

Medical Policy



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Title: Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With solid tumors (located in the breast, lung, pancreas, kidney, or bone) 	Interventions of interest are: <ul style="list-style-type: none"> Cryosurgical ablation 	Comparators of interest are: <ul style="list-style-type: none"> Surgical resection Other ablative techniques No intervention 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Quality of life Treatment-related morbidity

DESCRIPTION

Cryosurgical ablation (hereafter referred to as cryosurgery or cryoablation) involves freezing of target tissues; this is most often performed by inserting a coolant-carrying probe into the tumor. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

OBJECTIVE

The objective of this policy is to determine whether cryoablation of miscellaneous solid tumors (located in areas such as the breast, lung, pancreas, kidney, or bone) will improve the net health outcome.

BACKGROUND

Breast Tumors

Early-stage primary breast cancers are treated surgically. The selection of lumpectomy, modified radical mastectomy, or another approach is balanced against the patient's desire for breast conservation, the need for tumor-free margins in resected tissue, and the patient's age, hormone receptor status, and other factors. Adjuvant radiotherapy decreases local recurrences, particularly for those who select lumpectomy. Adjuvant hormonal therapy and/or chemotherapy are added, depending on presence and number of involved nodes, hormone receptor status, and other factors. Treatment of metastatic disease includes surgery to remove the lesion and combination chemotherapy.

Fibroadenomas are common benign tumors of the breast that can present as a palpable mass or a mammographic abnormality. These benign tumors are frequently surgically excised to rule out a malignancy.

Lung Tumors

Early-stage lung tumors are typically treated surgically. Patients with early-stage lung cancer who are not surgical candidates may be candidates for radiotherapy with curative intent. Cryoablation is being investigated in patients who are medically inoperable, with small primary lung cancers or lung metastases. Patients with more advanced local disease or metastatic disease may undergo chemotherapy with radiation following resection. Treatment is rarely curative; rather, it seeks to retard tumor growth or palliate symptoms.

Pancreatic Cancer

Pancreatic cancer is a relatively rare solid tumor that occurs almost exclusively in adults, and it is largely considered incurable. Surgical resection of tumors contained entirely within the pancreas is currently the only potentially curative treatment. However, the nature of the cancer is such that few tumors are found at such an early and potentially curable stage. Patients with more advanced local disease or metastatic disease may undergo chemotherapy with radiation following resection. Treatment focuses on slowing tumor growth and palliation of symptoms.

Renal Cell Carcinoma

Localized renal cell carcinoma is treated with radical nephrectomy or nephron-sparing surgery. Prognosis drops precipitously if the tumor extends outside the kidney capsule because chemotherapy is relatively ineffective against metastatic renal cell carcinoma.

Cryosurgical Treatment

Cryosurgical treatment of various tumors including malignant and benign breast disease, lung cancer, pancreatic cancer, and renal cell carcinoma has been reported in the literature. The hypothesized advantages of cryosurgery include improved local control and benefits common to any minimally invasive procedure (eg, preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

REGULATORY STATUS

Several cryoablation devices have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process for use in open, minimally invasive, or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery, and ear, nose, and throat. Examples include:

- Cryocare® Surgical System (Endocare);
- CryoGen Cryosurgical System (Cryosurgical);
- CryoHit® (Galil Medical) for the treatment of breast fibroadenoma;
- SeedNet™ System (Galil Medical); and
- Visica® System (Sanarus Medical).

Food and Drug Administration product code: GEH.

POLICY

- A. Cryosurgical ablation may be considered **medically necessary** to treat localized renal cell carcinoma that is no more than 4 cm in size when either of the following criteria is met:
1. Preservation of kidney function is necessary (ie, the patient has 1 kidney or renal insufficiency defined by a glomerular filtration rate of <60 mL/min/m²), and standard surgical approach (ie, resection of renal tissue) is likely to worsen kidney function substantially; OR
 2. The patient is not considered a surgical candidate.
- B. Cryosurgical ablation may be considered **medically necessary** to treat lung cancer when either of the following criteria is met:
1. The patient has early-stage non-small-cell lung cancer and is a poor surgical candidate; OR
 2. The patient requires palliation for a central airway obstructing lesion.

