Therefore, in an effort to minimize the morbidity of urinary incontinence and erectile dysfunction associated with conventional radical treatments (i.e., robotic radical prostatectomy and whole-gland radiotherapy),[5] contemporary treatment has shifted to the promise of focal ablation, especially given advancements in prostate imaging and index lesion localization fostered by multiparametric prostate MRI (mpMRI). Certainly, organ-preserving focal therapies now dominate the treatment landscape for the majority of solid organ malignancies, including kidney, breast, liver, and lung. There are many focal ablation technologies currently in use, including cryoablation, high-intensity focused ultrasound, TULSA (transurethral ultrasound ablation), focal laser ablation (FLA), and irreversible electroporation (IRE). The present review will focus on focal cryoablation.

While active surveillance is often adopted for very-low and low-risk patients, the paradigm of "super-active surveillance" with incorporation of focal ablation is a strategy that may benefit select patients. This offers an intermediate option between active surveillance and radical treatments. Super-active surveillance entails the addition of ablation of the lesion combined with MRI, PSA, and biopsy at pre-specified or risk-adapted intervals.[6] Focal cryoablation is an application of a familiar technology that has been utilized in the context of this treatment paradigm, offering an intermediary between radical treatments and active surveillance.[4,8]

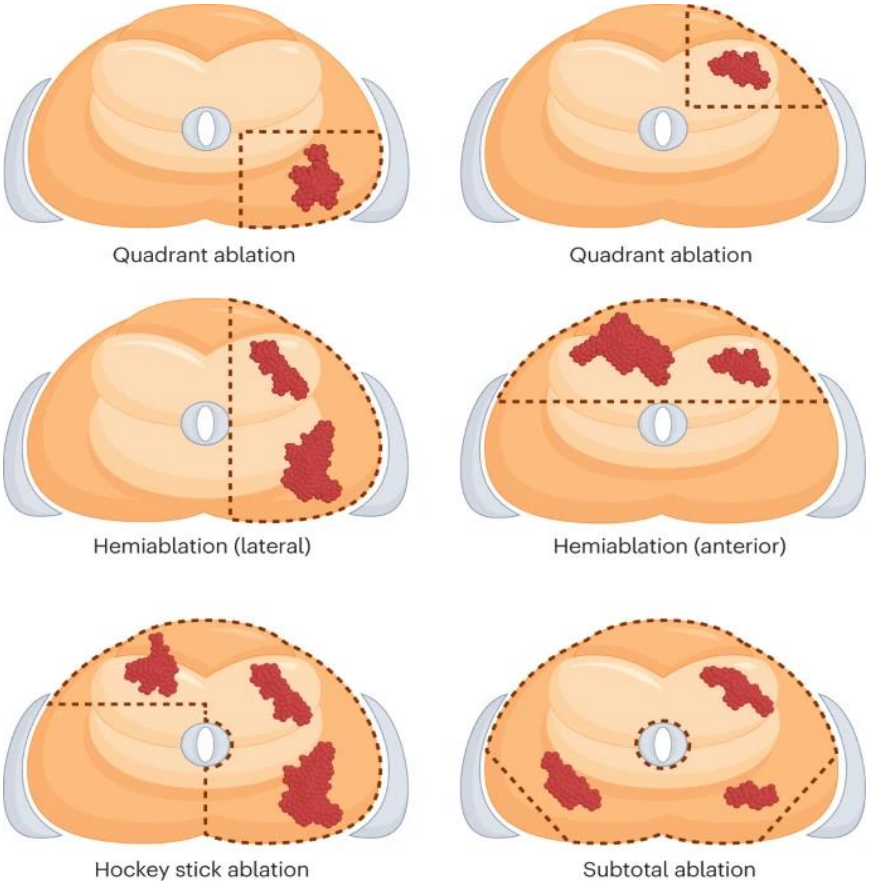
Focal cryotherapy of localized prostate cancer offers an attractive option for select patients with a well-defined cancer lesion with low- or intermediate-risk pathology. Studies have shown improved functional outcomes (i.e., urinary continence), as well as reduced severe morbidity (i.e., rectourethral fistula), as well as comparable periods of non-recurrence when compared to radical whole-gland prostatectomy.[8-9] Due to these promising outcomes, there have been an increased number of studies further analyzing this treatment over the past 20 years.

Treatment Procedure

Cryoablation was first used to treat clinically significant prostate cancer in the 1960s through an open-perineal procedure. This approach often led to high morbidity. In 1993, the treatment was revived with a technique to monitor the treatment as it was performed: using transrectal ultrasound (TRUS).[5] Image-guided focal cryoablation is unique in that it uses mpMRI technique to freeze malignant areas in a precise, minimally invasive manner. Similar to other prostate cancer treatments, patients first undergo an mpMRI to visualize gland size, along with the presence, size, and topographical location of regions of interest (ROIs, i.e., potential sites of malignancy) with relation to adjacent critical structures (i.e., urethra, rectum, neurovascular bundle, bladder neck). This imaging is used to perform MRI-TRUS fusion biopsy to sample the ROIs along with an extended systematic template to increase detection rate of clinically-significant disease and to ensure no para-ROI disease exists (see Patient Selection below). Next, an ultrasound probe and "brachytherapy template" grid are used to direct the cryoablation needles percutaneously into the target areas to form a select number of ice balls, creating an aggregate ablation zone. A urethral warming catheter is used to prevent urethral sloughing. Two freeze-thaw cycles maximize tissue destruction and represent standard of care.

The ablation configuration may be customized or follow any of the proposed patterns of quadrant-, hemi-, hockey-stick-, or sub-total ablation, based on the position of the cancer. A description of these configurations can be seen in the figure below.

Figure 1. Common ablation technique patterns.[8]

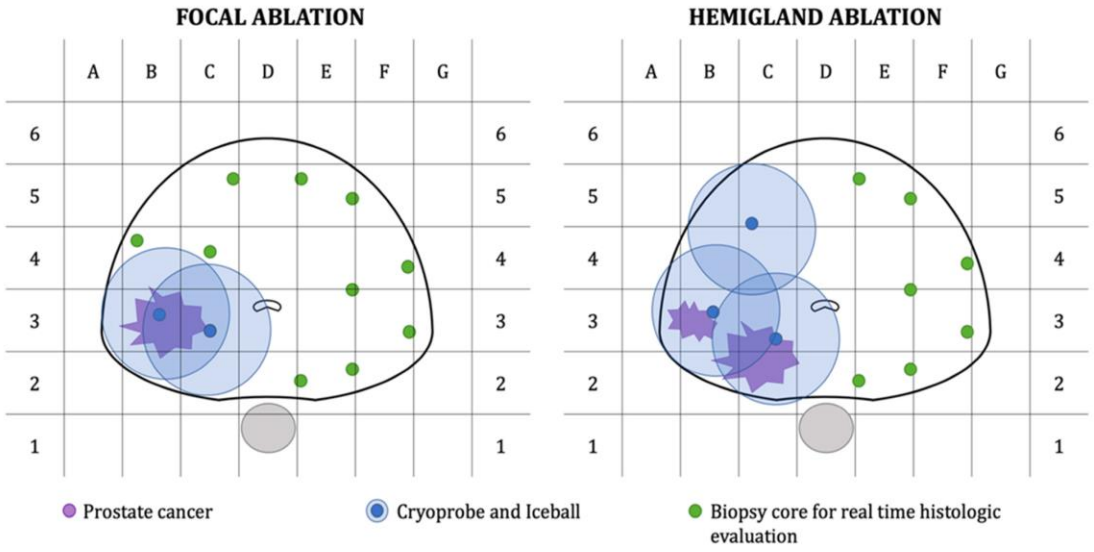


[a] Reproduced with permission of Elsevier. *Nature Reviews of Urology,* 2023.
[8] Tan WP, Wysock JS, Lepor H. Partial gland cryoablation for prostate cancer — Where are we? *Nature Reviews Urology*. 2023;20(3):127-128. doi:10.1038/s41585-022-00685-z

