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Cryosurgical Ablation of the Prostate

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Related Policies (if applicable)
None

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Coverage

Whole gland cryosurgical ablation of the prostate **may be considered medically necessary** as treatment of clinically localized (organ-confined) prostate cancer when performed as:

- Initial treatment; **OR**
- Salvage treatment of disease that recurs following radiation therapy.

Subtotal cryosurgical ablation of the prostate **is considered experimental, investigational and/or unproven** in the treatment of prostate cancer.

Policy Guidelines

None.

Description

Prostate cancer is the second most common cancer diagnosed among men in the United States (U.S.). According to the National Cancer Institute, nearly 288,300 new cases are estimated to be diagnosed in the U.S. in 2023, associated with around 34,700 deaths. (1) Prostate cancer is more likely to develop in older men and in non-Hispanic Black men. About 6 in 10 cases are diagnosed in men who are ≥65 years of age, and it is rare in men <40 years of age. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era identified incidental cancerous foci in 30% or men 50 years of age, with incidence reaching 75% at age 80 years. (2) However, the National Cancer Institute Surveillance Epidemiology and End Results Program data have shown that age-adjusted cancer-specific mortality rates for men with prostate cancer declined from 40 per 100,000 in 1992 to 19 per 100,000 in 2018. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Cryoablation

Cryoablation, also known as cryotherapy or cryosurgery, is a procedure that attacks cancer cells using extremely cold gas. This technique can be used to treat prostate cancer by percutaneously inserting thin, needle-like cryoprobes into the prostate gland and then sending very cold gas down the cryoprobes to rapidly freeze and thaw the tissue, causing necrosis.

Treatment

Whole Gland Cryoablation of Prostate Cancer

Whole gland (also known as total) cryoablation is one of several methods used to treat clinically localized prostate cancer and may be considered an alternative to radical prostatectomy or external-beam radiotherapy (EBRT). Additionally, whole gland cryoablation may be used for salvage of nonmetastatic relapse following initial therapy for clinically localized disease. Using percutaneously inserted cryoprobes, the glandular tissue is rapidly frozen and thawed to cause tissue necrosis. Cryosurgical ablation is less invasive than radical prostatectomy and recovery time may be shorter. External-beam radiotherapy requires multiple treatments, whereas cryoablation usually requires a single treatment.

Subtotal Prostate Cryoablation (Focal Treatment) for Localized Prostate Cancer

Subtotal prostate cryoablation is also being evaluated as a form of more localized therapy (referred to by some as focal or organ-preserving therapy or male lumpectomy) for small localized prostate cancers. Focal treatment seeks to remove cancerous lesions at high-risk of progression, leaving behind uninvolved glandular parenchyma. The overall goal of any focal treatment is to minimize the risk of early tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum. (3-7) Although focal treatments are offered as an alternative middle approach to manage localized prostate cancer, several key issues must be considered in choosing it. These include patient selection, lesion selection, therapy monitoring, and modalities used to ablate lesions.

Regulatory Status

Cryoablation of prostate cancer is a surgical procedure that uses previously approved and available cryoablation systems; as a surgical procedure, it is not subject to regulation by the U.S. Food and Drug Administration.

Some cryoablation devices cleared by the FDA through the 510(k) process for cryoablation of the prostate include Visual-ICE (Galil Medical), Ice Rod CX, CryoCare® (Galil Medical), IceSphere (Galil Medical), and Cryocare® Systems (Endocare®; HealthTronics). FDA product code: GEH.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Primary Prostate Cryoablation

Clinical Context and Therapy Purpose

The purpose of whole gland cryoablation in individuals considered initial treatment for localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals considering initial treatment for localized prostate cancer.

Interventions

The intervention of interest is cryoablation of the whole prostate gland. Cryoablation uses freezing to destroy tumor cells in a relatively noninvasive procedure, which can be conducted under spinal anesthesia.

Comparators
The following therapies and practices are currently being used to make decisions about localized prostate cancer: radiotherapy, radical prostatectomy, and active surveillance.

Outcomes
The general outcomes of interest are overall survival (OS), disease-free survival, cancer recurrence, and treatment-related adverse events (e.g., sexual dysfunction, incontinence). Follow-up for treatment-related morbidity is months post-procedure. The follow-up to monitor for recurrence is measured in years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Gao et al. (2016) reported the results of a systematic review and meta-analysis comparing cryoablation with radiotherapy and radical prostatectomy for the treatment of localized prostate cancer. (8) The search included articles published up to December 2015. Because the pooled estimates combined primary and salvage treatment, the individual studies are presented in the following sections in lieu of pooled data here. Six studies described primary treatment (including the 2 RCTs described below, [9-11] 2 prospective observational, [12, 13] and 2 retrospective [14, 15]). Cryotherapy had a similar OS and disease-specific survival rate as radiotherapy and radical prostatectomy in trials of primary treatment. There was significantly more sexual bother for cryoablation (compared with radiotherapy) at all times reported ($p<0.01$).