- C. Cryosurgical ablation is considered **experimental / investigational** as a treatment for benign or malignant tumors of the breast, lung (other than defined above), pancreas, or bone and other solid tumors or metastases outside the liver and prostate and to treat renal cell carcinomas in patients who are surgical candidates.

RATIONALE

This evidence review was created in October 2003 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through May 7, 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.

Cryosurgical Treatment

Cryosurgical treatment of various tumors has been reported for malignant and benign breast disease, lung cancer, pancreatic cancer, renal cell carcinoma, and bone cancer. The following sections summarize studies that adequately described baseline characteristics of the patient populations and the methods used for cryosurgery; these studies report treatment outcomes for 8 or more patients with the same diagnosis or 8 or more procedures on the same malignancy.

Clinical Context and Therapy Purpose

The purpose of cryosurgical ablation in patients who have solid tumors 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 cryosurgical ablation improve the net health outcome in patients with solid tumors other than the liver, prostate, or dermatologic tumors?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with solid tumors located in the breast, lung, pancreas, kidney, or bone.

Interventions

The therapy being considered is cryosurgical ablation.

Comparators

The following practice is currently being used to make decisions: surgical resection is the standard therapy for solid tumors other than the liver, prostate, or dermatologic tumors.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, and morbidity due to the treatment.

Potential complications of cryosurgery include those caused by hypothermic damage to normal tissue adjacent to the tumor, structural damage along the probe track, and secondary tumors if cancerous cells are seeded during probe removal.

Timing

Morbidity due to treatment would be observed in the immediate postoperative period. OS would be observed over a period of years.

Setting

Cryosurgery is administered as an inpatient procedure by a surgeon experienced in resecting solid tumors.

Breast Diseases

Breast Cancer

Systematic Reviews: Zhao and Wu (2010) reported on a systematic review of minimally invasive ablative techniques of early-stage breast cancer.¹ They noted that studies assessing cryoablation for breast cancer were primarily limited to pilot and feasibility studies in the research setting. Complete ablation of tumors was reported within a wide range (36%-83%). Reviewers raised many areas of uncertainty, including patient selection criteria and the ability to precisely determine the size of tumors and achieve 100% tumor cell death. They suggested minimally invasive thermal ablation techniques for breast cancer treatment, including cryoablation, be limited until results from prospective, RCTs become available.

Randomized Controlled Trials: A prospective, single-arm, phase 2 trial was published by Simmons et al (2016) for the American College of Surgeons Oncology Group Z1072.² This trial enrolled 86 evaluable patients from 19 institutions with invasive ductal breast carcinoma that was 2 cm or less in size. The primary end point was complete ablation, defined as no residual evidence of tumor on magnetic resonance imaging. The investigators assigned a priori the success rates indicating that cryoablation would be a potentially efficacious treatment (>90%) or that the results of cryoablation would be unsatisfactory (<70%). Following cryoablation and

determination of complete ablation, all patients underwent surgery according to standard protocols for treatment of early breast cancer. Of 87 cancers in 86 patients, complete ablation was achieved in 66 (75.9%; 95% confidence interval CI., 67.1% to 83.2%). Most cases without complete ablation were the result of multifocal disease outside the targeted lesion. Success rates were intermediate, indicating that cryoablation is not potentially efficacious, nor are the results of cryoablation satisfactory.

Nonrandomized Studies: Niu et al (2013) reported on a retrospective study of 120 patients with metastatic breast cancer, including 30 metastases to the contralateral breast and other metastases to the lung, bone, liver, and skin treated with chemotherapy (n=29) or cryoablation (n=91, 35 of whom also received immunotherapy).³ At 10-year follow-up, the median OS of all study participants was 55 months in the cryoablation group vs 27 months in the chemotherapy group (p<0.001). Moreover, the median OS was greater in patients receiving multiple cryoablations and in those receiving immunotherapy. Complications with cryotherapy to the breast included ecchymosis and hematoma, pain, tenderness, and edema all these complications resolved within 1 week to 1 month.

