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# Cryosurgical Ablation of the Prostate

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| Related Policies (if applicable) |
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## Disclaimer

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Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## 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 248,530 new cases are estimated to be diagnosed in the U.S. in 2021, associated with around 34,130 deaths. 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. (1) 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 induces cell death through direct cellular toxicity from disruption of the cell membrane caused by ice-ball crystals and vascular compromise from thrombosis and ischemia secondary to freezing below -30°C. Using a transperineal prostate mapping template, cryoablation is performed by transperineal insertion under transrectal ultrasound guidance of a varying number of cryoprobe needles into the tumor.

**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. 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. (2, 3, 4, 5, 6) 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; and, as a surgical procedure, it is not subject to regulation by the U.S. Food and Drug Administration (FDA).

Many cryoablation systems and cryoprobes have general surgical FDA 510(k) marketing clearance. 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

This medical policy was created in 1994 and has been updated regularly with searches of the PubMed database and review of scientific literature. The most recent literature update was performed through July 28, 2021.

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 Test Purpose

The purpose of whole gland cryoablation in patients 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 question addressed in this medical policy is: Does the use of whole gland cryoablation improve the net health outcomes in patients with localized prostate cancer?

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

*Populations*
The relevant population of interest are 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 treatment of localized prostate cancer. (7) 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 RCTs described below, [8, 9, 10] 2 prospective observational, [11, 12] 2 retrospective [13, 14]). Cryotherapy had a similar OS and disease-specific survival rates 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 ($p<0.01$).

Ramsay et al. (2015) prepared a health technology assessment for the National Institute for Health Research. (15) Reviewers compared the clinical effectiveness of ablative therapies with radical prostatectomy, external-beam radiotherapy (EBRT), and active surveillance. The literature search included RCTs and non-RCTs published through March 2013. Meta-analyses were performed using a Bayesian indirect mixed-treatment comparison. Fourteen case series, 1 RCT, and 4 non-RCT comparative studies (total n=3995 patients) evaluated cryoablation. Reviewers included studies of primary and salvage treatment as well as whole and focal cryoablation. All studies were considered at high-risk of bias. Only pooled estimates of primary, whole cryoablation are described here. Two publications provided data on OS for cryoablation versus EBRT; there was no evidence of a difference in OS for cryotherapy and EBRT at four years. The probability that cryoablation was superior to EBRT was 0.73. The predicted survival rate in the mixed-treatment comparison model at 4 years was 93% for cryoablation and 91% for EBRT. Reviewers concluded there was insufficient evidence to form any clear recommendations on the use of ablative therapies.

A network meta-analysis by Xiong et al. (2014) evaluated the comparative efficacy and safety of radical prostatectomy for several regimens of EBRT, cryoablation, and observational management. (16) Evidence from 2005 to 2012 was included. This analysis incorporated evidence from 21 RCTs (total N=7350 patients) that reported OS and prostate cancer–specific survival rates at 5 years, and late gastrointestinal (GI) and late genitourinary (GU) toxicities at 3 years. Reviewers used Bayesian network analysis with informative prior distributions based on external evidence for heterogeneity variances to compute odd ratios with 95% confidence intervals (CIs) for all pairwise comparisons of interventions. The rank order of superiority of each intervention was compared with all the others using the surface under the cumulative ranking (SUCRA) curve statistic. The SUCRA curve is expressed as a percentage that ranges from 0% if an intervention is certainly the worst to 100% if an intervention is certainly the best. If all interventions are equal, all SUCRA curve values will approximate a percentage of 50%. Overall, the network analysis showed no evidence of the superiority of any treatment for OS (based on SUCRA curve values that ranged from 18% [observational management] to 69% [conformal low-dose EBRT]). Cryoablation had a SUCRA curve value of 50%, which yielded a ranking of fourth-best treatment. However, the SUCRA curve values for late GI (99%) and GU (77%) events with cryoablation rated this intervention in first place for those specific outcomes. These analyses are consistent with a positive balance of benefits and harms associated with total cryoablation compared with radical prostatectomy, EBRT, and observational management.

In a comparative effectiveness report from the Prostate Cancer Results Study Group (2012), which included studies published between 2000 and 2010, treatment effectiveness measured by prostate-specific antigens (PSA) levels following various prostate cancer treatments, including cryoablation, was noted to be difficult to evaluate, because very few studies comparing results from treatment options were identified. (17) Additionally, variations in methods of evaluating outcomes and reporting results complicated the analysis. No recommendations for cryoablation were made by the Prostate Cancer Results Study Group.