A meta-analysis by Deivasigamani et al. (2023) evaluated the efficacy and safety of primary whole gland cryoablation and high-intensity focused ultrasound for the treatment of local prostate cancer. (16) Evidence through 2022 was included. This analysis incorporated evidence from 1 RCT and 13 retrospective or prospective studies that reported on biochemical recurrence-free survival (BCRFS), recurrence-free survival, metastasis-free survival, disease-specific survival, OS, and the incidence of major adverse events through 5 years of follow-up. The median sample size was 226.5 (range, 75 to 2166) with a median follow-up of 65 months

(range, 60 to 147 months). The included patients had a median age of 70 years with mean PSA values of 8.2 ng/mL. At 5 years follow-up the rate of OS was 91% (95% CI, 87 to 94; I^2, 69%). Metastases-free survival was 93% (95% CI, 86 to 97; I^2, 73%) and disease-specific survival was 98% (95% CI, 96 to 99; I^2, 75%). The pooled frequency of BCRFS at 5 years was 64% (95% CI, 53 to 74; I^2, 97%) with recurrence-free survival rates ranging from 69% to 83%. Adverse events were less uniformly reported, but events reported by more than one study included urinary retention (6%; 95% CI, 3% to 13%; I^2, 93%) and rectourethral fistula (0.8%; 95% CI, 0.5 to 1.2; I^2, 0%). Unassisted erectile function was reported by a mean of 23% (95% CI, 9% to 48%; I^2, 94%) of participants after cryoablation. The authors compared the safety and efficacy of cryoablation to high-intensity focused ultrasound in a meta-regression and found that the therapies appeared similar for the above outcomes at 5 years follow-up for the treatment of localized prostate cancer.

Randomized Controlled Trials

Chin et al. (2008, 2012) reported on a randomized trial comparing cryoablation with EBRT in patients who had clinical stage T2C-T3B prostate cancer. (9, 10) These patients had node-negative disease and had received 6 months of hormonal therapy, starting 3 months before treatment. Only 64 of the planned 150 patients were accrued; entry was limited due to changes in practice and difficulty beginning cryoablation at one of the sites. Twenty-one (64%) of 33 in the cryoablation group and 14 (45%) of 31 in the EBRT-treated group were classified as treatment failures. The mean biochemical disease-free survival (bDFS) was 41 months for the EBRT group and 28 months for the cryoablation group. The 4-year bDFS rate for the EBRT and cryoablation groups were 47% and 13%, respectively. (9) The 8-year bDFS rate for the EBRT and cryoablation groups were 59.1% and 17.4%, respectively. Disease-specific survival rates and OS rates were very similar and, at the 8-year follow-up, the rates still did not differ significantly. (10) Serious complications were uncommon in both groups. EBRT patients exhibited adverse GI effects more frequently. The trialists concluded that taking into account the relative deficiency in numbers and the original trial design, this prospective randomized trial indicated that the results of cryoablation were less favorable than those of EBRT and that cryoablation was suboptimal primary therapy in locally advanced prostate cancer.

Donnelly et al. (2010) reported on a randomized trial of 244 patients with newly diagnosed localized prostate cancer, during the period from 1997 through 2003, to compare cryoablation with EBRT. (11) All patients began neoadjuvant androgen-deprivation therapy (ADT) before local treatment and continued for a period of 3 to 6 months. The median follow-up was 100 months. At 36 months, the biochemical failure rate (PSA nadir + 2 ng/mL) was 17.1% in the cryoablation group and 13.2% in the radiotherapy group. The OS rate at 5 years was 89.7% in the cryoablation group, and 88.3% in the radiotherapy group (p=0.78). At 36 months, radiotherapy patients had significantly more positive prostate biopsies (22/76 patients) than the cryoablation group (7/91 patients; p<0.001). Observed failure rates at 60 months were similar in both groups but were less likely with cryoablation at 84 months. Using the National Cancer Institute of Canada Common Toxicity Criteria, 12 cryoablation patients experienced 13 grade 3 adverse events versus 16 grade 3 adverse events in 14 radiotherapy patients. Urinary retention was the most common grade 3 adverse event in both treatment arms. The trialists

were unable to establish that cryoablation was noninferior to radiotherapy at 36 months due to the wide confidence interval. The trialists also noted several issues that limited interpretation of trial results, including the use of uncommonly low radiation dosages (68 gray, 70 gray, 73.5 gray, respectively), and early trial closure due to lack of patient enrollment.