The surgeon positions the probes and thermocouples using sonographic guidance and uses the appropriate number of needles based on length, width, and height of the ablation zone. Contemporary methods utilizing MRI-TRUS fusion software may also be employed to ensure accurate and adequate coverage of the index lesion. There are several commercially available platforms for MRI-TRUS fusion imaging. The Artemis and BioJet fusion devices work to overlay the images using robotic tracking by a mechanical arm with encoders built in. The UroNav device uses electromagnetic tracking to overlay the images. Finally, the Urostation device overlays the images by tracking using a 3D ultrasound probe.[10] In a study performed by Valerio, et al (2017), an additional 12-15 minutes were required during each procedure to interpret, contour, and align the images. Overall, MRI-TRUS fusion allowed for easier placement of probes in determining the margins of the treatment zone.[11]

The suitable treatment margin is controversial, not only necessitating compensation for registration error from the fusion platform technology, patient motion, and anatomical distortion from needle placement, but also for radiolucent tumor extension beyond the perceived border of the visible ROI. In fact, whole-mount pathologic sections have suggested up to ~1 cm extension beyond the radiographic border of the tumor.[12] Therefore, expert consensus dictates that the ablation zone should include around 1 cm of tissue surrounding the lesion to be sure not to leave behind any cancerous tissue.[13-15] The positioning should follow a triangular pattern to allow for adequate covering of the cryoablation area, as seen below.

Figure 2. "Graph representation of treatment plan and biopsy core template for patients undergoing focal or hemigland cryoablation."[16]



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[16] Selvaggio O, Falagario UG, Bruno SM, et al. Intraoperative digital analysis of ablation margins (DAAM) by fluorescent confocal microscopy to improve partial prostate gland cryoablation outcomes. *Cancers*. 2021;13(17):4382. doi:10.3390/cancers13174382

Postoperative care for patients is consistent with other transurethral procedures, relatively minimal, and often involves the use of a catheter for several days after the procedure, along with symptomatic treatment of patient discomfort. This may include medications such as analgesics, alpha antagonists, and well as prophylactic antibiotics. There may be consideration for preemptive suprapubic tube placement for men with large planned-ablation zones.

Patient Selection

NCCN® low- and intermediate-risk patients, including select patients with high-volume disease, are ideal candidates for cryotherapy.[9] Below are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for risk stratification.

Table 1. Risk stratification for clinically localized prostate cancer.[17]

Risk Group	Clinical/Pathologic Features		
Very low	Has all of the following: ● cT1c ● Grade Group 1 ● PSA < 10 ng/mL ● Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core ● PSA density < 0.15 ng/mL/g		
Low	Has all of the following but does not qualify for very low risk: ● cT1 – cT2a ● Grade Group 1 ● PSA < 10 ng/mL		
Intermediate	Has all of the following: ● No high-risk group features ● No very-high-risk group features ● Has one or more	Favorable intermediate	Has all of the following: ● 1 IRF ● Grade Group 1 or 2 ● < 50% biopsy cores positive

Risk Group	Clinical/Pathologic Features		
	intermediate risk factors (IRFs): ○ cT2b – cT2c ○ Grade Group 2 or 3 ○ PSA 10–20 ng/mL		(e.g., < 6 of 12 cores)
		Unfavorable intermediate	Has one or more of the following: ● 2 or 3 IRFs ● Grade Group 3 ● ≥ 50% biopsy cores positive (e.g., ≥ 6 of 12 cores)
High	Has no very-high-risk features and has exactly one high-risk feature: ● cT3a OR ● Grade Group 4 or Grade Group 5 OR ● PSA > 20 ng/mL		
Very high	Has at least one of the following: ● cT3b – cT4 ● Primary Gleason pattern 5 ● 2 or 3 high-risk features ● > 4 cores with Grade Group 4 or 5		

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[17] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed [July 27, 2023]. To view the most recent and complete version of the guideline, go online to NCCN.org.

The NCCN® criteria are a risk stratification system that divides patients into low, intermediate and high-risk groups taking into account clinical tumor stage, PSA level, and biopsy Gleason grade group.[18] While exact consensus for patient selection has not been achieved (namely whether Gleason Grade Group (GG) 3 patients should be routinely offered focal ablation vs. restricting this approach to grade groups 1-2), it is generally recognized that NCCN® high-risk patients (i.e., GG4-5) are not suitable candidates for this treatment approach.[8,19] In addition, patients with solitary MRI visible lesions are best suited for focal cryotherapy,[8] with systematic template biopsy demonstrating no other areas of clinically significant prostate cancer (csPCa; i.e., >GG1).

Contraindications

While there are no absolute contraindications for cryosurgery, there are a few limiting factors that have been cited in the context of whole-gland cryoablation. Prostate volumes higher than 60 cc have been cited as a relative contraindication because of the limited diameter of the ice-ball created by the cryoprobes, difficulty achieving uniform intraprostatic temperature, and pubic arch interference. Higher temperature gradients and more cryoprobes increase the risk of tissue damage. Neoadjuvant hormonal therapy can decrease prostate size prior to cryosurgery; however, studies have not shown any beneficial outcomes in this setting.[20-21] Prostate volume is not as much of a factor for focal ablation.

A history of transurethral resection of the prostate (TURP) is a relative contraindication even in the focal ablation setting because there is an increased risk of urethral sloughing and urinary retention due to failure of the urethral warming device to make complete contact with the mucosa.[20-22] Patients with previous obstructive lower urinary tract symptoms have a higher risk of urinary obstruction after treatment. Other relative contraindications include previous pelvic and urethral surgeries that have distorted anatomy, inflammatory bowel disease due to increased risk of anorectal fistulas, and severe lower urinary tract symptoms (especially with history of acute urinary retention) due to benign prostatic hyperplasia (BPH).[21-22]

Defining Success/Failure

Currently, there is no single method of defining success following focal therapy. Relying on PSA decline may be unpredictable given the influence of multiple factors, including baseline PSA, prostate volume, and volume of the ablation zone. Often, definitions used in radiation oncology have been utilized for use in focal therapies as well. The ASTRO criteria, introduced in 1993, defines biochemical failure as three consecutive rises in PSA after initial nadir. The Phoenix criteria updated this definition in 2005 to PSA nadir +2 ng/ml.[23]

However, these definitions were designed to define success following radiation. Radiation is a non-ablative technology, damaging DNA, and prompting cell death in a delayed fashion (i.e., later on when the cell tries to divide and cannot overcome this irreparable DNA damage). Biochemical response may take even 12-18 months to achieve nadir. Conversely, cryotherapy destroys the tissue in real-time, resulting in immediate, contemporaneous biochemical response. For this reason, these ablative and non-ablative treatments simply cannot be assessed with the same criteria. Because focal cryotherapy leaves behind intact prostatic tissue by intention, targeted biopsies at 6-12 months have been utilized to measure success via the presence of residual disease rather than biochemical control.

