

7.01.79 Whole Gland Cryoablation of Prostate Cancer			
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Section:	7.0 Surgery	Page:	Page 1 of 15

Policy Statement

- I. Whole gland cryoablation of the prostate may be considered **medically necessary** as treatment of clinically localized (organ-confined) prostate cancer when performed for **either** of the following:
 - A. As initial treatment
 - B. As salvage treatment of disease that recurs following radiotherapy

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The following CPT code is a specific for this procedure:

- **55873:** Cryosurgical ablation of the prostate (includes ultrasonic guidance and monitoring)

Description

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. This review evaluates evidence on the use of total (whole gland, definitive therapy) cryoablation. Subtotal (focal) cryoablation and alternative procedures are considered in Blue Shield of California Medical Policy: Focal Treatments for Prostate Cancer.

Related Policies

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Focal Treatments for Prostate Cancer
- Intensity-Modulated Radiotherapy of the Prostate
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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.

Rationale

Background

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer and the third leading cause of cancer deaths among men in the U. S., with an estimated 161,360 new cases and 26,730 deaths in 2017.¹ The diagnosis and grading of prostate cancer are performed by taking a biopsy of the prostate gland.

Treatment

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.

Literature Review

Evidence reviews 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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Primary Prostate Cryoablation

Clinical Context and Therapy 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 following PICO was used to select literature to inform this review.

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.² 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,^{3,4,5} 2 prospective observational,^{6,7} and 2 retrospective^{8,9}). 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 ($p < .01$).

A network meta-analysis by Xiong et al (2014) evaluated the comparative efficacy and safety of radical prostatectomy for several regimens of external beam radiotherapy (EBRT), cryoablation, and observational management.¹⁰ Evidence from 2005 to 2012 was included. This analysis incorporated evidence from 21 RCTs (N=7350) that reported on 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 odds 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 the 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.

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.^{3,4} 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 1 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.³ 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.⁴ 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.⁵ 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 (prostate-specific antigen [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 ($p=.78$). At 36 months, radiotherapy patients had significantly more positive prostate biopsies (22/76 patients) than the cryoablation group (7/91 patients; $p<.001$). 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 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,⁵ Robinson et al (2009) reported on QOL outcomes in the same 244 patients.¹¹ 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; $p < .001$; 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 vs. mean EBRT, 32.9; $p < .001$). 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 cancer prostate.^{6,7,8,9,12,13,14,15,16,17,18,19,20,21} 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.²² 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 2006 through 2009.²³ Only a single 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.⁶ 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.²⁴ 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.²⁵ 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).²⁶ 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 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 following PICO was used to select literature to inform this review.

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**

A health technology assessment by Ramsay et al (2015),²⁷ identified 2 single-arm studies (Chin et al [2001]²⁸; Robinson et al [2006]²⁹) 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.³⁰ 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.³¹ 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 cryoablation group. Severe GU 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.^{32,33,34,35,36,37} 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 2019.³² 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 pubosymphseal 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 2004.³³ 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 ADT during follow-up was associated with significantly better OS (hazard ratio [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.³⁴ 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 to 70.70 ng/mL) at a median follow-up of 2.6 months (range, 2.0 to 67.3 months). The PSA nadir was the only predictor of recurrence ($p < .001$) and disease-specific survival ($p = .012$) 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 2009.³⁸ The authors used propensity score analyses to compare overall and prostate cancer-specific mortality. Overall mortality was significantly higher (21.6 vs. 6.1 deaths/100 person-years, $p < .001$) for prostatectomy than for cryoablation. Prostate cancer-specific death rates were numerically higher for prostatectomy than for cryoablation (6.5 vs. 1.4 deaths/100 person-years, $p = .061$).

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 cryotherapy may be associated with better survival outcomes than prostatectomy, although confirmatory evidence from well-designed, prospective studies is lacking.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2009. There was strong agreement that cryoablation should be considered medically necessary as an option in the initial treatment of organ-confined prostate cancer, as well as for use as salvage therapy for disease recurrence after radiotherapy.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.1 2023) for prostate cancer indicate cryosurgery and high-intensity focused ultrasound are options for radiotherapy recurrence in patients who have no evidence of metastatic disease (Grade 2B).³⁹ NCCN does not recommend cryotherapy as routine primary therapy for localized prostate cancer due to limited long-term data comparing cryotherapy with radiation or radical prostatectomy.