In a second article from the Donnelly et al. (2010) trial, (11) Robinson et al. (2009) reported on QOL outcomes in the same 244 patients. (17) With few exceptions, study participants reported QOL at high levels in both the cryoablation and radiotherapy treatment arms. Acute urinary dysfunction, which eventually resolved, occurred more often with cryoablation, as measured using the University of California at Los Angeles Prostate Cancer Index (mean urinary function after cryoablation was 69.4 vs 90.7 after EBRT; $p<0.001$; higher scores indicate better function and less bother). The University of California at Los Angeles Prostate Cancer Index sexual function decreased in both arms at 3 months. However, reduced sexual function was reported more frequently in the cryoablation arm (mean cryoablation, 7.2 versus mean EBRT, 32.9; $p<0.001$). Decreased sexual function continued at the 3-year evaluation, with the mean score 15 points lower in the cryoablation group.

Nonrandomized Comparative Studies

Many nonrandomized studies have assessed cryoablation for localized prostate cancer. (12-15, 18-27) A sample is discussed here.

Aus (2008) reported that cryoablation using third-generation equipment and that long-term follow-up from these newer devices, which emerged around 2000, would be needed. (28) The newer devices use more ultra-thin probes and argon gas (as opposed to liquid nitrogen) and create smaller ice balls. Lian et al. (2011) reported on early results of cryoablation using third-generation technology as a primary treatment for 102 patients with localized prostate cancer during the period of 2006 through 2009. (29) Only one patient developed biopsy-confirmed prostate cancer recurrence. The PSA levels were elevated in 7 patients; however, biopsies were negative. Mild incontinence, urethral sloughing, and erectile dysfunction occurred in 4%, 4.9%, and 64% of patients, respectively.

Ball et al. (2006) reported on QOL outcomes on a subset of 719 patients with localized prostate cancer treated with various techniques including cryosurgical ablation. (12) The authors reported that, in an older population, the tissue destruction resulting from cryoablation appeared to relieve obstructive and irritative urinary symptoms but at the sacrifice of sexual function compared with palladium 103 brachytherapy.

Registry Studies

Williams et al. (2012) compared data from the U.S. Surveillance, Epidemiology, and End Results Medicare-linked data on 10,928 patients with localized prostate cancer treated with primary cryoablation or brachytherapy. (30) Urinary and erectile dysfunction occurred significantly more frequently after cryoablation (41.4% and 34.7%) than brachytherapy (22.2% and 21%), respectively. Androgen-deprivation therapy was also used significantly more often after cryoablation than after brachytherapy, suggesting a higher rate of recurrence after cryoablation

(1.4 vs 0.5 per 100 person-years). Bowel complications, however, occurred significantly more frequently with brachytherapy (19%) than cryoablation (12.1%).

The Cryo Online Data Registry is a database established and supported by a cryoablation manufacturer. The data are maintained independently. Physicians submit standardized forms to the database and participation is voluntary. The Registry contains case report forms of pretreatment and posttreatment information for patients undergoing whole gland or partial gland (focal) prostate cryoablation. Patients are stratified into low-, intermediate-, and high-risk groups. Jones et al. (2008) reported the initial outcome for 1198 men with primary whole gland prostate cryoablation. (31) Mean follow-up was 24.4 months; 136 men had 5-year data. The 5-year bDFS rate (Phoenix definition) for the entire population was 73%; rates by category were 91%, 79%, and 62%, for the low-, intermediate-, and high-risk groups, respectively. The rectal fistula rate was 0.4%. Incontinence was reported by 5% of men, with 3% of men using pads. Twenty-five percent of men reported having sexual intercourse, but only 9% did so without pharmaceutical or device assistance. Outcomes for 300 men in the Cryo Online Data Registry who underwent primary whole gland cryotherapy for high-grade (Gleason score ≥8), localized prostate cancer were published by Tay et al. (2016). (32) Mean follow-up was 28.4 months. The estimated 2- and 5-year bDFS rates were 77% (95% CI, 71% to 88%) and 59% (95% CI, 50% to 67%), respectively. At 12-month follow-up, complete continence was reported by 91% of men and potency by 17% of men. The incidence of recto-urethral fistulae was 1.3%. Urinary retention requiring intervention beyond temporary catheterization was reported by 3% of men.

Section Summary: Primary Prostate Cryoablation

Evidence for the use of whole gland cryoablation to treat localized prostate cancer comes from systematic reviews, 2 RCTs, and many comparative and noncomparative observational studies. The most recent systematic reviews have reported similar OS and disease-specific survival rates for whole gland cryoablation compared with radical prostatectomy and EBRT.

Salvage Prostate Cryoablation

Clinical Context and Therapy Purpose

The purpose of whole gland cryoablation in individuals who have recurrent localized prostate cancer following radiotherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals in need of salvage treatment for recurrent localized prostate cancer after radiotherapy.