Radiographic surveillance via mpMRI has also been utilized, and in fact is a fundamental component of post-focal therapy targeted biopsies. The exact schedule of repeat imaging, as well as targeted- and systematic biopsies are largely institution-dependent and tailored to a patient's risk category,[24] but commonly fall around 3-6 months, 12-24 months, and 5 years after focal therapy. One of the caveats of focal ablation is not only "in-field" disease recurrence within the ablation zone, but the ever-looming threat of "out-of-field" disease or a second primary cancer zone.

Primary Treatment

Primary whole-gland and focal cryoablation can be used as an alternative to radical prostatectomy and radiation therapy for definitive prostate cancer treatment. One of the longest reported outcomes for whole-gland cryoablation comes from Cohen et al (2008).[25] The researchers looked at rates of biochemical progression-free survival (BPFS) using the Phoenix criteria in n=370 patients who had undergone whole-gland ablation over a ten-year period.[25] No patients received hormonal therapy. Overall biochemical recurrence free survival (BRFS) at ten years was 80%. When stratified by D'Amico risk groups, survival was highest for low risk at 80% (63-90% CI); intermediate risk was 74% (62-82% CI); and high risk was 45% (31-58% CI). Additionally, they found factors predictive of failure were pre-treatment PSA (HR 1.05), increased age (HR 1.08) and post-treatment PSA nadir (HR 2.11). Of note, individuals that subsequently had biochemical recurrence had a PSA nadir of ≥ 0.4 ng/mL, which is consistent with other studies suggesting a PSA > 0.4 ng/mL was associated with increased rates of recurrence.[25-26]

1. FOCAL PRIMARY CRYOTHERAPY

Restricted and careful patient selection is imperative for focal therapy success. In a single-institution study on focal cryoablation of n=64 patients, 7 treatment failures were reported in a cohort of 48 patients with low-risk primary prostate cancer after median follow-up of 13.2 months (14.5%).[27] Of the 46 out of 48 patients who received a post-focal cryotherapy biopsy at one-year follow-up, there were 26% positive findings, and 17% of patients underwent a secondary treatment.[27] Similarly, another study found that of 62 patients with low risk disease, 12 (19%) had positive one-year biopsy results.[28] Chuang et al (2020) concluded that, following treatment, 82% (50 of 61) of patients who underwent hemigland cryoablation as a primary treatment for NCCN® intermediate and low risk patients had no biopsy-detectable clinically significant prostate cancer at 6-month near-term follow-up, and 82% (22 of 27) of patients reaching the 18-month intermediate-term remained biopsy negative.[29] A more recent study found that, at 12-month follow-up mpMRI and biopsy, 22 of 28 patients (78.6%) had no detectable clinically significant prostate cancer.[30]

In a 2023 prospective study by Aker et al, n=143 patients diagnosed with unilateral clinically significant prostate cancer were enrolled in an observational trial of partial gland cryotherapy between 2017 and 2019 at UCLA Medical Center.[31] Participants underwent MRI-guided biopsy (MRGB) assessments at the beginning of the study and at 6 months and 18 months following the treatment. The study revealed that partial gland cryotherapy was a reasonably safe and moderately effective approach for treating intermediate-risk prostate cancer. Biopsy at 6 months revealed no clinically significant prostate cancer in 76% of patients, and at 18 months, in 65% of patients. The assessment of cancer was also better determined by MRGB compared to MRI or PSA tests.[31]

Long-term efficacy via biochemical disease-free survival (BDFS) rates at five years were analyzed in two studies. One study found that the rates were 78%, 74%, and 55% for low, intermediate, and high-grade cancers, respectively in n=163 patients, while the other study found that the rate was 78%, 57%, and 67% for low, intermediate, and high-grade cancers, respectively in n=160 patients.[5,32] The second study also reported an 89% survival rate, a treatment failure-free survival rate of 85% and a metastasis-free survival rate of 100% at five years.[32] The first study's cohort included 27 patients (16.5%) with D'Amico low, 115 patients (70.5%) with intermediate, and 23 patients (14.1%) with high-risk prostate cancer. The biochemical recurrence rates were 27%, 26% and 46% for low,

intermediate, and high-grade cancers, respectively, five years post-treatment. Genetic testing Decipher score analysis of biopsy tissue revealed that the highest risk groups had the highest probability of biochemical recurrence.[5] The focal primary cryoablation results are summarized in the table below.

Table 2. Contemporary series of focal primary cryotherapy.

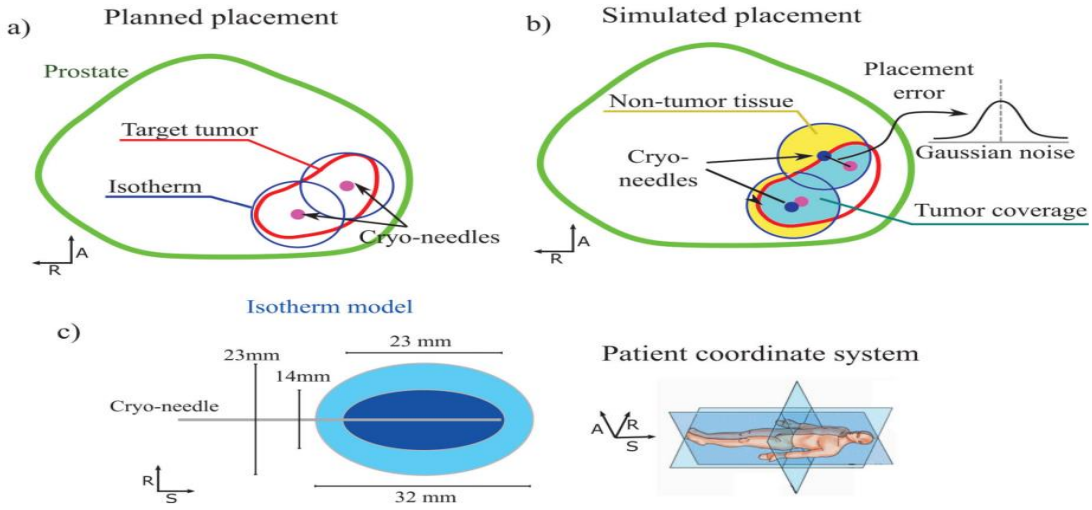
References	Institution	No. of Pts	Mos. Follow-up	Risk Categories	Stage	Use of ADT	Failure Criteria	% Pos. Biopsy Rate
Tan et al, 2023	Multiple, Singapore	28	12	85.7% intermediate 14.3% high	NR	NR.	csPCa absence: 78.6	21.4
Khan et al, 2023	Creighton University School of Medicine, Omaha, NE, USA	163	Median 39	16.5% low 70.5% intermediate 14.1% high	T1c	9.4% for salvage treatment	ASTRO: 78 (D'Amico low-risk), 74 (intermediate), 55 (high)	NR
Chuang et al, 2020	University of California, Los Angeles, CA, USA	67	6 and 18	All intermediate or higher	NR	NR	csPCa absence: 82	18
Oishi et al, 2019	Keck School of Medicine, University of Southern California, CA, USA	160	40	18% low 66% intermediate 16% high	T1c- T2b	Neoadjuvant discontinued, no adjuvant given	Phoenix: 78 (low), 57 (intermediate), 67 (high)	NR
Durand et al, 2014	Multiple, France	48	Median 13.2	100% low	T1c-T2a	2% for salvage treatment	BR: 27	13
Barqawi et al, 2014	University of Colorado, Denver School of Medicine, CO, USA	62	Median 28	100% low	T1-T2b	NR	Negative biopsy at 1 year: 81	19
Aker et al, 2023	David Geffen School of Medicine at University of California, Los Angeles, CA, USA	143	6 and 18	NR	NR	None	csPCa absence at 6 months: 76 At 18 months: 65	24 at 6 months, 25 at 18 months

