# Whole Gland Cryoablation of Prostate Cancer

**Policy Number:** 7.01.79  
**Origination:** 2/1996  
**Last Review:** 7/2018  
**Next 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

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
  - Who are considering initial treatment for localized prostate cancer | Interventions of interest are:  
  - Whole gland cryoablation | Comparators of interest are:  
  - Radiotherapy  
  - Radical prostatectomy  
  - Active surveillance | Relevant outcomes include:  
  - Overall survival  
  - Disease-specific survival  
  - Symptoms  
  - Functional outcomes  
  - Quality of life  
  - Treatment-related morbidity |

| Individuals:  
  - Who need salvage treatment for recurrence of localized prostate cancer following radiotherapy | Interventions of interest are:  
  - Whole gland cryoablation | Comparators of interest are:  
  - Radical prostatectomy  
  - Brachytherapy | Relevant outcomes include:  
  - Overall survival  
  - Disease-specific survival  
  - Symptoms  
  - Functional outcomes  
  - Quality of life  
  - Treatment-related morbidity |
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**

Whole gland (also known as total) cryoablation is one of several methods available to treat clinically localized prostate cancer and may be considered an alternative to radical prostatectomy or EBRT. It also 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 such that tissue necrosis follows. Cryosurgical ablation is less invasive than radical prostatectomy and recovery time may be shorter. EBRT requires multiple treatments, whereas only one treatment is usually required for total cryoablation.

**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 review was performed for the period of through June 22, 2017.

Primary Prostate Cryoablation

Systematic Reviews
This evidence review was informed by a 2001 TEC Assessment that focused on total cryoablation for primary localized prostate cancer. At that time, available evidence was heterogeneous with insufficient information on baseline characteristics of enrolled patients. Where data were available, outcomes appeared to be generally comparable across treatment methods. However, data from cryoablation studies were sparse and did not permit conclusions on oncologic outcomes. Perioperative mortality and acute life-threatening consequences of cryoablation appeared negligible. Patients had the highest likelihood of impotence after cryoablation compared with radical prostatectomy or 3-dimensional conformal radiotherapy (3D-CRT). The frequency of incontinence appeared similar to that after 3D-CRT, and potentially less than that after radical prostatectomy. Adverse gastrointestinal (GI) consequences typical of 3D-CRT were not noted after cryoablation. Long-term consequences of cryoablation were uncertain because follow-up was inadequate.

The conclusions of the 2001 TEC Assessment contrasted with a 2001 analysis from the Centers for Medicare & Medicaid Services (CMS) supporting Medicare’s decision that cryosurgical ablation was eligible for coverage. The TEC Assessment sought data on clinical health outcomes, whereas the CMS assessment used an intermediate outcome, changes in prostate-specific antigen (PSA) levels. As noted in the CMS assessment, “Data shows that a significant number of patients are able to sustain undetectable levels of PSA for a period of time of at least 24 months. This compares favorably with the biopsy data following external beam irradiation.”

A 2007 Cochrane review of 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.
A 2008 comparative effectiveness review of therapies for clinically localized prostate cancer from the Agency for Healthcare Research and Quality also found that no randomized trials had evaluated cryoablation. The report noted that, in general, neither overall survival (OS) nor prostate cancer–specific survival was reported for this technique. Progression-free survival (PFS) in patients with T1 or T2 stages ranged from 29% to 100%.

A subsequent systematic review of localized prostate cancer treatments prepared for the Agency for Healthcare Research and Quality was published in late 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.

In a 2012 comparative effectiveness report from the Prostate Cancer Results Study Group, treatment effectiveness measured by 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 network meta-analysis published in 2014 evaluated the following: the comparative efficacy and safety of radical prostatectomy, several regimens of external-beam radiotherapy (EBRT), cryoablation, and observational management. This analysis incorporated 21 randomized controlled trials (RCTs; total N=7350 patients) that reported OS and prostate cancer–specific survival rates at 5 years, and late GI and late genitourinary (GU) toxicities at 3 years. It used Bayesian network analysis with informative prior distributions based on external evidence for heterogeneity variances to compute odd ratios (ORs) 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 (this was 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 2015, a Health Technology Assessment was reported by the National Institute for Health Research. Reviewers compared the clinical effectiveness of ablative therapies with radical prostatectomy, EBRT, and active surveillance. The 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.