Interventions

The intervention of interest is cryoablation of the whole prostate gland. Cryoablation uses freezing to destroy tumor cells in a relatively noninvasive procedure, which can be conducted under spinal anesthesia.

Comparators
The following therapies and practices are currently being used to make decisions about recurrent localized prostate cancer: radical prostatectomy and brachytherapy.

Outcomes
The general outcomes of interest are OS, disease-free survival, cancer recurrence, and treatment-related adverse events (e.g., sexual dysfunction, incontinence). Follow-up for treatment-related morbidity is months post-procedure. The follow-up to monitor for recurrence is measured in years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
The health technology assessment by Ramsay et al. (2015), (33) identified 2 single-arm studies (Chin et al. [2001] [34]; Robinson et al. [2006] [35]) assessing salvage whole gland cryoablation. One study reported 1- and 4-year bDFS rates of 71% and 54%, respectively. Both reported functional outcomes. With a median follow-up of 19 months, the incontinence rate was 20%, bladder neck stenosis rate was 25%, and the recto-urethral fistula rate was 3%. The sexual dysfunction rate was 69% at 1 year, and 52% at 2 years.

Mouraviev et al. (2012) reviewed the literature published between 1991 and 2012 to compare salvage cryoablation for radio-recurrent prostate cancer with other salvage treatments. (36) Reviewers found comparisons difficult to make because no prospective, randomized studies were identified and PSA failure was defined variously. However, they noted that studies had reported salvage cryoablation outcomes as being comparable to those for salvage radical prostatectomy (for an intermediate term). The following criteria were identified as favorable prognostic factors for defining patients for salvage cryoablation: a PSA level less than 10 ng/mL, a Gleason score 8 or less, and a clinical stage T1c or T2 before salvage cryoablation therapy.

Nonrandomized Comparative Studies
Peters et al. (2013) reported on the results of retrospective data from 129 men from 5 Dutch centers. (37) Forty-four men underwent salvage prostatectomy, 54 underwent salvage cryoablation, and 31 underwent salvage brachytherapy. The mean follow-up for each procedure was 29 months, 22 months, and 14 months, respectively. Biochemical failure

occurred in 25 (81%) men in the brachytherapy group, 29 (66%) men in the prostatectomy group, and 33 (61%) men in the cryosurgery group. Severe genitourinary and GI toxicity (grade >3) using the Common Toxicity Criteria for Adverse events (v.3.0), definition was observed in up to 30% of patients in all 3 groups. There were 12 (27%), 5 (9%), and 14 (45%) deaths in the prostatectomy, cryoablation, and brachytherapy groups, respectively.

Case Series
Numerous case series have reported on the effect of salvage cryoablation for locally recurrent prostate cancer. (38-43) As results from these studies are generally consistent, only the most recent and largest studies with the longest follow-up are described below.

Tan et al. (2023) performed a retrospective study of men who received whole-gland salvage cryoablation for locally recurrent prostate cancer following radiotherapy at a single tertiary care center from 2002 to 2019. (38) A total of 110 men met the inclusion criteria and were followed for a mean of 71 months (interquartile range [IQR], 50 to 111 months). The primary outcome was biochemical recurrence-free survival (bRFS) which had rates of 85%, 79%, and 71% at 1-, 3-, and 5-year follow-ups; a univariate analysis suggested that patients with a higher PSA nadir were associated with worse rates of bRFS. Secondary outcomes included metastases-free survival and cancer-specific survival, which showed rates of 71% and 98.8% at 5 years, respectively. American Urological Association (AUA) symptom scores worsened from a baseline score of 7 (IQR, 4 to 11) to 12 (IQR, 7 to 33) with salvage whole gland cryoablation. The International Index of Erectile Function (IIEF-5) showed a similar result with a median score of 5 (IQR, 1 to 15.5) prior to treatment which worsened to 1 (IQR, 1 to 4) after cryoablation. A total of 10 Clavien-Dindo grade 2 complications (2 clot retention, 4 urinary retention,1 urethral stricture, and 3 urinary tract infection) and 3 grade 3a complications (2 osteomyelitis due to pubosymphyseal urinary fistula, and 1 rectal fistula) were reported.

Chin et al. (2021) reported on mortality and morbidity in 268 men from 2 centers who underwent salvage cryoablation for locally recurrent prostate cancer following radiotherapy between 1992 and 2004. (39) Median duration of follow-up was 124 months (IQR, 63 to 167 months). Overall survival rates at 5, 10, and 15 years were 90%, 77%, and 54%, respectively. Corresponding disease-specific survival rates were 94%, 81%, and 70%. Initiation of neoadjuvant ADT during follow-up was associated with significantly better OS (HR, 0.22; 95% CI, 0.10 to 0.46) and disease-specific survival (HR, 0.41; 95% CI, 0.20 to 0.85) relative to no ADT. Development of castration-resistant prostate cancer occurred in 14%, 24% and 26% of men at 5-, 10-, and 15-year follow-up. Incontinence was the most commonly reported adverse event during follow-up, reported by 55% of men, including 38% who reported mild or moderate incontinence and 16% reporting severe incontinence.