NR= not reported; csPCa= clinically significant prostate cancer; BR= biochemical recurrence; ADT = androgen deprivation therapy

Overall, PSA concentration does not correlate well with biopsy results and is an unreliable tool for tracking recurrence and progression after focal cryotherapy.[27] Studies suggest that complementary mpMRI with mandatory repeat biopsy provides the most comprehensive assessment of oncological outcomes after focal therapy.[27,30]

It is worth mentioning that there are significant technical challenges involved in using and appropriately placing cryo-needles to sufficiently cover the target tumor. Placement errors in focal cryoablation as a primary treatment can occur due to needle deviation and prostate movement. However, these challenges can lead to positive ablation margins.[33] In a recent study, Moreira et al (2021) analyzed the effects of cryo-needle misplacement on the coverage of the target tumor and the probability of positive margins.[33] An analysis of retrospective MRI data of 15 patients with biopsy-proven, unifocal, and MRI visible prostate cancer was conducted to determine the impact of placement error on the volume of the tumor covered by the −40°C and −20°C isotherms with one to four cryo-needles. They found that three or four cryo-needles were more resistant to placement errors than two needles. An average tumor coverage above 90% could be reached using two, three, and four needles with a standard deviation of the needle placement error up to 5 mm when considering the −20°C isotherm as the lethal ablation zone. Positive margins and tumor coverage were more likely to be affected by needle placement errors when the -40°C isotherm was used as the boundary for the lethal ablation zone due to its smaller footprint.[33] The figure below demonstrates the planned and simulated cryo-needle placement in the study by Moreira et al, 2021.

Figure 3. Noise and isotherm models used to determine needle placement error. [33]



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[33] Moreira P, Tuncali K, Tempany CM, Tokuda J. The impact of placement errors on the tumor coverage in MRI-guided focal cryoablation of prostate cancer. *Academic Radiology*. 2021;28(6):841–848. doi:10.1016/j.acra.2020.07.013

2. COMPARING WHOLE-GLAND AND FOCAL CRYOTHERAPY

In a retrospective matched-comparison study of n=634 patients from 2007 to 2013, Mendez et al (2015) compared the oncologic and functional outcomes for men with low-risk prostate cancer following whole-gland or focal ablation therapy.[34] The BRFS rates at one year post-treatment were 80.1% for whole-gland and 71.3% for focal, according to the Phoenix definition (p=0.5), and 82.1% for whole-gland and 73% for focal, according to the ASTRO definition (p=0.1). At 24 months post-treatment, for the whole-gland and focal cohorts, 46.8% and 68.8%, respectively, recovered erectile function, defined as ability to have intercourse (p=0.001). At this time-point, continence rates, defined as no pad use, were 98.7% for whole-gland and 100% for focal (p=0.02). Urinary retention was measured at 6, 12, and 24 months; the whole-gland cohort measured 7.3%, 1.9%, and 0.6%, respectively, while the focal cohort measured 5%, 1.3%, and 0.9%, respectively. Lastly, in each group, only one fistula was reported. These results show that focal cryoablation and whole-gland cryoablation led to similar BRFS rates at one-year post-treatment. The authors concluded that the rates of urinary retention, continence, and fistula were also similar between the two cohorts. However, patients who underwent focal ablation had higher erectile function 24 months after treatment.[34]

Tay et al (2017) performed a propensity score-matched comparison to measure the efficacy of whole versus partial gland cryotherapy for men with intermediate-risk prostate cancer.[35] Their

results showed there was no difference in BPFS (using the ASTRO and Phoenix criteria) between the whole and partial cryotherapy groups, but the partial ablation group had better sexual function post-treatment (46.8% 12-month rate of effective intercourse compared to 29.5% for whole-gland).[35]

Taken together, past research shows that whole-gland and partial gland/focal cryotherapy led to similar oncologic outcomes, but focal ablation leads to better functional outcomes. For this reason, focal treatment may be preferred, especially for men for whom erectile function is important.

3. COMPLICATIONS FOLLOWING TREATMENT:

Physician reported complications from primary cryosurgery can be divided into short-term and long-term complications. Short-term complications include acute urinary retention that usually persists for up to two weeks postoperatively.[20] Urinary retention can occur in up to 17% of patients and can be treated with a suprapubic or Foley catheter.[36,20] Penile and/or scrotal swelling is common in the first two weeks post-procedure but is typically self-limiting.[20]

Long-term complications include incontinence, erectile dysfunction, and urethral sloughing (especially in the post-TURP setting). Urinary incontinence is rare (0-5%) and the vast majority of patients recover within a few weeks.[36] Using a large single-institute database, it was found that argon-based cryosurgery led to a decrease in serious side effects such as incontinence and fistula formation when compared to the use of nitrogen-based cryosurgery.[37] While erectile dysfunction can occur in 0-46% of patients, baseline function and ablation template are the most significant predictive factors for postoperative erectile dysfunction.[36] The reported incidence of urethral sloughing despite use of urethral-warming catheters ranges from 0-15%.[20]

In a 2014 prospective study of n=108 patients with localized prostate cancer treated by primary whole-gland cryoablation, Rodríguez et al (2014) observed incontinence in 5.6% of the patients, urinary tract obstruction in 1.9%, urethral sloughing in 5.6%, hematuria in 1.9%, perineal pain in 11.1%, and prostatorectal fistula in 0.9%. An overall impotence rate of 98.1% was reported, although 62% of the patients had erectile dysfunction before treatment.[22]

Khan et al (2023) performed a retrospective study of n=163 patients. During the medium follow-up period of 39 months, of patients who underwent focal cryoablation, only 3.1% reported erectile dysfunction and only 1.8% reported urinary incontinence.[5]

Overall, the safety profile following focal cryotherapy is very good in experienced hands.

Salvage Treatment

Salvage focal cryotherapy may be a useful option for many patients interested in minimally-invasive treatment for prostate cancer recurrence after prior radiation therapy. There may be an advantage to cryotherapy over HIFU in the salvage setting especially with prior prostate brachytherapy or in the presence of significant post-radiation intraprostatic calcifications, which can create acoustic shadowing and even reflection of sound waves that create dangerous “pre-focal heat” during salvage HIFU. Chin and Lynn (2022) performed a systematic review of focal and salvage cryotherapy and assessed post-procedural complications in the salvage setting. They found that in five studies, reported erectile dysfunction ranged from 25.0-86.2% and urinary retention ranged from 2.13-25.3%. In four studies, reported recto-urethral fistulas ranged from 1.27-3.7%. In two studies, reported pelvic perineal pain ranged from 10.71-31.25%.[38] It should also be noted that within this systematic review, it was reported that approximately one-third of patients had recurrent disease after primary external beam radiation therapy (63% of recurrences) or primary radical prostatectomy (20% of recurrences).[39]

1. POST-RADIATION RECURRENCE

Although there are multiple alternatives for salvage treatment, many patients with cancer recurrence following radiation therapy receive palliative care with androgen deprivation therapy. Salvage radical prostatectomy is the most established salvage treatment; however, it has a significant morbidity rate. Salvage cryoablation following radiation therapy is a promising alternative with lower morbidity to patients.[40] Cryoablation of radiation-resistant cancer may be a suitable option for patients with recurrent and residual localized disease. In patients with biochemical recurrence, cryoablation offers a salvage treatment option with the dual objectives of disease cure and functional preservation in the domains of urinary continence and erectile function, in contrast to other salvage treatment modalities such as salvage radical prostatectomy, which carries the almost universal risk of erectile dysfunction and high rates of stress incontinence, not to mention high positive surgical margin rates.[41-42] However, one must consider the nature of post-radiation recurrent prostate tumors, including site, size, and multifocality as evidenced by mpMRI and post-radiation biopsy, along with

pathology. Proper patient selection for focal therapy in this setting is paramount.