Randomized Controlled Trials

Chin et al. (2008, 2012) reported on a randomized trial of cryoablation comparing with EBRT in patients with clinical stage T2C-T3B prostate cancer. (8, 9) 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. (8) 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. (9) 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. (10) All patients began neoadjuvant androgen-deprivation therapy 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 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 (CI). 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, (10) Robinson et al. (2009) reported on the QOL outcomes in the same 244 patients. (18) 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. (11, 12, 13, 14, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31) 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. (32) 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. (33) 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%, respectively.

Ball et al. (2006) reported on the QOL outcomes on a subset of 719 patients with localized prostate cancer treated with various techniques including cryosurgical ablation. (11) They 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. (34) 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 initial outcome for 1198 men with primary whole gland prostate cryoablation. (35) 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). (36) 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 several 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 Test Purpose

The purpose of whole gland cryoablation in patients 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 question addressed in this medical policy is: Does the use of whole gland cryoablation improve the net health outcomes in patients with recurrence of localized prostate cancer following radiotherapy?

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

*Populations*

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), (15) described previously, identified 2 studies (Chin et al. [2001] [37]; Robinson et al. [2006] [38]) assessing salvage whole gland cryoablation. Both were single-arm studies. One 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 literature published between 1991 and 2012 to compare salvage cryoablation for radio-recurrent prostate cancer with other salvage treatments. (39) 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.

In a systematic review, Punnen et al. (2013) evaluated management approaches, including cryoablation, for salvage treatment (biochemical recurrence) after primary treatment for localized prostate cancer. (40) Reviewers identified six studies using salvage cryoablation and concluded there was limited evidence, cryoablation as a treatment option for salvage therapy; randomized trials are needed.

Nonrandomized Comparative Studies

Peters et al. (2013) reported on results of retrospective data from 129 men from 5 Dutch centers. (41) Forty-four men underwent salvage prostatectomy, 54 underwent salvage cryoablation, and 31 underwent salvage brachytherapy. The mean follow-up 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

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. (42) Median duration of follow-up was 124 months (interquartile range 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 androgen deprivation therapy (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 reporting 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. (43) Data were analyzed from 328 patients, with a median follow-up of 47.8 months (range, 1.6-203.5 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.

Williams et al. (2011) retrospectively reviewed 176 patients receiving salvage cryoablation for locally recurrent prostate cancer during the period of 1995 to 2004. (44) Patients were followed a mean of 7.46 years, with 52 patients having been followed for more than 10 years. The 10-year disease-free survival rate was 39%. The authors identified certain risk factors for prostate cancer recurrence following salvage cryoablation, including presalvage PSA levels, preradiation, and presalvage Gleason scores. Early recurrence was highly predicted by a PSA nadir greater than 1.0 ng/dL after salvage cryoablation.

Ng et al. (2007) reported on a series of 187 patients with locally recurrent prostate cancer after radiotherapy who underwent salvage cryoablation, with a mean follow-up of 39 months. (45) Serum PSA level at cryoablation was a predictive factor for biochemical recurrence on univariate and multivariate analyses ($p<0.001$). Patients with a precryoablation PSA level less than 4 ng/mL had 5- and 8-year biochemical relapse-free survival (bRFS) rates of 56% and 37%, respectively. In contrast, patients with precryoablation PSA levels of 10 ng/mL or greater had 5- and 8-year bRFS rates of only 1% and 7%, respectively. Patients with precryoablation PSA levels ranging from 4 to 9.99 ng/mL had intermediate survival outcomes. Five- and 8-year OS rates were 97% and 92%, respectively. The authors concluded that salvage cryoablation was a viable treatment option for patients with prostate cancer for whom radiotherapy has failed; they

further concluded that salvage cryoablation should be performed when the serum PSA level is still relatively low because in these patients, the repeat procedure may potentially be curative.

Ismail et al. (2007) reported on 100 patients treated between 2000 and 2005 with cryoablation for recurrent prostate cancer after radiotherapy; the mean follow-up was 33.5 months. (46) All patients had biopsy-confirmed recurrent prostate cancer. BRFS was defined using a PSA level of less than 0.5 ng/mL and using the American Society for Therapeutic Radiology and Oncology definition for biochemical failure. Patients were stratified into 3 risk groups: high-risk (68 men), intermediate-risk (20 men), and low-risk (12 men). There was no surgery- or cancer-related deaths; the 5-year actutimes bRFS rates were 73%, 45%, and 11% for the low-, intermediate- and high-risk groups, respectively. Complications included incontinence (13%), erectile dysfunction (86%), lower urinary tract symptoms (16%), prolonged perineal pain (4%), urinary retention (2%), and recto-urethral fistula (1%). The authors concluded that salvage cryoablation was a safe and effective treatment for localized prostate cancer recurrence after radiotherapy.

