Whole Gland Cryoablation of Prostate Cancer

Policy Number: 7.01.79   Last Review: 7/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for cryoablation of prostate cancer when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Whole gland cryoablation of the prostate may be considered medically necessary as treatment of clinically localized (organ-confined) prostate cancer when performed:
- As initial treatment or
- As salvage treatment of disease that recurs following radiotherapy

When Policy Topic is not covered

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<th>Description of Procedure or Service</th>
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<td>Individuals: Who are considering initial treatment for localized prostate cancer</td>
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Cryoablation, also known as cryotherapy or cryosurgery, of prostate cancer is a technique in which cryoprobes are inserted percutaneously into the prostate gland to rapidly freeze and thaw 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 a separate MPRM policy.

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, and many comparative and noncomparative observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. High-quality data comparing cryoablation to external-beam radiotherapy, radical prostatectomy, or active surveillance are lacking, but available data suggest similar overall survival and disease-specific survival rates compared to radical prostatectomy and external-beam radiotherapy. The evidence is sufficient to conclude that cryoablation leads to improvement in net health outcome.

For individuals who need 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 to salvage prostatectomy.

Relevant outcomes are overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. High-quality data comparing cryoablation to prostatectomy is mixed and evidence comparing cryotherapy to brachytherapy is lacking. Men in this group have few other options and prostatectomy can be difficult in tissue that has been irradiated. The evidence is sufficient to conclude that cryoablation leads to improvement in net health outcome.

**Background**

**Prostate Cancer**

Prostate cancer is the most commonly diagnosed cancer and the third leading cause of cancer deaths among men in the United States, with an estimated 161,360 new cases and 26,730 deaths in 2017. 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.
**Regulatory Status**
Cryoablation of prostate cancer is a surgical procedure that uses previously approved and available cryoablation systems. As a surgical procedure cryoablation of the prostate is not subject to FDA approval.

**Rationale**
This evidence review was created in August 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 4, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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 evidence review is: Does the use of whole gland cryoablation improve the net health outcomes in patients with localized prostate cancer?

The following PICOTS were used to select literature to inform this review.
Patients
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 (eg, sexual dysfunction, incontinence).

Timing
Follow-up for treatment-related morbidity is months post-procedure. Follow-up to monitor for recurrence measured in years of follow-up.

Setting
Cryoablation is administered by urologists in a tertiary care setting.

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 longer 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.

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. 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 (2 RCTs, 2 prospective observational, 2 retrospective). 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. 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 vs EBRT; there was no evidence of a difference in OS for cryotherapy and EBRT at 4 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 that 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. Evidence from 2005 to 2012 was included. This analysis incorporated evidence from 21 RCTs (total N=7350 patients) that reported on OS and prostate cancer-specific survival rates at 5 years, and late gastrointestinal (GI) and late genitourinary 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 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 genitourinary (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. 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.

A systematic review by Chou et al (2011) assessed localized prostate cancer treatments on behalf of the Agency for Healthcare Research and Quality. In a search of literature from 2002 to July 2011, reviewers found no studies comparing cryoablation with watchful waiting (surveillance) and no randomized trials or cohort studies evaluating OS or prostate cancer-specific survival 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.

A comparative effectiveness review by Wilt et al (2008), which evaluated therapies for clinically localized prostate cancer on behalf of the Agency for Healthcare Research and Quality, also found that no randomized trials had evaluated cryoablation. Reviewers noted that, in general, neither OS nor prostate cancer-specific survival was reported for this technique. Progression-free survival in patients with T1 or T2 stages ranged from 29% to 100%.

A Cochrane review by Shelley et al (2007), which assessed cryoablation for localized prostate cancer, found no randomized trials comparing cryoablation with other therapies for the primary treatment of localized prostate cancer; studies identified included case series. The patients recruited in the case series (total N=1483 patients) ranged in age from 41 to 84 years, and their conditions were classified by stage: stages T1: 0% to 43%; T2: 24% to 88%; T3: 1% to 41%; and T4: 0% to 14%. The mean preoperative PSA level ranged from 9.7 to 39 ng/mL, with Gleason scores less than 7 in 9% to 37% of patients. Reviewers concluded that cryoablation offered a potential alternative to standard therapies for the primary treatment of localized prostate cancer and that patients who select cryoablation as their therapeutic option should be informed of the relevant data (eg, efficacy, complications, low-grade evidence) associated with such treatment; however, due to the poor quality of the available studies, it was difficult to determine the relative benefits of cryoablation.