Bilateral, high-grade, large, and bulky tumors pose a challenge to focal cryoablation.[43] In a study by Leibovici et al, of the patients who underwent primary radiation therapy and subsequent salvage radical prostatectomy, one-third of patients had multifocal recurrence, 74% of patients had bilateral recurrence and 74% of tumors were 5 mm from the urethra.[43]

a. Whole-gland salvage cryotherapy

Ghafar et al (2001) performed salvage cryosurgery on n=38 men with recurrent prostate cancer following failed radiation treatment.[44] All patients had biochemical disease recurrence, a positive biopsy, and no metastatic disease by conventional staging imaging (i.e., CT scan and bone scan). All patients underwent three months of NADT before cryotherapy. Median follow-up time was 20.7 months. BRFS at 1 year was 86% and at 2 years was 74%. Complications following treatment were as follows: 39.5% rectal pain, 2.6% urinary tract infection, 7.9% incontinence, 7.9% hematuria, 10.5% scrotal edema. No patients (0%) had rectourethral fistula, urethral sloughing, or urinary retention.[44]

Other studies to note involved post-radiation salvage therapy with whole-gland cryoablation. In a study by Wenske et al in 2013, it was found that post-radiation whole-gland cryoablation had a BCRF survival rate of 63% at the 5-year mark, and 37% at the 10-year mark.[45] Out of the 328 patients that were involved in the study, 11 experienced a second failure after radiation treatment (RT) and salvage cryotherapy (SC), and 20 patients (49%) experienced recurrence at the 20-month mark. Failure was defined using the Phoenix definition, in addition to other evidence (i.e. radiographic) of recurrence.[45] Other oncologic outcomes included 5- and 10-year disease-free survival of 47% and 42%, respectively, disease-specific survival of 100% and 83%, and overall survival of 87% and 81%.[45]

A study by Spiess et al in 2013 assessed the variables predicting BPFS after salvage prostate whole-gland cryotherapy. It was found that the nadir PSA after salvage cryotherapy and pre-salvage biopsy Gleason score best predicted BPFS. More specifically, a pre-cryoablation biopsy Gleason score of 7 or above and post-cryoablation PSA nadir of over 2.5 ng/mL were risk factors for salvage whole-gland cryotherapy failure. In addition, it was noted that the BRFS rate at the 5-year mark was 45.5%.[46]

Additional risk factors for failure that were noted from the Cryo On-Line Database (COLD) registry included a biopsy with a Gleason score over 8, prostate tumor stage of cT3-4, castrate-resistant prostate cancer and a pre-cryotherapy PSA value of over 10 ng/m.[7] In an earlier study by Spiess et al in 2013, risk for failure criteria was defined as a pre-cryotherapy PSA level of over 5 ng/mL. In this study, oncologic efficacy rates were divided into patients with a pre-salvage PSA level under 5 ng/mL and those patients whose pre-salvage PSA level was above 5 ng/mL. It was found that BDFS at the 5-year mark was 78.3% for PSA < 5 ng/mL and 52.9% for PSA > 5 ng/mL.[47]

Recent advances in technology have reduced the complication rates associated with salvage cryosurgery following external beam radiotherapy treatment (EBRT). Despite these improvements, pain and incontinence rates in the salvage setting have been reported to be higher than in patients who underwent primary cryosurgery.[20,48] Complications have also been attributed to retraumatization of previously damaged tissue.[48] Patients with initial clinical stage T1-2N0M0 disease and PSA of < 10 ng/ml are better candidates for salvage whole-gland cryotherapy for locally recurrent prostate cancer after EBRT. These patients have higher rates of negative biopsies following salvage treatment.[48] Additionally, to maximize the potential success of salvage cryotherapy, two freeze-thaw cycles and at least 5 cryoprobes should be utilized in treatment.[49]

The outcomes of salvage whole-gland cryoablation provide a benchmark to which we can compare outcomes from salvage focal cryoablation studies.

b. Focal salvage cryotherapy

In a study of n=100 patients with biopsy-confirmed recurrent prostate cancer, Ismail et al (2007) examined the use of targeted cryoablation of the prostate for recurrence of localized prostate cancer following radiotherapy.[50] The patients were separated into three risk-stratified groups with 68 high-risk patients, 20 intermediate-risk patients, and 12 low-risk patients. PSA of <0.5 ng/mL and the ASTRO definition for biochemical failure were used to determine BRFS. At 5-year follow-up, BRFS was 73%, 45%, and 11% for low-, intermediate-, and high-risk groups, respectively. Complications associated with treatment included incontinence in 13% of patients, erectile dysfunction in 86% of patients, lower urinary tract symptoms in 16% of patients, prolonged perineal pain in 4% of patients, urinary retention in 2% of patients, and recto-urethral fistula in 1% of patients. The researchers concluded that cryoablation is a safe and effective

salvage treatment for radio-recurrent prostate cancer.[50] However, if erectile function is of strong importance to a patient, they must weigh this in their choice of treatment.

Using the COLD registry, Li et al (2015) looked at salvage focal cryoablation for locally recurrent prostate cancer in n=91 patients and found it to be an effective treatment option.[51] The study considered all patients regardless of neoadjuvant hormone ablation status. At 1, 3, and 5 years, the biochemical free survival rates were 95.3%, 72.4%, and 46.5%, respectively. Biochemical failure was defined using the Phoenix definition (nadir + 2 ng/ml). Local failure was observed in 4 out of 14 patients (28.6%) who underwent biopsy following salvage treatment. Urinary retention post catheter removal was observed in 6 patients (6.6%), and 1 patient (1.1%) required transurethral resection to remove sloughed tissue. Rectourethral fistula was observed in 3 patients (3.3%). Incontinence was defined as requiring the use of pads, and potency was defined as having the ability to have intercourse. The 12-month incontinence rate was reported in 5 patients (5.5%), and of 20 patients reporting potency pre-salvage treatment, 10 (50%) remained potent post-treatment.[51]

A retrospective, single-institute review of n=65 patients examined whether salvage focal cryotherapy could delay the use of androgen deprivation therapy.[52] The primary treatment for 86.2% of patients was radiation therapy, and 63.1% had no prior history of androgen deprivation therapy. At 1- and 3-year follow-up, survival analysis showed a biochemical free survival rate of 48.1%. By the time the study was published, 52 patients (80%) had not received androgen deprivation therapy after receiving salvage treatment. Eight patients (12.3%) experienced complications: 3 (4.1%) has urethral strictures; 3 (4.1%) had prolonged catheterization (>4 days); 4 (6.1%) reported having incontinence; and 14 (21.5%) reported erectile dysfunction.[52]

These studies reveal that salvage focal cryotherapy following radiation as primary treatment is accompanied by relatively low complication rates and majority positive oncologic outcomes.

2. POST-PRIOR FOCAL ABLATION RECURRENCE

Focal ablation has shown promise in decreasing recurrence rates with some studies reporting biopsy-free recurrence rates of 60-94%.[53] It was noted that for cases of recurrence, the identified areas were often in untreated areas of the prostate.