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. (47) 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, $p=0.061$).

Spiess et al. (2013) reported outcomes from the Cryo Online Data Registry for 156 men with data on who underwent salvage cryoablation without neoadjuvant hormonal ablative therapy. (48) The bDFS rates at 1, 2, and 3 years were 89.0%, 73.7%, and 66.7%, respectively. For men with presalvage PSA levels less than 5 ng/mL, the bDFS rates were 95.3%, 86.7%, and 78.3% versus 81.4%, 58.4%, and 52.9% for those with PSA levels of 5 ng/mL or more.

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 non-comparative case series. A small number of retrospective comparative studies have compared salvage cryoablation with salvage prostatectomy but with contradictory findings. Men in this group have few other options and prostatectomy can be difficult in tissue that has been irradiated.

**Subtotal (Focal) Cryoablation of Prostate**

Clinical Context and Test Purpose

The purpose of focal therapy 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 question addressed in this medical policy is: Does the use of focal therapy improve the net health outcomes in men with primary localized prostate cancer?

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 focal therapy 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, cryoablation and active surveillance.

*Outcomes*
The general outcomes of interest are overall survival (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. Thereafter, follow-up is conducted over at least 10 years to monitor for tumor(s) progression and possible definitive therapy.

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- Cryoablation**
Systematic Reviews
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. (49) 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. (50) 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 continence, 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. (51) 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 several systematic reviews, 2 randomized controlled trials (RCTs), and many comparative and noncomparative observational studies. The 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 a meaningful 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 includes primarily noncomparative case series and a few retrospective studies comparing salvage cryoablation with salvage prostatectomy. The relevant outcomes are OS, disease-specific survival, symptoms, functional outcomes, QOL, and treatment-related morbidity. High-quality data comparing cryoablation with prostatectomy was mixed, and evidence comparing cryotherapy to brachytherapy is lacking. Men in this group have few options and prostatectomy can be difficult in tissue that has been irradiated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary localized prostate cancer who receive subtotal (focal) therapy using cryoablation, the evidence includes 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. 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

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.2.2021) recommend only cryosurgery and high-intensity focused ultrasound (HIFU) as local therapy options for radiotherapy recurrence in the absence of metastatic disease. Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy. (52)

American Urological Association et al.

The American Urological Association, along with the American Society for Radiation Oncology and the Society for Urologic Oncology (2017), updated their joint guidelines on the management of clinically localized prostate cancer. (53) The guidelines included the following recommendation on focal treatments:

- "Clinicians should inform low-risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)"
- "Clinicians should inform intermediate-risk prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)"
- "Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial. (Expert Opinion)"

The American Urological Association, the American Society for Therapeutic Radiology and Oncology, and Society of Urologic Oncology (2017) jointly issued guidelines on clinically localized prostate cancer. (53) Table 1 provides the guideline recommendations for cryosurgery by severity and risk group and Table 2 the clinical guidance specific to cryosurgery.

**Table 1. Cryosurgery Recommendations by Prostate Cancer Severity and Risk Group**

| Severity/Risk Group | Recommendation | LOE | GOE |
|---|---|---|---|
| Very low/low-risk disease | Clinicians should inform low-risk prostate cancer patients considering whole gland cryosurgery that consequent side effects are considerable and survival benefit has not been shown in comparison to active surveillance. | Conditional | C |
| Intermediate-risk disease | In selected patients with intermediate-risk localized prostate cancer, clinicians may consider other treatment options such as cryosurgery. | Conditional | C |

| | | | |
|---|---|---|---|
| High-risk disease | Cryosurgery, focal therapy, and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial. | Expert opinion | N/A |

GOE: grade of evidence; HIFU high-intensity focused ultrasound; LOE: level of evidence.

