

**Subject: Cryotherapy for Prostate Cancer**

**Background:** Cryotherapy is a minimally invasive treatment modality for prostate cancer in which freezing is used to destroy tumor cells. Cryotherapy is thought to be associated with minimal blood loss and pain and can be performed under spinal rather than general anesthesia. Techniques can be applied to the entire prostate gland or partially to localized areas where cancer is present.

**Authorization:**

Prior authorization is required for all cryotherapy procedures requested for members enrolled in commercial (HMO, POS, and PPO) products.

**Policy and Coverage Criteria:****Initial Treatment**

Harvard Pilgrim Health Care (HPHC) considers cryotherapy as reasonable and medically necessary when documentation confirms member has localized prostate cancer, stages T1-T3.

**Recurrent Treatment**

Harvard Pilgrim Health Care (HPHC) considers salvage cryosurgery of the prostate for recurrent cancer as reasonable and medically necessary for individuals with localized disease when documentation confirms ALL the following:

- Member has failed a trial of radiation therapy as their primary treatment; AND
- Member meets one of the following conditions:
  - Stage T2B or below, OR
  - Gleason score <9, OR
  - Prostate-specific antigen (PSA) <8 ng/mL

**Exclusions:** Harvard Pilgrim Health Care (HPHC) considers cryotherapy for prostate cancer as experimental/investigational for all other indications. In addition, HPHC does not cover:

- Focal cryoablation of the prostate

**Supporting Information:**

Cryoablation, also referred to as cryosurgery, cryotherapy, or cryosurgical ablation of the prostate (CSAP), is a minimally invasive surgical technique that involves in situ freezing by applying extremely cold temperature to destroy prostate tissue and reduce the size of the prostate gland. Cryotherapy is performed under local or general anesthesia. Multiple cryoprobes are placed through the perineum directly into the prostate. The cryoprobes are specially designed to conduct a continuous flow of liquid nitrogen or high-pressure argon gas to the tip. This produces very cold temperatures very rapidly, freezing the prostatic tissue in an expanding or spherical fashion around each probe. Generally, two freeze/thaw cycles are used. Transrectal ultrasound (TRUS) is used to monitor the freezing process. TRUS is used in real time throughout the procedure. In addition, TRUS

**HPHC Medical Review Criteria****Cryotherapy for Prostate Cancer****Page 1 of 9**

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clearly delineates the leading edge of the ice balls forming in the prostate during the procedure, allowing the surgeon to accurately limit the extent of the ice ball's growth, thereby minimizing any freezing damage to structures which are close to or surround the prostate. To prevent freezing of the urethra, a urethral warming device is simultaneously employed. The goals of prostate cryoablation are to cure patients with organ-confined disease and to achieve local disease control and improve survival in patients with locally advanced disease and in individuals with recurrent disease who have failed prior therapy.

Cryoablation, or cryotherapy, of the prostate has been investigated as primary treatment alternative to surgery or radiotherapy for localized prostate cancer. It has also been evaluated as a second line or salvage treatment for patients with residual or recurrent cancer following radical prostatectomy or irradiation.

Li et al (2015) reported contemporary outcomes of salvage focal cryoablation for locally recurrent PCa after radiotherapy within the Cryo On-Line Data Registry. The outcomes indicated that salvage focal cryoablation can be an effective treatment with encouraging potency preservation for patients with locally recurrent PCa after radiotherapy. The authors noted that further studies are needed.

A prospective study by Rodriguez et al. (2014) including 108 patients with localized prostate cancer at clinical stage T1c-T2c were treated by primary cryoablation. The biochemical progression-free survival (BPFS) for low-, medium-, and high-risk patients was 96.4%, 91.2%, and 62.2%, respectively. Cancer-specific survival was 98.1%. Overall survival reached 94.4%. The authors concluded that cryotherapy is an effective and minimally invasive treatment for primary PC in well-selected cases, with low surgical risk and good results in terms of BPFS, cancer-specific survival, and overall survival.