Wenske et al. (2013) reported on salvage cryoablation in a series of 396 consecutively treated patients who had failed cryoablation or radiotherapy. (40) Data were analyzed from 328 patients, with a median follow-up of 47.8 months (range, 1.6 to 203.5 months). Fifty-five (16.7%) of these patients received subtotal (focal) salvage cryoablation. At the 5- and 10-year follow-ups, disease-free survival rates were 63% and 35%, disease-specific survival rates were

91% and 79%, and OS rates were 74% and 45%, respectively. After salvage cryoablation, the median PSA nadir was 0.2 ng/mL (range, 0.01-70.70 ng/mL) at a median follow-up of 2.6 months (range, 2.0-67.3 months). The PSA nadir was the only predictor of recurrence ($p<0.001$) and disease-specific survival ($p=0.012$) based on multivariate analyses. Complications occurred in 0.6% to 4.6% of patients.

Registry Studies
Friedlander et al. (2014) compared salvage cryoablation with salvage radical prostatectomy in 440 men retrospectively identified in the U.S. Surveillance, Epidemiology, and End Results database who were treated between 1992 and 2009. (44) The authors used propensity score analyses to compare overall and prostate cancer-specific mortality. Overall mortality was significantly higher (21.6 versus 6.1 deaths/100 person-years, $p<0.001$) for prostatectomy than for cryoablation. Prostate cancer-specific death rates were numerically higher for prostatectomy than for cryoablation (6.5 versus 1.4 deaths/100 person-years, $p=0.061$).

Section Summary: Salvage Prostate Cryoablation
The evidence for the use of salvage prostate cryoablation in men with localized, recurrent prostate cancer following radiotherapy primarily includes case series and registry studies. Limited evidence from a single retrospective cohort study and one registry study suggests that salvage cryoablation may be associated with better survival outcomes than prostatectomy, although confirmatory evidence from well-designed, prospective studies is lacking.

Subtotal (Focal) Cryoablation of Prostate
Clinical Context and Therapy Purpose
The purpose of focal therapy (FT) using cryoablation in men who have primary localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is men with primary localized prostate cancer.

Interventions
The therapy being considered is FT using cryoablation.

Comparators
The following therapies and practices are currently being used to make decisions about managing men with primary localized prostate cancer: surgery (radical prostatectomy), external-beam radiotherapy, and active surveillance.

Outcomes
The general outcomes of interest are OS, tumor progression and recurrence, incontinence, and sexual dysfunction.

As a therapy situated between active surveillance and definitive therapy, focal therapy is a tissue-sparing procedure intended to maximize quality of life (e.g., incontinence, sexual dysfunction) by treating the index lesion. An international multidisciplinary panel of urologists, radiologists and biomedical engineers recommended that follow-up after focal therapy should be a minimum of 5 years and should include multiparametric MRI, biopsies, assessment of erectile function, QoL, urinary symptoms and incontinence. (45)

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Sidana et al. (2024) reported findings after thirty-six men underwent MRI-US fusion-guided FT cryoablation at a single center from 2018 to 2023 as a primary treatment for intermediate-risk prostate cancer (PCa). (46) Following FT, quarterly prostate-specific antigen (PSA) testing and a 6-to-9-month combined MRI-US targeted and systematic biopsy were performed. Oncological outcomes were determined using several endpoints containing biochemical recurrence, imaging failure, and pathological failure. Functional outcomes were measured using reported erectile dysfunction/potency rates, urinary incontinence rates, and the American Urologic Association Symptom Score (AUA-SS) and Sexual Health Inventory for Men (SHIM) indices. Median follow-up was 29.1 months, most (75%) of whom had grade group 2 prostate cancer. Out of the 36 men, 32 (88.9%) completed the combined MRI-targeted and systematic biopsy follow-up after treatment. The study had no major complications, but 12 (33.3%) patients experienced Clavien-Dindo grade II or lower complications. For oncological outcomes, 6 (16.7%) men had biochemical recurrence, 9 (25%) showed imaging failure, and 8 (22.2%) met the criteria for positive biopsy- out-of-field vs. in-field. 88.2% of previously potent patients remained potent postoperatively at 12 months. All patients were continent at 12 months. There were no statistically significant changes in the AUA-SS and SHIM scores postoperatively. MRI-US-guided cryoablation to target lesions in intermediate-risk PCa appears to be a safe treatment option, with functional outcomes indicating minimal short and intermediate-term morbidity and acceptable oncological outcomes. However, despite close monitoring and follow-up, there is still a limitation in accurately predicting/detecting pathological failure after FT. The long-term durability of FT for intermediate-risk, organ-confined PCa remains uncertain.