In 2016, Gao et al reported results of a systematic review and meta-analysis comparing cryoablation with radiotherapy and radical prostatectomy for treatment of localized prostate cancer. The search included articles published up to December 2015. Because the pooled estimates combined primary and salvage treatment, we present the individual studies in the following sections and do not present pooled data here. Six studies described primary treatment (2 RCTs, 2 prospective observational, 2 retrospective). Cryotherapy had 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).

**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. 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. 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. All patients began neoadjuvant antiandrogen 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; the two did not differ statistically (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 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 [Gy], 70 Gy, 73.5 Gy, respectively), and early trial closure due to lack of patient enrollment.

In a second article from the Donnelly trial (2010), Robinson et al (2009) reported on quality of life outcomes in the same 244 patients. With few exceptions, Robinson et al found study participants reported 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 (UCLA) 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). UCLA Prostate Cancer Index sexual function decreased in both arms at 3 months. However, reduced sexual function was reported more 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 reported on cryoablation for localized prostate cancer. In 2002, the largest single-institution series reported on the 7-year actuarial rate of bDFS for 590 consecutively treated patients. However, 59% of the patients were treated using an older liquid nitrogen system, which the authors asserted "... yields inferior results compared with the argon-based cryomachines we now use...." Even so, reported results combined outcomes obtained from both systems.

Aus (2008) reported that cryoablation is now 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. 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 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 (SEER) 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 (COLD) 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. 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. In 2016, outcomes for 300 men in the COLD Registry who underwent primary whole gland cryotherapy for high-grade (Gleason score ≥8), localized prostate cancer were published. 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. High-quality data comparing cryoablation with other treatments are lacking, but available data suggest similar OS and disease-specific survival rates compared with radical prostatectomy and EBRT.

Salvage Prostate Cryoablation
Studies have described results from using cryoablation in men with recurrent, localized prostate cancer following radiotherapy.

Systematic Reviews
The 2015 Health Technology Assessment (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.

In 2012, Mouraviev et al reviewed literature published between 1991 and 2012 to compare salvage cryoablation for radio-recurrent prostate cancer with other salvage treatments. They found comparisons difficult to make because no prospective, randomized studies were identified and PSA failure was defined in various ways. 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 2013 systematic review, Punnen et al evaluated management approaches, including cryoablation, for salvage treatment (biochemical recurrence) after primary treatment for localized prostate cancer. Reviewers noted, while there was limited evidence, cryoablation was a possible treatment option for salvage therapy although randomized trials are needed.

Nonrandomized Comparative Studies
Peters et al (2013) reported on results of retrospective data from 129 men from 5 high-volume Dutch centers. 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 GU and GI toxicity (grade >3) using 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, respectively.

Pisters et al (2009) compared retrospective data between groups; the first group consisted of 38 men who underwent salvage radical prostatectomy at a U.S. clinic
between 1990 and 1999; the second group consisted of 34 men who underwent salvage cryoablation at U.S. cancer center between 1992 and 1995.\textsuperscript{28} Mean follow-up was 7.8 years in the prostatectomy group and 5.5 years in the cryoablation group. The bDFS rate was 42\% for cryoablation and 66\% for prostatectomy at 5 years (p=0.002). The OS rate at 5 years was 85\% for cryoablation and 95\% for prostatectomy (p=0.001). There was no significant difference in disease-specific survival rates at 5 years (96\% cryoablation vs 98\% prostatectomy, p=0.283).