A 2013 systematic review by Valerio et al. noted current, radical, whole-gland treatments for organ-confined prostate cancer are being questioned with respect to their side effects, cancer control, and cost. The review investigated focal cryotherapy as an alternative treatment and focused on baseline characteristics of the target population; preoperative evaluation to localize disease; and perioperative, functional, and disease control outcomes following focal therapy. The authors found focal therapy was mainly delivered to men with low and intermediate disease. Studies follow-up time varied between 0 and 11.1 years. For men who underwent focal cryotherapy as an initial treatment, pad-free continence ranged from 95-100%, erectile function ranged from 55-100%, and absence of clinically significant cancer ranged from 83-100%. Valerio et al. noted when the therapy is used with intention to treat, the perioperative, functional, and disease control outcomes are encouraging. However, follow times are short to medium-term. The authors called for robust comparative effectiveness studies to further validate the treatment.

An additional review by Kasivisvanathan et al. (2013) discussed the current status of focal therapy, highlighting controversies and emerging strategies that can influence treatment outcomes for the future. The group notes current trials do not present medium- and long-term oncological outcome data or comparisons with existing standards of care and there is no consensus on whether oncological control should be deemed the absence of any cancer or the absence of clinically significant cancer and whether this should be limited to the treated area or include the untreated prostate. Patient selection criteria are also inconsistent. The review notes there are several prospective trials in progress and further RCTs are needed comparing active surveillance or radical therapy with focal therapy.

Nguyen et al. (2013) reviewed clinical literature on focal cryotherapy for clinically localized prostate cancer. Outcomes on cancer control, complications and quality of life were reviewed and assessed. The authors found the biochemical disease-free survival at 5 years is comparable to whole gland treatment modalities. They

## **HPHC Medical Review Criteria**

### **Cryotherapy for Prostate Cancer**

**Page 2 of 9**

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concluded the treatment is safe and effective, and may improve failure rates in men who initially pursue active surveillance methods.

A 2013 review by Sverrisson et al. assessed the oncologic and functional outcomes of cryosurgery for localized prostate cancer. The review found the outcomes of cryosurgery improved over time with intermediate biochemical disease-free survival rates now comparable to other treatments.

A 2011 review by Finley and Beldegrun looked at salvage cryotherapy for radiation-recurrent prostate cancer. Their analysis of the literature found technological inroads have led to salvage cryotherapy as a viable treatment option with curative intent for radio-recurrent prostate cancer. Durable biochemical relapse-free rates range from 34% to 68% depending on the definition. They also found complication rates have trended down with advances in technique and technology.

Simmons et al. (2011) published a practical guide to prostate cancer diagnosis and management. The review noted refinements in cryoablative therapy have improved the safety and efficacy of the procedure in the last decade. While it is recognized by the American Urological Association as a viable primary cancer monotherapy, it is most commonly used as a salvage therapy after failure of radiation therapy.

Turpen and Rosser (2009) discussed the treatments options available for prostate cancer such as expectant management, radiation therapy (brachytherapy and external beam radiotherapy), and surgery (cryosurgical ablation and radical prostatectomy). They note that these treatments are effective but the treatment morbidities are significant. Using focal therapy to target only the cancer tissues within the prostate and spare the non-cancerous tissue is a treatment they consider appealing, yet controversial. Turpen and Rosser also caution that before focal treatment is embraced the community needs to be able to accurately identify index lesions within the prostate, image cancers within the prostate, and methodically study the litany of focal therapeutic options available.