In 2022, Kotamarti et al. performed a comprehensive review of the contemporary literature regarding both functional and oncologic outcomes after primary focal cryotherapy for PCa, providing these results as a foundation for discussing recent developments in the realm of focal

therapy. (47) A systematic search was performed of the PubMed and Embase databases to identify articles pertaining to primary focal PCa cryoablation since 2016. The search protocol yielded 13 studies that were identified for inclusion after thorough assessment. Eight studies were single center series, while three were multicenter cohorts and two were derived from the Cryo On-Line Data (COLD) multi-center registry. All included reports discussed primary focal prostate cryoablation. The review found that primary focal cryoablation for localized disease is well tolerated with overall minimal impact on urinary and sexual function. In this review, at least two risk groups were included in nine of the 11 studies that offered preoperative biopsy pathology and 61.5% of cohorts included high risk patients, possibly contributing to the variation in certain results. Intuitively, different ablation patterns should have differing amounts of residual PSA-secreting prostate tissue remaining, making standardized biochemical definitions challenging. While some have suggested mandatory biopsy within 12 months to assess efficacy of the procedure, only 4 of 13 included studies featured mandatory re-biopsy, with most implementing a "for cause" biopsy based on a PSA trigger in consideration of biochemical recurrence. Further controversy exists regarding whether repeat focal therapy offers acceptable oncologic outcome compared to whole gland approaches however, this is likely due to patient selection factors. Authors note that focal cryoablation in recent years has continued to demonstrate promising functional outcomes and adequate short-to-intermediate term oncologic outcomes. The current level of available data is primarily low and retrospective in nature, highlighting the need for further investigations. Research is needed to elucidate the optimal means to monitor these patients post-procedure and consider the best salvage option in cases of failure. With furthering of technologic advancements and research efforts, it is reasonable to expect continued improvement of patient selection and outcomes, as well as for the sustained expansion of potential indications.

Lian et al. (2016) reported on long-term results of a case series of 40 low- to intermediate-risk patients treated with primary focal cryoablation between 2006 and 2013 by a single urologist in China. (48) Biochemical recurrence was defined using the Phoenix definition, and treatment failure was defined as at least one positive biopsy or biochemical recurrence. Mean follow-up was 63 months (range, 12-92 months). Two (5%) of 40 patients met the criteria for biochemical failure and 4 (10%) patients experienced treatment failure. Of the men who were potent before cryotherapy, 20 (77%) remained potent after treatment. Ninety-eight percent of the men were completely continent during follow-up.

A matched cohort study by Mendez et al. (2015) included 317 men who underwent focal cryoablation with 317 men who underwent whole-gland cryoablation. (49) Patients were entered into the Cryo Online Data Registry between 2007 and 2013. The median age at the time of the procedure was 66 years, and median follow-up was 58 months. All patients were preoperatively potent men who had low-risk disease according to the D'Amico risk criteria and were matched by age at surgery. Outcomes included biochemical recurrence-free survival, defined using ASTRO and Phoenix criteria and assessed by Kaplan-Meier curves. Only patients with PSA nadir data were included in oncologic outcome analysis. Functional outcomes were assessed at 6, 12, and 24 months after the procedure for erectile function (defined as the ability to have intercourse with or without erectile aids), urinary

retention, and rates of fistula formation. After surgery, 30% (n=95) and 17% (n=55) of the men who underwent whole-gland cryoablation and focal cryoablation, respectively, underwent biopsy, with positive biopsy rates of 12% and 14%, respectively. Biochemical recurrence-free survival rates at 60 months using the Phoenix definition were 80% and 71% in the whole-gland and focal therapy cohorts, respectively, with a hazard ratio of 0.827 (p>0.1). Using the ASTRO definition, biochemical recurrence-free survival rates were 82% and 73%, respectively (p>0.1). Erectile function data at 24 months were available for 172 whole-gland and 160 focal therapy-treated men. Recovery of erectile function was achieved in 47% and 69% of patients in the whole-gland and focal therapy cohorts, respectively (p=0.001). Urinary function data at 24 months were available for 307 whole-gland and 313 focal therapy patients. Urinary continence rates were 99% and 100% for the whole-gland and focal therapy groups, respectively (p=0.02). Urinary retention rates at 6, 12, and 24 months were reported as 7%, 2%, and 0.6%, respectively, in the whole-gland treated patients versus 5%, 1%, and 0.9%, respectively, in the focal therapy cohort. One fistula was reported in each group.