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. 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. 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.15 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 the National Cancer Institute of Canada Common Toxicity Criteria, 12 cryoablation patients experienced 13 grade 3 adverse events vs 16 grade 3 adverse events in 14 radiotherapy patients. Urinary retention was the most common grade 3 adverse event in both treatment arms. The trialists were unable to establish that cryoablation was noninferior to radiotherapy at 36 months due to the wide confidence interval. The trialists also noted several issues that limited interpretation of trial results, including the use of uncommonly low radiation dosages (68 gray, 70 gray, 73.5 gray, respectively), and early trial closure due to lack of patient enrollment.

In a second article from the Donnelly trial (2010),15 Robinson et al (2009) reported on the quality of life outcomes in the same 244 patients.16 With few exceptions, study participants reported the quality of life 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 vs 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.5,6,7,8,17,18,19,20,21,22,23,24,25,26 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. 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. Only 1 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 quality of life outcomes on a subset of 719 patients with localized prostate cancer treated with various techniques including cryosurgical ablation. 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. 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. 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). Mean follow-up was 28.4 months. The estimated 2- and 5-year bDFS rates were 77% (95% confidence interval, 71% to 88%) and 59% (95% confidence interval, 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. Earlier systematic reviews, with literature searches through mid-2011 did not find evidence supporting the use of whole gland cryoablation; however, more 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 evidence review 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 PICOTS were used to select literature to inform this review.

**Patients**
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 (eg, sexual dysfunction, incontinence).

**Timing**
Follow-up for treatment-related morbidity is months post-procedure. Follow-up to monitor for recurrence measured in years of follow-up.
Setting
Cryoablation is administered by urologists in a tertiary care setting.

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 longer 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.

Systematic Reviews
The health technology assessment by Ramsay et al (2015), described previously, identified 2 studies (Chin et al [2001]; Robinson et al [2006]) 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. 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. Reviewers identified 6 studies using salvage cryoablation and concluded that while there was limited evidence, cryoablation was 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. 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 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
Siddiqui et al (2016) reported long-term outcomes for 157 men undergoing salvage cryoablation for biopsy-proven, localized radio-recurrent prostate cancer at a single institution from 1995 to 2004. Median follow-up was 117 months (interquartile range, 55-154 months). OS rates at 5 and 10 years were 93% and 76%, respectively. The bDFS rates at 10 and 15 years were 35% and 23%, respectively. Recto-urethral fistula developed in 2.5% of patients and was successfully repaired in all cases. Fifty-two percent of men reported no incontinence while 44% required 0 or 1 pad per day.

Wenske et al (2013) reported on salvage cryoablation in a series of 396 consecutively treated patients who had failed cryoablation or radiotherapy. 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. 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 who underwent salvage cryoablation, with a mean follow-up of 39 months. 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 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. All patients had biopsy-confirmed recurrent prostate cancer. Biochemical RFS 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. 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<0.001) 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=0.061).

Spiess et al (2013) reported on outcomes from the Cryo Online Data Registry for 156 men with data on who underwent salvage cryoablation without neoadjuvant hormonal ablative therapy. 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% vs 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 noncomparative 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.
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 RCTs, and many comparative and noncomparative observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, 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 overall survival 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. Relevant outcomes are overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. High-quality data comparing cryoablation with prostatectomy was mixed, and evidence comparing cryotherapy with 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.

SUPPLEMENTAL INFORMATION

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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

European Association of Urology et al
The European Association of Urology (2017) published joint guidelines on prostate cancer with the European Society for Radiotherapy and Oncology and the International Society of Geriatric Oncology. For nonmetastatic prostate cancer,
the guidelines have recommended that cryotherapy and high-intensity focused ultrasound be offered only in a clinical trial.

In cases of recurrence following radiotherapy, guidelines from the European Association of Urology and 3 other medical societies indicated that the health care provider should “offer/discuss high intensity focused ultrasound, cryosurgical ablation, and salvage brachytherapy to/with patients without evidence of metastases and with histologically proven local recurrence. Inform patients about the experimental nature of these approaches” (level of evidence: 3; grade: B).

**National Comprehensive Cancer Network**
The National Comprehensive Cancer Network guidelines (v.3.2018) for prostate cancer indicate cryosurgery and high-intensity focused ultrasound are options for radiotherapy recurrence in patients who have no evidence of metastatic disease.

**American Urological Association et al**
The American Urological Association, American Society for Therapeutic Radiology and Oncology, and Society of Urologic Oncology (2017) jointly issued guidelines on clinically localized prostate cancer. 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**

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<tr>
<td>Very low/low-risk disease</td>
<td>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.</td>
<td>Conditional</td>
<td>C</td>
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<tr>
<td>Intermediate-risk disease</td>
<td>In select patients with intermediate-risk localized prostate cancer, clinicians may consider other treatment options such as cryosurgery.</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td>High-risk disease</td>
<td>Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial</td>
<td>Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>

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

**Table 2. Recommendations Related to Cryosurgery**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
<th>GOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 &gt;10 year life expectancy.</td>
<td>Expert opinion</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td>Defects from prior transurethral resection of the prostate are a relative contraindication for whole gland cryosurgery due to the increased risk of urethral</td>
<td>Clinical principle</td>
<td></td>
</tr>
</tbody>
</table>

Whole Gland Cryoablation of Prostate Cancer 7.01.79
sloughing.