Ritch and Katz (2009) also discussed recent data on cryotherapy for localized prostate cancer. They noted stage migration has led to an increased incidence of localized and low-risk prostate cancer. Intermediate-term data are emerging on the efficacy of cryotherapy, but direct comparison to other therapeutic modalities is difficult because the parameters for recurrence are not well defined. Ritch and Katz found that studies using the American Society for Therapeutic Radiation and Oncology and the Phoenix (nadir plus 2) criteria for biochemical recurrence show that primary cryotherapy appears to be comparable for low-risk prostate cancer as other treatment modalities. In addition, health-related quality-of-life measures have improved with the most recent third-generation systems demonstrating low incontinence and urethrorectal fistula rates. Erectile dysfunction is high with whole gland ablation, but focal therapy by reduce these rates while still ablating unilateral cancerous tissue. However, even with these promising results, Ritch and Katz note long-term data are still needed to establish a definitive role for cryosurgery in prostate cancer treatment. In another 2009 review Ritch and Katz reported that with respect to biochemical recurrence rates, cryotherapy appears to be as effective for low-risk prostate cancer as other modalities. Yet, the definition of recurrence remains problematic. Most recent studies are using both the American Society for Therapeutic Radiation Oncology and Phoenix criteria. Whole-gland cryoablation has high erectile dysfunction rates, but incontinence and urethrorectal fistula rates appear to be low with third-generation cryo-systems. Focal cryotherapy has encouraging short-term efficacy in terms of biochemical disease-free survival rate for unifocal disease, and rates of erectile dysfunction are dramatically lower than those seen with whole-gland cryoablation. The authors reiterated that cryosurgery has a promising role in primary and salvage treatment of select prostate cancer patients, and that focal cryotherapy has the added benefit of minimal adverse effects. As in their other review, Ritch and Katz noted the need for long-term data to support cryotherapy.

## **HPHC Medical Review Criteria**

### **Cryotherapy for Prostate Cancer**

**Page 3 of 9**

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Langenhuijsen et al. (2008) assessed the oncological results and complication rates of modern cryosurgery for prostate cancer. Their analysis found that the introduction of gas-based third-generation cryotechnology significantly decreased side effects with similar oncological results when compared to older techniques. Severe complications such as urethrorectal fistulas occurred in less than 1% of patients; however, rates of erectile dysfunction remain high, 90%. Salvage cryotherapy has more side effects with an average incontinence rate of 8% and fistulas up to 3.4%. Even with these complications, the authors felt the minimally invasive treatment remains an option for radio-recurrent prostate cancer. Based on low-level evidence, focal cryotherapy is considered experimental though it has intermediate-term biochemical disease-free survival rates of 60-90%. These rates are comparable to those from other treatment modalities. Langenhuijsen et al. concluded from their review that randomized trials comparing outcomes of the different treatment modalities and long-term follow-up data are needed to clearly define the ultimate role of cryosurgery in the treatment of localized prostate cancer.

Polascik and Mouraviev (2008) discussed that a select cohort of patients with low-risk unifocal or unilateral prostate cancer lesions may benefit from ablative treatment for focal therapy of the lesions. This type of treatment may be an alternative to extreme treatments of radical prostatectomy for those with clinically relevant cancers, watchful waiting for those with less aggressive forms of the disease. The authors note the concept of focal therapy is evolving along with the understanding of the biologic variability of various prostate cancer lesions that may require or benefit from different treatment approaches.

In another 2008 review, Polascik et al. again discussed the need for trials with longer follow oncologic follow up to evaluate focal cryoablation of unifocal lesion(s) in select patients. They also noted more accurate imaging-based techniques need to be developed along with image-guided prostate biopsy sampling and image-guided prostate cryoablation. Along with the technologic advancements, Polascik et al. call for established patient selection criteria, the development of molecular and imaging parameters of cryoablative efficacy, and regular follow-up of treated patients.