The Cryo Online Data Registry is a database established and supported by a cryotherapy manufacturer. The data are maintained independently. Physicians submit standardized forms to the database and participation is voluntary. The registry contains case report forms of pretreatment and posttreatment information for patients undergoing whole-gland or partial-gland (focal) prostate cryoablation. Patients are stratified into low-, intermediate-, and high-risk groups. Ward and Jones (2012) have described characteristics of the focal cryotherapy registry patients. (50) Biochemical success was defined using the ASTRO definitions. The analysis included 1160 patients treated with focal cryoablation and 5853 treated with whole-gland cryoablation between 1997 and 2007. Reports on the use of focal cryoablation increased dramatically between 1999 (46 reports) and 2005 (567 reports, p<0.01). The biochemical success at 36 months for focal cryotherapy was 75.7% and was similar to that of whole-gland cryoablation (75.5%); no significant differences between biochemical success for whole-gland and focal cryoablation were observed for low-, intermediate-, or high-risk groups (p-values not given). Urinary continence was 98.4% in focal and 96.9% in whole-gland cryoablation.

Section Summary: Subtotal (Focal) Cryoablation of Prostate

The evidence for the use of focal cryoablation for individuals who have primary localized prostate cancer includes systematic reviews, studies from a registry cohort, and numerous observational studies. No prospective, comparative evidence was found for the majority of focal ablation techniques versus current standard treatment of localized prostate cancer. Methods have not been standardized to determine which and how many identified cancerous lesions should be treated for best outcomes. No evidence supports which, if any, of the focal techniques leads to better functional outcomes.

Summary of Evidence

For individuals who are considering initial treatment for localized prostate cancer who receive whole gland cryoablation, the evidence includes systematic reviews, 2 randomized controlled trials (RCTs), and many comparative and noncomparative observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, symptoms, functional outcomes,

quality of life (QOL), and treatment-related morbidity. High-quality data comparing cryoablation with external-beam radiotherapy, radical prostatectomy, or active surveillance are lacking, but available data have suggested similar OS and disease-specific survival rates compared with radical prostatectomy and external-beam radiotherapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have salvage treatment for recurrence of localized prostate cancer following radiotherapy who receive whole gland cryoablation, the evidence primarily includes case series and a few retrospective studies comparing salvage cryoablation with salvage prostatectomy or brachytherapy. The relevant outcomes are OS, disease-specific survival, symptoms, functional outcomes, QOL, and treatment-related morbidity. High-quality data comparing salvage cryoablation with salvage prostatectomy or brachytherapy are lacking, though limited evidence suggests that salvage cryotherapy may be associated with better survival outcomes than prostatectomy. Men with recurrent localized prostate cancer have limited treatment options and prostatectomy can be difficult in tissue that has been irradiated. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have primary localized prostate cancer who receive subtotal (focal) therapy using cryoablation, the evidence includes systematic reviews, a case series, and studies from a registry cohort. The relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, functional outcomes, QOL, and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. No prospective, comparative evidence was found for focal ablation techniques versus current standard treatment of localized prostate cancer, including radical prostatectomy, external-beam radiotherapy, or active surveillance. No evidence supports which, if any, of the focal techniques leads to better functional outcomes. Although high disease-specific survival rates have been reported, the short follow-up periods and small sample sizes preclude conclusions on the effect of any of these techniques on OS rates. The adverse event rates associated with focal therapies appear to be superior to those associated with radical treatments (e.g., radical prostatectomy, external-beam radiotherapy); however, the evidence is limited in its quality, reporting, and scope. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines (v.4.2024) for prostate cancer indicate cryosurgery (Grade 2A) and high-intensity focused ultrasound (Grade 2B) are options for radiotherapy recurrence in patients who have no evidence of metastatic disease. (51) Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to limited long-term data comparing these treatments with radiation or radical prostatectomy.

American Urological Association et al.

The American Urological Association, in collaboration with the American Society for Radiation Oncology with additional representation from the American Society of Clinical Oncology, and the Society for Urologic Oncology, published updated guidelines on the management of clinically localized prostate cancer in 2022. (52) The guidelines included the following recommendation on focal treatments:

- "Clinicians should inform patients with intermediate-risk prostate cancer who are considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)"
- " Clinicians should not recommend whole gland or focal ablation for men with high-risk localized prostate cancer outside of a clinical trial. (Expert Opinion)"

In the guideline, treatment recommendations are stratified according to risk group, and ablative techniques are discussed in general with no recommendations specific to whole-gland cryoablation (Table 1).