For whole gland cryosurgery treatment, clinicians should utilize a third or higher generation, argon-based cryosurgical system for whole gland cryosurgery treatment.

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.

Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery that erectile dysfunction is an expected outcome.

Clinicians should inform localized prostate cancer patients considering whole gland cryosurgery about the adverse events of urinary incontinence, irritative and obstructive urinary problems.

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

**U.S. Preventive Services Task Force Recommendations**

Asystematic review of localized prostate cancer treatments was prepared by Chou et al (2011) for the Agency for Healthcare Research and Quality, updating the 2002 U.S. Preventive Services Task Force recommendation.12 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.

**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 T3.48 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 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00774436</td>
<td>A Phase II Study of Focal Cryoablation in Low-Risk Prostate Cancer</td>
<td>50</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT02615223</td>
<td>A Prospective Multi-Center Study to Compare the QOL and Efficacy of Endocrine Therapy with or without Cryoablation for Stage IV Prostate Cancer</td>
<td>120</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02605226</td>
<td>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)</td>
<td>240</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02459912</td>
<td>Unilateral Nerve-Sparing Cryoablation for Low-Risk, Clinically-Localized, Unilateral Prostate Cancer (POTENT-C)</td>
<td>86</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT</td>
<td>Study Title</td>
<td>Estimated Enrollment</td>
<td>Start Date</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>NCT03348722</td>
<td>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</td>
<td>3000</td>
<td>Nov 2019</td>
</tr>
<tr>
<td>NCT03492424</td>
<td>Outcomes of Focal Therapies for Prostate Cancer</td>
<td>200</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>NCT01727284</td>
<td>Technical Success, Safety, and Short and Long-Term Efficacy for MR-Guided Cryoablation of Prostate Bed Recurrences</td>
<td>100</td>
<td>Jan 2022</td>
</tr>
<tr>
<td>NCT01398657</td>
<td>Cryotherapy With or Without Short-term Adjuvant Androgen-Deprivation Therapy for High-Risk Localized Prostate Cancer - Open-Label Randomized Clinical Study</td>
<td>182</td>
<td>Jun 2016 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES

Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>55873</td>
<td>Cryosurgical ablation of the prostate (includes ultrasonic guidance for interstitial cryosurgical probe placement)</td>
</tr>
<tr>
<td>55899</td>
<td>Unlisted procedure, male genital system</td>
</tr>
</tbody>
</table>

Additional Policy Key Words

N/A

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Update Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/1/96</td>
<td>New policy. Added to surgery section, considered investigational.</td>
</tr>
<tr>
<td>2/1/00</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>2/1/01</td>
<td>Policy statement revised to read treatment for Stage A, B or C prostate cancers may be considered medically necessary.</td>
</tr>
<tr>
<td>2/1/02</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>2/1/03</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>6/1/04</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>2/1/05</td>
<td>No policy statement changes.</td>
</tr>
</tbody>
</table>
No policy statement changes.

2/1/08 Policy statement revised to indicate this procedure is investigational for all indications. Since these results from recent studies come primarily from uncontrolled case series with short follow-up times, they must be confirmed by prospective studies in which patients are randomized to cryoablation or standard therapy such as prostatectomy or radiotherapy. These studies must follow patients for a time sufficient to evaluate long-term disease-free survival, so that the true efficacy of cryoablation for prostate cancer can be determined.

No policy statement changes.

2/1/09 No policy statement changes.

4/24/09 Policy revised. Policy statement for primary cancer changed to medically necessary; new policy statement added that treatment of recurrent localized prostate cancer may be considered medically necessary; new policy statement added that subtotal cryoablation is investigational. "Clinically localized" removed from policy title.

4/1/10 No policy statement changes.

4/1/11 No policy statement changes.

4/1/12 No policy statement changes.

4/1/13 No policy statement changes.

7/1/13 No policy statement changes.

7/1/14 Regulatory Status added to Background. No policy statement changes. Removed cpt: 49203, 49204, and 49205.

7/1/15 Changed title to “Whole Gland Cryoablation of Prostate Cancer”. Information on focal therapy was removed from Policy and the policy statement on focal therapy was deleted; “whole gland” was added to medically necessary policy statement.

7/1/16 No policy statement changes.

7/1/17 No policy statement changes.

7/1/18 Removed investigational statement.

7/1/19 No policy statement changes.

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