Polascik et al. (2007) reported the results of the treatment of localized prostate cancer (n=50) using a "transrectal ultrasound-guided, third-generation, argon/helium cryosurgical system". Preoperative hormone therapy was administered to patients with a 40 centimeter or larger prostate for downsizing. Tumor stages included T1c, T2a, and T2b. Following ablation, physical examination and PSA levels were conducted every three months, with radiology and biopsy follow-up as indicated. A PSA of 0.5 ng/mL or greater following ablation was considered a failure. Follow-up ranged from 3–43 months. The type of cryoprobe used during ablation varied depending upon the size of the prostate. Following ablation, 45 patients had a PSA level less than 0.5 ng/mL, and five patients had a level of 0.5 ng/mL or greater. Two patients experienced recurrence. The group experienced an overall survival rate of 100%. Two patients experienced mild incontinence and three reported persistent impotence, existing preoperatively, unresponsive to pharmacotherapy following ablation.

Chin et al. (2007) conducted a randomized controlled trial to "evaluate the relative efficacy" of external beam radiation therapy (EBRT) (n=31) compared to cryoablation (CRYO) (n=33) for the treatment of locally advanced prostate cancer. Patients who met inclusion criteria were either stage T2c, T3a, or T3b, demonstrated no signs of metastases based upon negative abdomen and pelvic CT and bone scan, and had a serum PSA less than 25 nanograms/milliliters (ng/mL). Biochemical failure was defined as three consecutive increases in PSA levels following nadir, with an alternate definition being a PSA level of 2 ng/mL above the nadir. At a mean 37-month follow-up, 21 patients in the CRYO group and 14 patients in the EBRT group met failure criteria. The mean biochemical disease-free survival rate for the EBRT group was 41 months compared to 28 months for the CRYO group (p=0.027). The four-year biochemical disease-free survival rate was 47% for the EBRT group and 13% for the CRYO group (p=0.027). There were no significant differences in the disease-specific survival and overall survival rates between the two groups. Serious complications were not reported in either group. The

#### **HPHC Medical Review Criteria**

#### **Cryotherapy for Prostate Cancer**

**Page 4 of 9**

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EBRT group experienced more gastrointestinal adverse effects than the CRYO group.

Ellis et al. (2007) reported on the outcomes of cryoablation used for the treatment of 416 consecutive men, mean age of 69.4 years, diagnosed with prostate cancer. Patients were free of metastasis and offered cryoablation, prostatectomy or radiation therapy as the treatment option. Tumor characteristics of the patient population prior to ablation included a mean PSA of 8.7 ng/mL, median Gleason score of 6, and median tumor stage of T1c (78.6% ≤ T2a; 21.4% ≥ T2b). Follow-up ranged from 1.5–60 months. Patients were stratified according to risk groups. Biochemical survival was determined if four PSA measurements were obtained following cryoablation. With a follow-up range of 9–60 months; 291 patients met this criterion. Following ablation, a mean PSA level less than 0.4ng/dl was experienced by 79.7% of the population. By risk group, the four-year biochemical disease-free survival was 83.6 ± 3.8% for low-risk, 82.3 ± 3.6% for moderate risk, and 69.1 ± 5.5% for high-risk patients. Postoperative biopsies were obtained from 168 patients. Seventeen (10.1%) of the biopsies were positive at a mean 10.2 months following ablation. Complications included incontinence (i.e., any leakage of urine; 4%) and impotence (i.e., 100% of patients experienced impotence immediately following the procedure).