**Nonrandomized Noncomparative Studies**

Wenske et al (2013) reported on salvage cryoablation in a series of 396 consecutively treated patients who had failed cryoablation or radiotherapy.\textsuperscript{39} 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 was 63\% and 35\%, disease-specific survival was 91\% and 79\%, and OS was 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). PSA nadir was the only predictor of recurrence and disease-specific survival based on multivariate analyses (p<0.001 and p=0.012, respectively). Complications occurred in 0.6\% to 4.6\% of patients.

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.\textsuperscript{40} 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 recurrence-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. Overall 5- and 8-year survival 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 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.\textsuperscript{41} All patients had biopsy-confirmed recurrent prostate cancer. The definition for bRFS was defined using a PSA level of less than 0.5 ng/mL and by applying 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 actuarial 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.

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 found certain risk factors for prostate cancer recurrence following salvage cryoablation, and these risk factors were: 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.

In 2016, Siddiqui et al 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 successfully repaired in all cases. Fifty-two percent of men reported no incontinence while 44% required 0 or 1 pad per day.

Registry Studies
Friedlander et al (2014) compared salvage cryoablation with salvage radical prostatectomy in 440 men retrospectively identified in the SEER 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).

In 2013, Spiess et al reported outcomes for 156 men who underwent salvage cryoablation without neoadjuvant hormonal ablative therapy from the COLD Registry. 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 includes primarily 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 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 with external-beam radiotherapy, radical prostatectomy, or active surveillance are lacking, but available data suggest 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 to prostatectomy is 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.

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 that recurs after radiotherapy.

Practice Guidelines and Position Statements

European Association of Urology et al
In 2017, the European Association of Urology 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.

**National Comprehensive Cancer Network**
The National Comprehensive Cancer Network (NCCN) guidelines (v.2.2017)\(^{47}\) 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**
The 2008 American Urological Association best practice statement (reaffirmed 2010)\(^{48}\) has recognized cryoablation of the prostate as an appropriate treatment option for newly diagnosed or radio-recurrent organ-confined prostate cancer. However, this statement indicated cryoablation in patients with clinical T3 disease (locally advanced, tumor extends through the prostate capsule) is undetermined.

**U.S. Preventive Services Task Force Recommendations**
In 2011, a systematic review of localized prostate cancer treatments was published by the Agency for Healthcare Research and Quality, updating the 2002 U.S. Preventive Services Task Force recommendation.\(^{5}\) 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 indicated total cryotherapy is medically necessary and appropriate as primary treatment for clinically localized prostate cancer in stages T1 to T3.\(^2\) 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 failure of other therapies is not covered.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT00824928(^a)</td>
<td>A Prospective Multicenter Registry of Salvage Cryotherapy in Recurrent Prostate Cancer Study (SCORE)</td>
<td>60</td>
<td>Dec 2012 (terminated)</td>
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<tr>
<td>NCT01398657</td>
<td>Cryotherapy With or Without Short-term Adjuvant Androgen-Deprivation Therapy for High-Risk Localized Prostate Cancer — Open-Label Randomized</td>
<td>182</td>
<td>Jun 2016 (unknown)</td>
</tr>
</tbody>
</table>
Clinical Study

NCT: national clinical trial.

\(^a\) Denotes industry-sponsored or cosponsored trial.

References


Billing Coding/Physician Documentation Information

55873 Cryosurgical ablation of the prostate (includes ultrasonic guidance for interstitial cryosurgical probe placement)

55899 Unlisted procedure, male genital system

Additional Policy Key Words

N/A

Policy Implementation/Update Information

2/1/96 New policy. Added to surgery section, considered investigational.
2/1/00 No policy statement changes.
2/1/01 Policy statement revised to read treatment for Stage A, B or C prostate cancers may be considered medically necessary.
2/1/02 No policy statement changes.
2/1/03 No policy statement changes.
6/1/04 No policy statement changes.
2/1/05 No policy statement changes.
2/1/06 No policy statement changes.
2/1/07 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.

8/1/08  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.

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