**Table 2. Recommendations Related to Cryosurgery**

| Recommendation | LOE | GOE |
|---|---|---|
| Clinicians may consider whole gland cryosurgery in low- and intermediate-risk localized prostate cancer patients who are not suitable for either radical prostatectomy or radiotherapy due to comorbidities yet have > 10-year life expectancy. | Expert opinion | N/A |
| Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that cryosurgery has similar progression-free survival as did non-dose escalated external beam radiation (also given with neoadjuvant hormonal therapy) in low- and intermediate-risk disease but conclusive comparison of cancer mortality is lacking. | Conditional | C |
| Defects from prior transurethral resection of the prostate are a relative contraindication for whole gland cryosurgery due to the increased risk of urethral sloughing. | Clinical principle | N/A |
| For whole gland cryosurgery treatment, clinicians should utilize a third or higher generation, argon-based cryosurgical system for whole gland cryosurgery treatment. | Clinical principle | N/A |
| Clinicians should inform localized prostate cancer patients considering cryosurgery that it is unclear whether or not concurrent ADT improves cancer control, though it can reduce prostate size to facilitate treatment. | Clinical principle | N/A |
| Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that erectile dysfunction is an expected outcome. | Clinical principle | N/A |
| Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery about the adverse events of urinary incontinence, irritative and obstructive urinary problems. | Strong | B |

ADT: androgen deprivation therapy; GOE: grade of evidence; LOE: level of evidence.

**National Cancer Institute**

The National Cancer Institute (NCI; 2018) updated its information on prostate cancer treatments. (52) 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. (19, 20, 21, 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 3.

**Table 3. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT01727284 | Technical Success, Safety, and Short and Long-Term Efficacy for MR-Guided Cryoablation of Prostate Bed Recurrences | 100 | Dec 2023 |
| NCT04049747 | Imperial Prostate 4: Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer | 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 | 146 | Oct 2025 |
| ***Unpublished*** | | | |
| NCT01398657 | Cryotherapy with or Without Short-term Adjuvant Androgen- Deprivation Therapy for High-Risk Localized Prostate Cancer-Open-Label Randomized Clinical Study | 182 | Jun 2016 (unknown) |
| NCT02615223 | A Prospective Multi-Center Study to Compare the QOL and Efficacy of Endocrine Therapy with or without Cryoablation for Stage IV Prostate Cancer | 120 | Dec 2018 (unknown) |
| NCT02605226 | A Prospective Multi-Center Study to Compare the QOL and Efficacy of External Beam Radiation Therapy or | 240 | Dec 2018 (unknown) |

| | | | |
|---|---|---|---|
| | Cryoablation Therapy for Stage III Prostate Cancer (CRYO-PCA-III) | | |
| NCT03348722 | START (Active Surveillance or Radical Treatment for Newly Diagnosed Patients with a Localized, Low Risk, Prostate Cancer): an Epidemiological Study of the Oncology Network of Piemonte and Valle d'Asosta, Italy | 3000 | Nov 2019 (unknown) |

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 |
| **HCPCS Codes** | None. |

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

## References


1. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. Apr 15 2008; 112(8):1650-1659. PMID 18306379
2. Jacome-Pita F, Sanchez-Salas R, Barret E, et al. Focal therapy in prostate cancer: the current situation. Ecancermedicalscience. 2014; 8:435. PMID 24944577
3. Nguyen CT, Jones JS. Focal therapy in the management of localized prostate cancer. BJU Int. May 2011; 107(9):1362-1368. PMID 21223478
4. Lindner U, Lawrentschuk N, Schatloff O, et al. Evolution from active surveillance to focal therapy in the management of prostate cancer. Future Oncol. Jun 2011; 7(6):775-787. PMID 21675840
5. Iberti CT, Mohamed N, Palese MA. A review of focal therapy techniques in prostate cancer: clinical results for high-intensity focused ultrasound and focal cryoablation. Rev Urol. 2011; 13(4): e196-202. PMID 22232569
6. Lecornet E, Ahmed HU, Moore CM, et al. Conceptual basis for focal therapy in prostate cancer. J Endourol. May 2010; 24(5):811-818. PMID 20443699