Ng et al. (2007) conducted a study to “assess the short and intermediate-term efficacy” of salvage cryoablation of the prostate “with an emphasis on finding predictive factors that lead to improved outcome.” Salvage cryoablation was performed on 187 patients, age range 53.6–81.7 years, who had undergone EBRT (n=183), or brachytherapy (n=3), or EBRT and brachytherapy (n=1). The patients had experienced local disease recurrence with absence of identified metastases. Eighty-five percent of the patients were tumor grades T1 or T2. Median PSA level prior to ablation was 11 ng/mL. Preoperatively, hormonal therapy was received by 71% of patients for tumor downsizing. Biochemical failure was defined as a PSA of 2 ng/mL above the nadir. Transrectal ultrasound, 24-month biopsies, and bone scans were performed when feasible and as indicated. The study results demonstrated that PSA levels at the time of ablation were predictors of postoperative biochemical recurrence on multivariate analysis (p<0.001) (i.e., the lower the PSA at the time of ablation, the more effective the procedure). Patients with a PSA level of less than 4 ng/mL at the time of ablation had a five-year biochemical recurrence-free survival rate of 56%, with an eight-year rate of 37% compared to a five-year and eight-year rate of 14% and 7%, respectively, for patients with a pre-ablative PSA level of 10 ng/mL. Overall five-year survival rate was 97%, with an eight-year survival rate of 92%. At a mean 31-month postoperative period, 64 patients experienced disease progression, and ten patients underwent repeat ablation for persistent carcinoma. Surgical intervention was necessary for four patients who experienced severe incontinence and four patients who experienced urethrorectal fistulas.

Lambert et al. (2007) reported on safety and efficacy experience from their patients who underwent focal cryoablation of the prostate. Their patients all had low-risk unifocal prostate cancer and wished to maintain potency and preserve continence. In their research, from June 2002 to December 2005, 25 patients with primary unifocal prostate cancer were treated with focal cryoablation of the prostate. The patients were followed up with physical examinations, morbidity questionnaires, and prostate-specific antigen (PSA) determinations every 3 months for the first year and every 6 to 12 months thereafter. Patients with a PSA nadir greater than 1.0 ng/mL or a nadir plus 2 ng/mL underwent repeat biopsy to assess for cancer recurrence. In the study population the median age was 68 years (range 48 to 78). The median preoperative PSA level was 6.0 ng/mL, and the postoperative PSA nadir was 2.4 ng/mL. The median follow-up was 28 months. Seventeen patients remained potent. No patients reported worsened lower urinary tract symptoms, incontinence, rectal pain, perineal discomfort, or fistula formation. The median PSA nadir was 2.4 ng/mL, and 40% of patients had a PSA nadir of less than 1.0 ng/mL. Of the 25 patients, 21 (84%) had not experienced biochemical failure, defined as a greater than 50% PSA nadir reduction. Seven patients underwent repeat biopsy, and prostate cancer was detected in the contralateral gland in 2 patients and in the area of previous cryosurgery in 1 patient. From these results, Lambert et al. found Focal cryoablation of the prostate to exhibited minimal morbidity and promising efficacy. They also

#### **HPHC Medical Review Criteria**

#### **Cryotherapy for Prostate Cancer**

**Page 5 of 9**

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mentioned longer follow-up is necessary to determine its role in the treatment of patients with low-risk unifocal prostate cancer.

Ahmed et al. (2005) conducted a systematic literature review to compare the outcomes of salvage radical prostatectomy to salvage cryotherapy. They reported on 13 articles dating from 1995–2003. There were no prospective, randomized studies comparing prostatectomy to cryoablation. The advancement in technology has led to decreased complications with cryosurgery, with the most serious and challenging complication still being rectourethral fistula. Cryoablation avoids complications related to prostatectomy, including rectal injuries and blood loss. Both procedures reported related erectile dysfunction, but cryotherapy was less invasive and resulted in fewer complications.

Bahn et al. (2003) reported a seven-year retrospective analysis evaluating the morbidity and biochemical disease-free survival (bDFS) of cryosurgery for recurrent prostate cancer after radiation therapy. A total of 59 patients who had previously been treated with radiation therapy and had rising serum PSA values underwent salvage cryoablation of the prostate for localized, histologically proven, recurrent prostate cancer. Serial serum PSA testing and biopsies were performed at six, 12 and 24 months, and five years following cryosurgery, as well as at any time that the PSA level rose above 0.5 ng/mL. Patients were stratified along clinical parameters. The combined post-salvage rate was 59% using a PSA cutoff of 0.5 ng/mL and 69% with a cutoff of 1.0 ng/mL. Using a PSA threshold of 0.5 ng/mL as evidence of biochemical recurrence, 61% of patients with an initial PSA of < 4 ng/mL, 62% with 4–10 ng/mL, and 50% with > 10 ng/mL remained relapse-free at seven years. A threshold of 1.0 ng/mL yielded a disease-free status of 78%, 74%, and 46%, respectively. Patients' biopsies demonstrated no evidence of residual or recurrent disease