Table 1. Treatment Recommendations Related to Cryoablation by Prostate Cancer Risk Group

	Severity/Risk Group		
	Low-risk disease	**Intermediate-risk disease**	**High-risk disease**
Risk Definition	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a	PSA 10-<20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c	PSA>20 ng/mL OR Grade Group 4-5 OR clinical stageT3
Treatment Recommendation	For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option	Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance	Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial
LOE	Strong	Expert opinion	Expert opinion
GOE	A	--	--
Clinical Considerations	The Panel believes that the benefits of aggressive treatment do not outweigh the risk of treatment-related harms for	The Panel believes that ablation maybe considered in select, appropriately informed patients (with clinical	There is a lack of data supporting treatment of high-risk disease with ablation.

	most patients with low-risk disease. The Panel acknowledges that select patients with low-risk disease may elect definitive local therapy after an informed discussion between clinician and patient.	trial enrollment prioritized). Patients considering ablation should be counseled regarding side effects and recurrence risk and should be followed post-ablation with PSA, DRE, MRI, and biopsy tailored to their specific health and cancer characteristics.	

DRE: digital rectal exam; GOE: grade of evidence; LOE: level of evidence; MRI: magnetic resonance imaging; PSA: prostate-specfic antigen.

National Cancer Institute (NCI)

The NCI (2023) updated its information on prostate cancer treatments. (53) The NCI indicated that cryoablation, photodynamic therapy, and HIFU were new treatment options currently being studied in national trials. The NCI offered no recommendation for or against these treatments.

U.S. Preventive Services Task Force Recommendations

A systematic review of localized prostate cancer treatments was prepared by Fenton et al. (2018) for the Agency for Healthcare Research and Quality, updating the 2002 U.S. Preventive Services Task Force recommendation. (54) Reviewers found no studies comparing cryoablation with watchful waiting and no randomized trials or cohort studies evaluating overall survival or prostate cancer–specific mortality outcomes. The available evidence was mostly from uncontrolled studies and found to be very limited and not sufficiently reliable to estimate the benefits or harms of cryoablation.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01727284	MR-Guided Cryoablation of Prostate Bed Recurrences	107	Nov 2026

NCT04891536	Salvage Cryotherapy for Recurrent Prostate Cancer After Radiation Therapy (CRIOAND2021)	100	May 2026
NCT05454488	An Evidence-Based Focal Cryotherapy Protocol for Focal Ablation of Intermediate Risk Prostate Cancer	30	Jan 2026
NCT01835977	Multi-Center Randomized Clinical Trial Irreversible Electroporation for the Ablation of Localized Prostate Cancer	106	Jan 2025
NCT06223295	Effectiveness of Focal Therapy in Men With Prostate Cancer (ENFORCE)	356	Feb 2031
NCT04049747	Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer (IP4-CHRONOS)	2450	May 2027
NCT03531099	Phase 3, Multicenter, Randomized Study, Evaluating the Efficacy and Tolerability of Focused HIFU Therapy Compared to Active Surveillance in Patients With Significant Low Risk Prostate Cancer (HIFUSA)	108	Oct 2026
Unpublished			
NCT01398657	Cryotherapy with or Without Short-term Adjuvant Androgen-Deprivation Therapy in Prostate Cancer	182	Jun 2016
NCT02615223	Endocrine Therapy with or without Cryoablation for Stage IV Prostate Cancer (CRYO-PCA-IV)	120	Dec 2018
NCT02605226	Cryoablation Therapy or Radiotherapy Therapy for Stage III Prostate Cancer (CRYO-PCA-III)	240	Dec 2018
NCT03348722	Active Surveillance or Radical Treatment for Newly Diagnosed Patients with a Localized, Low Risk, Prostate Cancer START (START)	850	Mar 2023
NCT03668652	Focal Prostate Ablation Versus Radical Prostatectomy (FARP)	200	Sep 2024

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	55873, 55899
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
02/01/2025	Document updated with literature review. Coverage unchanged. Added references 1, 16, 38, 45-47, and 53; others updated.
11/15/2023	Reviewed. No changes.
04/15/2022	Document updated with literature review. Coverage unchanged. References 1, 2, 3, 4, 5, 6, 10, 18 and 42 added, others updated or deleted.
02/15/2021	Reviewed. No changes.
04/15/2020	Document updated with literature review. Coverage unchanged. The following references were added/updated: 1, 18-26, 44-49, and 51.
12/15/2018	Reviewed. No changes.
12/15/2017	Document updated with literature review. Medically necessary coverage statement modified to add the wording “whole gland”.
07/15/2016	Reviewed. Coverage unchanged.
04/01/2015	Document updated with literature review. Coverage unchanged.
01/01/2012	Document updated with literature review. Coverage unchanged.
09/01/2009	Coverage revised to allow for cryoablation of prostate as treatment of clinically localized (organ-confined) prostate cancer when performed as initial treatment or as salvage treatment of disease that recurs following radiation therapy. Subtotal prostate cryoablation is considered experimental, investigational and unproven.
06/15/2007	Revised/updated entire document
10/24/2003	Revised/updated entire document
11/01/2000	Revised/updated entire document
09/01/1996	Revised/updated entire document
05/01/1996	Revised/updated entire document
10/01/1994	New medical document