7. Gao L, Yang L, Qian S, et al. Cryosurgery would be an effective option for clinically localized prostate cancer: a meta-analysis and systematic review. Sci Rep. Jun 07, 2016; 6:27490. PMID 27271239
8. Chin JL, Ng CK, Touma NJ, et al. Randomized trial comparing cryoablation and external beam radiotherapy for T2C-T3B prostate cancer. Prostate Cancer Prostatic Dis. 2008; 11(1):40-45. PMID 17579613
9. Chin JL, Al-Zahrani AA, Autran-Gomez AM, et al. Extended follow-up oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). J Urol. Oct 2012; 188(4):1170-1175. PMID 22901586
10. Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer. Jan 15 2010; 116(2):323-330. PMID 19937954
11. Ball AJ, Gambill B, Fabrizio MD, et al. Prospective longitudinal comparative study of early health-related quality- of-life outcomes in patients undergoing surgical treatment for localized prostate cancer: a short-term evaluation of five approaches from a single institution. J Endourol. Oct 2006; 20(10):723-731. PMID 17094746
12. Elkjaer MC, Borre M. Oncological outcome after primary prostate cryoablation compared with radical prostatectomy: a single-centre experience. Scand J Urol. Feb 2014; 48(1):27-33. PMID 23597178
13. Gould RS. Total cryosurgery of the prostate versus standard cryosurgery versus radical prostatectomy: comparison of early results and the role of transurethral resection in cryosurgery. J Urol. Nov 1999; 162(5):1653-1657. PMID 10524891
14. Hubosky SG, Fabrizio MD, Schellhammer PF, et al. Single center experience with third-generation cryosurgery for management of organ-confined prostate cancer: critical evaluation of short-term outcomes, complications, and patient quality of life. J Endourol. Dec 2007; 21(12):1521-1531. PMID 18186694
15. Ramsay CR, Adewuyi TE, Gray J, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess. Jul 2015; 19(49):1-490. PMID 26140518
16. Xiong T, Turner RM, Wei Y, et al. Comparative efficacy and safety of treatments for localised prostate cancer: an application of network meta-analysis. BMJ Open. May 15, 2014; 4(5):e004285. PMID 24833678
17. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high-risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int. Feb 2012; 109 Suppl 1:22-29. PMID 22239226
18. Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer. Oct 15 2009; 115(20):4695-4704. PMID 19691092
19. Chou R, Dana T, Bougatsos C, et al. Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation (Report No. 12-05161-EF-1). Rockville (MD): Agency for Healthcare Research and Quality; 2011.

20. Wilt TJ, Shamliyan T, Taylor B, et al. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer (Report No. 08-EHC010-EF). Rockville (MD): Agency for Healthcare Research and Quality; 2008.
21. Shelley M, Wilt TJ, Coles B, et al. Cryotherapy for localised prostate cancer. Cochrane Database Syst Rev. Jul 18 2007(3):CD005010. PMID 17636783
22. Bahn DK, Lee F, Badalament R, et al. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. Urology. Aug 2002; 60(2 Suppl 1):3-11. PMID 12206842
23. Donnelly BJ, Saliken JC, Ernst DS, et al. Prospective trial of cryosurgical ablation of the prostate: five-year results. Urology. Oct 2002; 60(4):645-649. PMID 12385926
24. Ellis DS. Cryosurgery as primary treatment for localized prostate cancer: a community hospital experience. Urology. Aug 2002; 60(2 Suppl 1):34-39. PMID 12206846
25. Long JP, Bahn D, Lee F, et al. Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. Urology. Mar 2001; 57(3):518-523. PMID 11248631
26. Onik G. Image-guided prostate cryosurgery: state of the art. Cancer Control. Nov-Dec 2001; 8(6):522-531. PMID 11807422
27. Robinson JW, Donnelly BJ, Saliken JC, et al. Quality of life and sexuality of men with prostate cancer 3 years after cryosurgery. Urology. Aug 2002; 60(2 Suppl 1):12-18. PMID 12206843
28. Aus G, Pileblad E, Hugosson J. Cryosurgical ablation of the prostate: 5-year follow-up of a prospective study. Eur Urol. Aug 2002; 42(2):133-138. PMID 12160583
29. De La Taille A, Benson MC, Bagiella E, et al. Cryoablation for clinically localized prostate cancer using an argon- based system: complication rates and biochemical recurrence. BJU Int. Feb 2000; 85(3):281-286. PMID 10671882
30. Han KR, Cohen JK, Miller RJ, et al. Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. J Urol. Oct 2003; 170(4 Pt 1):1126-1130. PMID 14501706
31. Prepelica KL, Okeke Z, Murphy A, et al. Cryosurgical ablation of the prostate: high risk patient outcomes. Cancer. Apr 15 2005; 103(8):1625-1630. PMID 15747374
32. Aus G. Cryosurgery for prostate cancer. J Urol. Nov 2008; 180(5):1882-1883. PMID 18801502
33. Lian H, Guo H, Gan W, et al. Cryosurgery as primary treatment for localized prostate cancer. Int Urol Nephrol. Dec 2011; 43(4):1089-1094. PMID 21475948
34. Williams SB, Lei Y, Nguyen PL, et al. Comparative effectiveness of cryotherapy vs brachytherapy for localised prostate cancer. BJU Int. Jul 2012; 110(2 Pt 2):E92-98. PMID 22192688
35. Jones JS, Rewcastle JC, Donnelly BJ, et al. Whole gland primary prostate cryoablation: initial results from the cryo on-line data registry. J Urol. Aug 2008; 180(2):554-558. PMID 18550117
36. Tay KJ, Polascik TJ, Elshafei A, et al. Primary cryotherapy for high-grade clinically localized prostate cancer: oncologic and functional outcomes from the COLD Registry. J Endourol. Jan 2016; 30(1):43-48. PMID 26414656