### **Guidelines:**

The 2016 National Comprehensive Cancer Network (NCCN) Guideline for Prostate Cancer notes, "Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that achieves damage to tumor tissue through local freezing. Based on different definitions of biochemical failure, the reported 5-year biochemical disease-free rate following cryotherapy ranged from 65% to 92% in low-risk patients.

Based on a report from the National Institute for Health and Care Excellence (NICE) guidelines, current evidence on focal therapy using cryoablation for localized prostate cancer raises no major safety concerns. However, evidence on efficacy is limited in quantity and there is a concern that prostate cancer is commonly multifocal. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Cryosurgery of the prostate gland, also known as cryosurgical ablation of the prostate (CSAP), destroys prostate tissue by applying extremely cold temperatures in order to reduce the size of the prostate gland. It is safe and effective, as well as medically necessary and appropriate, as primary treatment for patients with clinically localized prostate cancer, Stages T1-T3.

The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) maintain the TNM classification system as a tool to stage different types of cancer based on certain standards. There are 4 categories to describe the local extent of a prostate tumor, ranging from T1 to T4 with subcategories.

<b>Category</b>	<b>Description</b>
<b>T1</b>	Digitally unrecognized tumor
<b>T1A</b>	Less than 5% of the transurethral resection of the prostate

### **HPHC Medical Review Criteria**

#### **Cryotherapy for Prostate Cancer**

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	(TURP) specimen, or low-to-medium grade tumor
<b>T1B</b>	Greater than 5% of the TURP specimen, or high-grade tumor
<b>T1C</b>	Tumor detected by elevated prostate-specific antigen (PSA)
<b>T2</b>	Digitally palpable tumor confined to the prostate
<b>T2A</b>	Less than ½ of one lobe
<b>T2B</b>	Greater than ½ of one lobe
<b>T2C</b>	Tumors involve both lobes
<b>T3</b>	Cancer extending beyond the prostate capsule
<b>T3A</b>	Tumor extends outside of the prostate, but not the seminal vesicles
<b>T3B</b>	Tumor has spread to the seminal vesicles

A 2008 Best Practice Guideline from the American Urological Association (AUA, 2010) concluded that cryosurgery guided by ultrasound and temperature monitoring is an option for recurrent clinically organ-confined prostate cancer after radiation therapy. As with other salvage therapies for curative intent, cryosurgery should be considered early for patients defined as radiation failures. Refinements in the surgical technique and equipment have resulted in significantly less morbidity than previously reported as well as encouraging short-term PSA results.

### Coding:

**Codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible.**

CPT® Codes	Description
<b>55873</b>	Cryosurgical ablation of the prostate (including ultrasonic guidance for interstitial cryosurgical probe placement)

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### HPHC Medical Review Criteria

#### Cryotherapy for Prostate Cancer

Page 7 of 9

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## HPHC Medical Review Criteria

### Cryotherapy for Prostate Cancer

Page 8 of 9

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**Summary of Changes:**

Date	Changes:
<b>3/18</b>	References and guidelines updated; policy coverage criteria refined

**Approved by Medical Policy Review Committee: 3/6/18**

**Reviewed/Revised: 10/09; 10/11; 10/13; 10/15; 4/17; 3/18**

**Initiated: 10/09**

**HPHC Medical Review Criteria**

**Cryotherapy for Prostate Cancer**

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