Aminsharifi et al (2019) performed a retrospective study of n=108 patients who had previous cryotherapy followed by local recurrence, proven by a biopsy.[54] The patients underwent salvage cryotherapy, either whole-gland or focal, based on the distribution of positive cores from the biopsy and considering the maximization of oncologic control and minimization of therapeutic harm. 53.7% of patients received either androgen deprivation therapy (ADT) (32.4%) or radiotherapy (21.3%) before salvage treatment. The salvage treatment was performed between 4-42 months after primary treatment. Using the Phoenix criteria, biochemical recurrence rates were 28.2% and 48.3% after 2 and 5 years, respectively. ADT or radiotherapy between cryotherapies, or the use of focal vs. whole-gland were not significant predictors of biochemical recurrence. D'Amico risk group was the only factor associated with biochemical recurrence. One year after the second cryoablation, urinary incontinence was reported in 7.4% of patients. Persistent incontinence was much higher for patients with radiation between the cryotherapy treatments (21.7% vs. 3.5%). After both cryotherapy treatments, only 13.8% of patients could have spontaneous or medication-assisted erections suitable for intercourse. A total of 3.7% of patients had temporary urinary retention. Rectourethral fistula was reported in 3.7% of patients, all of whom received whole-gland treatment and had high risk disease.[54]

Similarly, Chang et al (2015) performed a retrospective study of n=12 patients who received salvage cryotherapy for locally recurrent prostate cancer following primary cryotherapy.[55] Prior to salvage cryotherapy, patients had a median PSA level of 2.5 ng/ml. Following salvage cryotherapy, patients had a median PSA nadir of 1.32 ng/ml. Two patients received hormonal therapy following salvage cryotherapy, while two patients received repeat cryoablation. After salvage cryosurgery, one patient suffered from mild incontinence, one patient suffered from urethral sloughing, and two patients suffered from transient impotence. Taken together, these results reveal that the use of salvage cryotherapy is safe and effective for recurrent prostate cancer following failed primary cryoablation. Salvage cryotherapy also allowed for hormonal therapy to be delayed.[55]

3. POST-HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) RECURRENCE

High-intensity focused ultrasound (HIFU) is a treatment method that utilizes local ablative techniques to treat disease in a minimally invasive

setting. Tissue damage is induced by heating the target area up to 60-90 degrees Celsius. As a result, patients are more at risk for secondary damage to high temperatures, especially in the setting of excessive pre-focal heat created by acoustic reflection from intraprostatic calcifications or brachytherapy seeds. HIFU is typically considered a non-invasive ablative therapy and can be used in either the whole-gland or focal settings.[56] The literature is sparse in terms of salvage cryoablation following failed HIFU, perhaps given the possibility of repeating the HIFU rather than selecting a new modality in the setting of disease persistence or recurrence. Again, however, prostate calcifications post-primary HIFU ablation, which distort the ultrasound image due to post-acoustic shadowing, and more concerningly, reflect the ultrasound waves and generate excessive pre-focal heat, may preclude the ability to repeat the HIFU. Another study reported urinary tract infections in 11.3% of patients who underwent salvage focal cryotherapy for recurrence post-HIFU.[57] The literature contains little discussion on salvage cryotherapy post-HIFU, possibly because HIFU is also commonly used as a salvage treatment. This gap in literature is crucial to pursue in future research.

4. SALVAGE WHOLE-GLAND VS. PARTIAL GLAND CRYOABLATION

Salvage cryotherapy is used for local recurrences after primary radiation, HIFU, or ablative therapy. It provides similar oncological outcomes as salvage radical prostatectomy and whole-gland ablative treatment and causes less morbidity than whole-gland treatment.[58-59] In a small retrospective study of n=11 patients who received salvage partial gland cryoablation without androgen deprivation therapy, failure-free survival was 100%, 80%, and 40% at 12, 24, and 36 months, respectively, whereas metastasis-free survival was 100%, 75%, and 50% at 12, 24, and 36 months, respectively.[59] In a study of n=110 patients treated with salvage whole-gland cryoablation from 2002-2019, Tan et al (2023) observed BRFS of 85%, 81%, 79%, 75%, 71%, and 67% at 12, 24, 36, 48, 60, and 72 months, respectively.[60] The trend points to decreasing recurrence-free survival over time for salvage whole-gland cryoablation. Using multivariable Cox hazards analysis, researchers found that pre-cryoablation PSA of 4-10 ng/dL (HR 2.10, 95% CI 1.00-4.41) and PSA of > 10 ng/dL (HR 4.26, 95% CI 1.35-13.40) were associated with lower BRFS. A PSA nadir of > 0.5 ng/ml eventually led to biochemical recurrence in all patients.[59]

In a retrospective review using the COLD Registry, Tan et al (2020), found that n=72 patients treated with salvage focal cryotherapy (SFC) had no statistical difference in 2-year progression-free survival and post-treatment biopsy cancer control rates compared with patients treated with salvage total cryoablation (STC; n=313) after biopsy-proven radiation therapy-resistant disease.[61] In contrast, patients treated with SFC had a lower risk of urinary retention compared with STC.[61] The COLD registry data did not capture imaging, therefore the study authors could not determine factors that influenced clinicians' decision to treat with SFC versus STC. These results suggest that oncologic outcomes for salvage whole-gland and focal cryotherapy are similar, but morbidities are lower for focal treatment.

The results from the salvage focal cryoablation studies are summarized in tables 3a and 3b below.

Comparisons to Other Treatments

In general, focal therapies provide a better quality of life than whole-gland treatment.[62,36] When comparing focal treatment modalities, HIFU and cryoablation have the highest quality data available.[62,53] In a systematic review of focal therapies in the primary treatment of prostate cancer, Hayes et al (2021) found that intermediate-term (i.e., 5 years) oncologic outcomes, such as metastasis-free and cancer-specific survival, appear promising for HIFU and cryoablation.[63] Functional outcomes have shown promising superiority to those of any form of whole-gland therapy.[63] The authors concluded that patient selection is key. Overall, focal therapies minimize side effects on urinary and sexual function.[62-63] However, the outcomes of focal therapies must be further studied as most of the existing evidence supporting these therapies is heterogeneous, short-term, and with strict inclusion criteria.[62] The outcomes for focal therapies in the salvage setting require further study.[48]

Table 3a. Functional and oncological outcomes for salvage focal cryoablation studies (USA).

References	Institution	Initial therapy (No. of Pts)	Risk Categories	Preprocedural PSA (ng/ml), media-n (IQR)	Mos. Follow-up	Use of ADT, n (%)	Success/failure criteria	% Pos. Biopsy Rate	Urinary incontinence, n (%); erectile function, n (%)
Li et al (2014)	Cleveland Clinic, Cleveland, OH, USA	RT (91)	NR	4.8 (0–92.6)	Median 15	0 (0%)	BDFS at 1-year: 95.3%, 3-year: 72.4%, 5-year: 46.5%	28.6	5 (5.5); 10 (50)
Kongn-yuy et al (2017)	Winthrop University Hospital, Garden City, NY, USA	CR - 8 (12.3%) SR - 5 (7.7) BT - 13 (20.0) PBR - 1 (1.5) RT/other - 37 (57.0) Unknown - 1 (1.5) (n=65)	NR	4.0 (0.01–19.0)	Median 26.6	13, 20%	BR: 52.3%	20	4 (6.1); 14 (21.5)
Tan et al (2021)	Duke University Medical Center, Durham, NC, USA	NR (11)	NR	4.99 (2.23–7.86)	Median 28	0 (0%)	FFS at 12-months: 100%, 24-months: 80%, and 36-months: 40%	27.3	1 (0.1); NR
Tan et al (2020)	Multiple, USA	RT (72)	NR	4 (2.7-5.6)	Median 24.4	19 (26.4%)	BR: 16 of the 72 patients (22.2%)	33.3%	9.3%; 52.6%

RT = radiotherapy; NR = not reported; BRFS = biochemical recurrence free survival; BDFS = biochemical disease-free survival; FFS = failure-free survival; BR = biochemical recurrence; ED = erectile dysfunction; CR = cryotherapy; SR = Stereotactic radiotherapy; BT = Brachytherapy; PBR = proton beam radiation

Table 3b. Functional and oncological outcome parameters for salvage focal cryoablation studies (international).