37. Chin JL, Pautler SE, Mouraviev V, et al. Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. J Urol. Jun 2001; 165(6 Pt 1):1937-1941; discussion 1941-1932. PMID 11371885
38. Robinson JW, Donnelly BJ, Coupland K, et al. Quality of life 2 years after salvage cryosurgery for the treatment of local recurrence of prostate cancer after radiotherapy. Urol Oncol. Nov-Dec 2006; 24(6):472-486. PMID 17138127
39. Mouraviev V, Spiess PE, Jones JS. Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. Eur Urol. Jun 2012; 61(6):1204-1211. PMID 22421081
40. Punnen S, Cooperberg MR, D'Amico AV, et al. Management of biochemical recurrence after primary treatment of prostate cancer: a systematic review of the literature. Eur Urol. Dec 2013; 64(6):905-915. PMID 23721958
41. Peters M, Moman MR, van der Poel HG, et al. Patterns of outcome and toxicity after salvage prostatectomy, salvage cryosurgery and salvage brachytherapy for prostate cancer recurrences after radiation therapy: a multi- center experience and literature review. World J Urol. Apr 2013; 31(2):403-409. PMID 22903773
42. Chin JL, Lavi A, Metcalfe MJ, et al. Long-Term Outcomes of Whole Gland Salvage Cryotherapy for Locally Recurrent Prostate Cancer following Radiation Therapy: A Combined Analysis of Two Centers. J Urol. Sep 2021; 206(3):646-654. PMID 33908799
43. Wenske S, Quarrier S, Katz AE. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. Eur Urol. Jul 2013; 64(1):1-7. PMID 22840351
44. Williams AK, Martinez CH, Lu C, et al. Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. Eur Urol. Sep 2011; 60(3):405-410. PMID 21185115
45. Ng CK, Moussa M, Downey DB, et al. Salvage cryoablation of the prostate: follow-up and analysis of predictive factors for outcome. J Urol. Oct 2007; 178(4 Pt 1):1253-1257; discussion 1257. PMID 17698104
46. Ismail M, Ahmed S, Kastner C, et al. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int. Oct 2007; 100(4):760-764. PMID 17662081
47. Friedlander DF, Gu X, Prabe sad SM, et al. Population-based comparative effectiveness of salvage radical prostatectomy vs cryotherapy. Urology. Mar 2014; 83(3):653-657. PMID 24581527
48. Spiess PE, Levy DA, Pisters LL, et al. Outcomes of salvage prostate cryotherapy stratified by pre-treatment PSA: update from the COLD registry. World J Urol. Dec 2013; 31(6):1321-1325. PMID 23179729
49. Lian H, Zhuang J, Yang R, et al. Focal cryoablation for unilateral low-intermediate-risk prostate cancer: 63-month mean follow-up results of 41 patients. Int Urol Nephrol. Jan 2016; 48(1):85-90. PMID 26531063
50. Mendez MH, Passoni NM, Pow-Sang J, et al. Comparison of outcomes between preoperatively potent men treated with focal versus whole gland cryotherapy in a matched population. J Endourol. Oct 2015; 29(10):1193-1198. PMID 26058496

51. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int. Jun 2012; 109(11):1648-1654. PMID 22035200
52. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2021. Available at: <https://www.nccn.org> (accessed July 6, 2021).
53. American Urological Association (AUA). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. 2017; Available at: <http://www.auanet.org> (accessed July 6, 2021).
54. Fenton JJ, Weyrich MS, Durbin S, et al. U.S. Preventive Services Task Force. Evidence Summary for prostate cancer screening. Available at: <https://www.uspreventiveservicestaskforce.org> (accessed July 6, 2021).
55. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Cryosurgery of Prostate (230.9) (2001). Available at: <http://www.cms.gov> (accessed July 6, 2021).

## 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 <http://www.cms.hhs.gov>.

## Policy History/Revision

| Date | Description of Change |
|---|---|
| 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 |