American Urological Association et al

In 2022, the American Urological Association and the American Society for Radiology Oncology issued a joint, updated guideline on the treatment of clinical localized prostate cancer; the guideline was additionally endorsed by the Society of Urologic Oncology.⁴⁰ 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	Risk Definition	Treatment Recommendation	LOE	GOE	Clinical Considerations
Low-risk disease	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a	For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option			<p>The Panel believes that the benefits of aggressive treatment do not outweigh the risk of treatment-related harms for most patients with low-risk disease.</p> <p>The Panel acknowledges that select patients with low-risk disease may elect definitive local therapy after an informed discussion between clinician and patient.</p>
Intermediate-risk disease	PSA 10-<20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c	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	Expert opinion		<p>-The Panel believes that ablation may be considered in select, appropriately informed patients (with clinical trial enrollment prioritized).</p> <p>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.</p>
High-risk disease	PSA >20 ng/mL OR Grade Group 4-5 OR clinical stage T3	Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial	Expert opinion		<p>-There is a lack of data supporting treatment of high-risk disease with ablation.</p>

DRE: digital rectal exam; GOE: grade of evidence; HIFU: high-intensity focused ultrasound; LOE: level of evidence; MRI: magnetic resonance imaging; PSA: prostate-specific antigen.

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.⁴¹ 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, found to be very limited, and not sufficiently reliable to estimate the benefits or harms of cryoablation.

Medicare National Coverage

The Centers for Medicare & Medicaid Services have determined that total cryotherapy is medically necessary and appropriate as primary treatment for clinically localized prostate cancer in stages T1 to T3.⁴² Salvage cryoablation is only medically necessary and appropriate in localized disease when radiotherapy has failed as primary treatment, and the patient meets 1 of 3 criteria: stage T2B or below, Gleason score less than 9, or prostate-specific antigen level of less than 8 ng/mL. Salvage cryoablation after the failure of other therapies is not covered.

Ongoing and Unpublished Clinical Trials

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

Table 2. 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
NCT04891536	Salvage Cryotherapy for Recurrent Prostate Cancer After Radiation Therapy (CRIOAND2021)	100	May 2026
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; last updated Nov 2012)
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; last updated Jun 2017)
NCT02605226	A Prospective Multi-Center Study to Compare the QOL and Efficacy of External Beam Radiation Therapy or Cryoablation Therapy for Stage III Prostate Cancer (CRYO-PCA-III)	240	Dec 2018 (unknown; last updated Jun 2017)
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; last updated Nov 2017)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and radiation oncology consultation report including:
- Past radiotherapy treatment plan (if applicable)
- Past surgical procedures (pertaining to request)
- Primary cancer type and location
- Goals/requirements of whole gland cryoablation of the prostate treatment plan
- Radiology report(s)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance and monitoring)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/08/1994	New Policy Adoption
06/18/1997	Policy Review
07/01/2001	Policy Review
08/01/2005	Policy Review MPC accepted CTAF technology review
10/01/2005	Policy Review Title modification
12/18/2009	Policy title change from Cryosurgery/Cryoablation of the Prostate Policy revision with position change
03/29/2013	Policy revision without position change
10/30/2015	Policy title change from Cryosurgical Ablation of Prostate Cancer Policy revision with position change
05/01/2016	Administrative Update
12/01/2016	Policy revision without position change
10/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
10/01/2019	Policy revision without position change
10/01/2020	Annual review. No change to policy statement. Literature review updated.
10/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.
10/01/2022	Annual review. No change to policy statement. Literature updated.
10/01/2023	Annual review. No change to policy statement. Literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent

with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<div>Whole Gland Cryoablation of Prostate Cancer 7.01.79</div> <div>Policy Statement:</div> <div><div>I. Whole gland cryoablation of the prostate may be considered medically necessary as treatment of clinically localized (organ-confined) prostate cancer when performed for either of the following:</div><div><div>A. As initial treatment</div><div>B. As salvage treatment of disease that recurs following radiotherapy</div></div></div>	<div>Whole Gland Cryoablation of Prostate Cancer 7.01.79</div> <div>Policy Statement:</div> <div><div>I. Whole gland cryoablation of the prostate may be considered medically necessary as treatment of clinically localized (organ-confined) prostate cancer when performed for either of the following:</div><div><div>A. As initial treatment</div><div>B. As salvage treatment of disease that recurs following radiotherapy</div></div></div>