References	Institution	Initial therapy (No. of Pts)	Risk Categories	Preprocedural PSA (ng/ml), media-n (IQR)	Mos. Follow-up	Use of ADT, n (%)	Success/failure criteria	% Pos. Biopsy Rate	Urinary incontinence, n (%); erectile function, n (%)
Ismael, et al (2007)	The Royal Surrey County Hospital and St Luke's Cancer Centre, Guildford, Surrey, UK.	RT (100)	High: 68, intermedi-ate: 20, low 12	NR	33.5	NR	BRFS at 5-year: 73% (low-risk), 45% (intermediate), and 11% (high)	NR	13, ED: 86
Aminsh-arifi et al (2019)	Multiple (USA, Iran, Egypt)	CR (108)	D'Amico Low: 34 (31.5%), Medium: 40 (37.0%), High: 33 (30.6%), Unknown: 1 (0.9%)	Mean 7.08 (+/- 7.4)	43.1 +/- 40.8 months	35 (32.4%)	BR at 2-year: 28.2%, 5-year: 48.3%	15.7	8 (7.4), 13.8%
Chang et al (2015)	The Affiliated Hospital of Nanjing University Medical School, Jiangsu, China.	CR (12)	NR	2.5 (0.18–7.28)	Median 33.5	3 (25%)	BRFS: 7 (58.3%)	NR	1 (8.3), impotence: 2 (6.6)

RT = radiotherapy; CR = cryotherapy; NR = not reported; BRFS = biochemical recurrence free survival; BDFS = biochemical disease-free survival; BR = biochemical recurrence; ED = erectile dysfunction

In a systematic review, Hopstaken et al (2022) identified 72 studies exploring the use of eight modalities of focal treatment exclusively in the primary setting in n=5,827 patients with localized prostate cancer. The studies included HIFU (n=72), irreversible electroporation (IRE) (n=9), cryoablation (n=11), focal laser ablation (FLA) (n=8), focal brachytherapy (n=8), photodynamic therapy (PDT) (n=7), radiofrequency ablation (n=2), and prostatic artery embolization (n=1).[65] In general, functional outcomes were favorable for all modalities of focal therapy; no significant changes from baseline in urinary incontinence and erection sufficient for intercourse were reported for studies using HIFU, FLA, cryoablation, and PDT.[65] HIFU studies reported a median of 95% pad-free patients and a median of 85% patients with no clinically significant cancer (CSC) in the treated area. PDT studies reported no changes in continence and a median of 90% patients with no CSC.[65] They concluded that, although there is high-quality evidence for superior functional outcomes, definitive proof of the oncological effectiveness of focal therapy against standard of care is still uncertain.[65] Selected studies from the review are summarized in the table below.

Table 4. Functional and oncological outcome parameters for focal primary therapies.[65]

References	Institution	Therapy (No. of Pts)	Risk stratification, n (%)	Preprocess-dural PSA (ng/ml), median (IQR)	Mos Follo w-up	Absence of CSC in treated area, n (%)	Salvage therapy, n (%)	Change in continence, n (%); erectile function, n (%)
Al Hakeem et al, 2019	Macquarie University Hospital, New South Wales, AUS	FLA (n=49)	cT1c-T2a	5.8 (3.1)	18	40/49 (82)	RP: 5 EBRT: 1 FLA: 1	NS; NR
Bass et al, 2019	Multiple, Toronto, Ontario, CA	HIFU (n=150)	Low-intermediate risk	6.4 (4.2–9.1)	24	NR	37 (25)	NC: 131 (94.5); NC: 115 (86.5)
Johnston et al, 2019	Basingstoke and North Hampshire Hospital, UK	HIFU (n=107)	Low: 12% Intermediate: 66% High: 22%	Mean (range): 7.7 (1.2–26.2)	12	NR	RP: 6 (5.6) RT: 4 (3.7) ADT: 2	1 patient (1) new use of pads; NR
Langley et al, 2020	Stokes Centre for Urology, Guildford, UK	Focal BT (n=30)	cT1c: 16 (53.3) cT2a: 6 (20) cT2b: 7(23.3) cTx: 1 (3.3)	Mean (SD): 6.7 (3.1)	24	23/26 (88)	NR	NR; Preserved in 73%
Basourakos et al, 2020	Multiple, USA	CR (n=55)	NR	6.6 (7.7–9.2)	6	NR	RP: 3 RT: 3 Cryo: 5	NR; NR
Shah et al, 2019	Multiple, UK	CR (n=122)	cT2a: 32 (26.2) cT2b: 3 (2.5) cT2c: 60 (49.2) cT3a: 13 (10.7) cT3b: 9 (7.4) Missing: 5 (4.1)	10.8 (7.8–15.6)	Medi an 27.8	NR	RP: 5 RT: 4 Systemic therapy: 4	NR; NS
Noweski et al, 2019	Multiple, EU, CA	PDT (n=68)	NR	5.7	42	NR	RP: 8 Brachy: 5 HIFU: 1	NR; NR

NS = not significant; NR = not reported; NC = no change; ADT = androgen deprivation therapy; CSC = cancer stem cells; RP = radical prostatectomy; RT = radiotherapy; TURP = transurethral resection of the prostate; WG = whole-gland; CR = cryotherapy; BT = Brachytherapy

[65] Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: What has changed over the past 5 years? *European Urology*. 2022;81(1):5-33. doi:10.1016/j.eururo.2021.08.005

Marien, et al (2014) reviewed the literature on various focal therapies in the primary setting, including cryotherapy, HIFU, laser ablation, photodynamic therapy (PDT), radiation, and irreversible electroporation (IRE), to compare oncologic outcomes.[4] Their conclusions found that

each modality had its own advantages and disadvantages, without a definitively superior technology. Cryotherapy has the most literature, HIFU has less, and PDT and laser ablation even less, owing to the novelty of the latter technologies. In comparing focal cryotherapy and focal HIFU, both have limited, and quite similar, morbidity, as summarized in the table below.[4]

Table 5. Morbidity rates for focal cryotherapy and HIFU in the primary setting.[4]

	Potency	**Continence**	**Biopsy-proven recurrence rate**
Cryotherapy	65-90%	95-100%	4-23%
HIFU	95%	90-100%	8-23%

[4] Marien A, Gill I, Ukimura O, Nacim B, Villers A. Target ablation—image-guided therapy in prostate cancer. *Urologic Oncology: Seminars and Original Investigations*. 2014;32(6):912-923. doi:10.1016/j.urolonc.2013.10.014

In a single institutional study from 2009-2018 with n=309 on focal therapy for prostate cancer, Tourinho-Barbosa et al (2020), examined oncologic outcomes in patients treated either with HIFU (n=190) or cryotherapy (n=119).[66] Both focal therapies were mpMRI guided and had a focal therapy extension of a 10 mm margin, reflecting established contemporary treatment guidelines. Cryotherapy was performed using transperineal needles. Surveillance following treatment included assessing oncologic and functional outcomes at 1, 3, and 6 months after treatment, and every 6 months after that. PSA was tested at every visit and mpMRI was taken at one month post-treatment and annually afterward. Patients also received a systematic biopsy at one year post-treatment. If patients had two consecutive PSA rises or suspicious radiographic findings on mpMRI, systematic and targeted biopsies were performed earlier. In such cases, subsequent definitive treatment was offered.[66] Failure was defined as local or systematic salvage treatment, biopsy Gleason score of 7 or greater, prostate cancer metastasis, and prostate cancer-specific mortality. Researchers found no difference in failure-free survival for patients who underwent HIFU versus patients who underwent cryotherapy treatment. Median survival free of radical treatment also showed no difference between patients who received HIFU versus those who received cryotherapy.[66] These comparisons reveal that HIFU and cryotherapy not only have similar rates of morbidities, but also similar oncologic control outcomes.

A study by Donnelly et al (2010) compared disease progression, survival, and post-treatment biopsies following whole-gland cryotherapy versus EBRT in patients with T2-T3 localized prostate cancer.[67] Eligibility criteria also included pretreatment PSA level ≤ 20 ng/mL and gland volume ≤ 60 cc. Patients in both the cryotherapy and EBRT conditions also received 6 months of neoadjuvant androgen deprivation therapy (NADT). At 36 months, disease progression was similar in the two groups: 23.9% in patients who received cryoablation and 23.7% in patients who received EBRT. There was no observed difference between the treatment groups for overall or disease-specific survival. At 36 months, 28.9% of patients who received EBRT had cancer-positive biopsies compared to 7.7% of patients who received cryoablation. Furthermore, at 84 months, biochemical failure was lower in patients who received cryotherapy, and at five years, overall and disease-specific survival were higher in cryotherapy patients.[67] These results tend to suggest that cryotherapy has better oncologic outcomes compared to EBRT. However, these results are not specific to focal cryotherapy, so further research to compare focal cryotherapy to EBRT is crucial.

Considerations for Neoadjuvant Androgen Deprivation Therapy (NADT)

NADT has been incorporated as standard of care for treatment of unfavorable-intermediate and high-risk patients when combined with radiation therapy. There is a synergistic mechanism of action based on the androgen-mediated basis of DNA damage repair (homologous recombination repair): radiotherapy induces double-stranded DNA breaks, and in the castrate-state, the affected cell is unable to repair these breaks, so it undergoes apoptosis. The role of androgen suppression in the setting of an ablative technology with direct tissue destruction, rather than inducing DNA-damage and subsequent metachronous apoptosis, is unclear, and may not make mechanistic sense. In fact, the literature contains mixed results on the use of NADT with cryotherapy: some seem to support its use, showing beneficial oncologic outcomes, while others seem to suggest the opposite. Furthermore, all series included patients with whole-gland salvage, rather than focal, cryoablation.

The study by Ghafar et al (2001) examined the use of salvage cryosurgery following radiorecurrent prostate cancer.[44] All patients in the study underwent three months of NADT before cryoablation. Limited morbidity and complications post-treatment, including no reported cases of

rectourethral fistula, urethral sloughing, or urinary retention, support the use of NADT prior to cryotherapy.[44]

Grossgold et al (2014) retrospectively compared risk-stratified groups based on whether patients received NADT before primary whole-gland cryotherapy.[68] Results showed that there was no difference in fistula, incontinence, pad use, or potency when comparing each group. For those who did not receive NADT, urinary retention at 12 months was slightly lower. There was also no difference in BDFS (using the Phoenix criteria). At five years, the group with NADT had 66.9% disease-free survival while the non-NADT group had 66.5% (non-significant). However, when stratified by risk category, there was a difference in the NADT and non-NADT groups: for intermediate risk patients, BDFS at five years was 71.3% for the NADT group and 65.9% for the non-NADT group. Therefore, the results do not support using NADT for men undergoing primary whole-gland cryotherapy but could be used for men with larger prostates and in intermediate risk groups. The study showed that the use of NADT over 3-6 months can help shrink the size of the prostate, allowing for better freezing capacity of the cryotherapy probes, given that their freezing capacity is 2 cm.[68] While this study is not specific to focal cryotherapy, the necessity of gland volume reduction prior to therapy is not as clear.

Taken together, the conflicting results of NADT with whole-gland cryotherapy show that further research must be done to clarify the relationship between NADT and focal cryotherapy.

Future Directions

Experts have postulated that in order for cryotherapy to become a commonly used treatment for prostate cancer, consensus must be established regarding patient selection criteria, suitable treatment margins, role and accuracy of post-ablation imaging, and definitions of success/failure (including how to classify out-of-field de novo disease).[69,65] Without these optimized criteria, it remains difficult to synthesize all of the existing literature into a cohesive conclusion about the oncologic merits and limitations of focal cryotherapy in the primary and salvage setting, although the safety profile is favorable.

A recent study by Moreira et al (2023) may bring the field in the right direction by fine-tuning ablation margins.[70] In their study, researchers presented an artificial intelligence (AI) model to predict cryo-needle placement during treatment. Using algorithms based in deep learning models, researchers yielded accurate, real-time boundaries for optimal visualization of the ice ball. The study yielded other promising results such as tissue volume prediction in 0.4 seconds and prediction of ice ball boundaries with more accuracy than the conventional geometric model.[70] Further research could utilize this AI technique and measure the effects it has on oncologic outcomes following focal cryoablation.

In terms of the treatment itself, SpaceOAR are hydrogel spacers that can be used to limit toxic exposure during treatment. Using the guidance of a transrectal ultrasound, a needle is inserted into the space between the prostate and rectum and injects a sterile saline to hydro-dissect the area. Two solutions are mixed and injected simultaneously into the space. Upon the mixing of the solutions, they form a solid hydrogel which stays intact for 3 months, but slowly turns to liquid through hydrolysis afterward.[71]

It would be interesting to investigate whether there is any added benefit to using hydrogel spacers during or prior to planned cryotherapy treatment to limit damage to the rectum and especially to reduce the dreaded complication of rectourethral fistula. Impairment in intraoperative ultrasound visualization due to intra-gel trapped foci of air may limit the role of this technology in the synchronous setting, however. This is one domain where such hydrogel technology is applicable, in contrast to salvage HIFU, where the hydrogel would create dangerous pre-focal heat and increase morbidity.

In addition to optimization of the parameters listed above, future research should examine the role of salvage cryotherapy for recurrent prostate cancer post-HIFU treatment as well as the role of NADT.

Conclusion

Focal cryotherapy is a relatively novel application of a well-established and well-studied treatment modality that is especially exciting in the modern area of focal ablation for prostate cancer. It can be utilized to treat patients with focal prostate cancer lesions that are radiologically visible, and with absence of other clinically significant disease on systematic biopsies. The use of focal cryoablation as a primary treatment has shown promising oncologic outcomes, similar to that of whole-gland cryoablation, but with better functional outcomes. Focal cryotherapy as a salvage treatment has mixed results regarding efficacy and warrants further study. When compared to other focal treatments, cryotherapy leads to similar, or better, oncologic control outcomes. The use of NADT with cryotherapy may lead to better oncologic outcomes, but these results must be validated in future research.

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