In a case series by Manteni et al (2011), who assessed 15 breast cancer patients, percutaneous cryoablation (PCA) was performed 30 to 45 days before surgical resection.⁴ Resection of the lesions confirmed that complete necrosis had occurred in 14 patients, but 1 lesion had residual disease considered to be due to incorrect probe placement. In a small series of 11 patients with breast cancer tumors less than 2 cm in diameter, Pusztaszeri et al (2007) found residual tumors present in 6 cases when follow-up lumpectomies were performed approximately 4 weeks after cryoablation.⁵ A case series by Sabel et al (2004) explored the role of cryoablation as an alternative to surgical excision as a primary treatment for early-stage breast cancer.⁶ This phase 1 study included 29 patients who underwent cryoablation of primary breast cancers measuring less than 2 cm in diameter, followed 1 to 4 weeks later by standard surgical excision. Cryoablation was successful in patients with invasive ductal carcinoma less than 1.5 cm in diameter, and with less than 25% ductal carcinoma in situ identified in a prior biopsy specimen.

Other studies have described outcomes from cryosurgery for advanced primary or recurrent breast cancer.^{7, 8, 9, 10} Collectively, these reports either did not adequately describe selection criteria for trial enrollees, procedure details, or procedure-related adverse events or had inadequate study designs, analyses, and reporting of results.

Breast Fibroadenomas: A variety of case series have focused on the role of cryosurgery as an alternative to surgical excision of benign fibroadenomas. Kaufman et al (2002-2005) have published several case series on office-based ultrasound-guided cryoablation as a treatment of breast fibroadenomas.¹⁵ In this series, the authors also noted that cryoablation did not produce artifacts that could interfere with the interpretation of mammograms. These small case series, which were done by the same group of investigators, are inadequate to permit scientific conclusions.

Nurko et al (2005) reported on outcomes at 6 and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment registry by 55 different practice settings.¹⁶ In these patients, before cryoablation, 75% of fibroadenomas were palpable by the patient. Follow-up at 6- and 12-month intervals showed palpable masses in 46% and 35%, respectively.

When fibroadenomas were grouped by size, for lesions 2 cm or less in diameter, the treatment area was palpable in 28% of subjects at 12 months. For lesions more than 2 cm, the treatment area was palpable in 59% at 12 months.

It is unclear whether “nonpalpability” is the most appropriate medical outcome. Fibroadenomas are benign lesions with only a very remote probability of malignant conversion, and thus complete surgical excision may be recommended primarily to allay patients’ concerns about harboring a palpable lesion.

Section Summary: Breast Diseases

For the treatment of primary and recurrent breast cancer, available evidence has shown that complete ablation can be achieved in most cases for variably defined small tumors, but studies have not included control groups or compared outcomes of cryosurgery with alternative strategies for managing similar patients. Therefore, no conclusions can be made on the net health outcome of cryosurgery for breast cancer. For treatment of fibroadenomas, there is a small body of evidence. This evidence has demonstrated that most fibroadenomas become “nonpalpable” following cryoablation. However, there is a lack of comparative trials. Comparative trials with adequate long-term follow-up are needed to assess this technology and determine how this approach compares with surgery, as well as with vacuum-assisted excision and with observation (approximately one-third of fibroadenomas regress over time after cryoablation).

Lung Cancer

Systematic Reviews

Lee et al (2011) conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors.¹⁷ Included in the review were 15 case studies and a comparative observational study. Cryoablation was performed for inoperable, advanced lung and bronchial cancers in most studies. Some studies included patients with comorbid conditions and poor general health who would not be considered surgical candidates. Complications occurred in 11.1% of patients (10 studies) and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients.

Niu et al (2012) reviewed the literature on lung cryoablation and reported on their own experience with PCA in 150 patients with non-small-cell lung cancer followed for 12 to 38 months.¹⁸ The study population had stage IIIB or IV lung cancer. OS rates at 1, 2, and 3 years were 64%, 45%, and 32%, respectively. Thirty-day mortality was 2.6% and included cardiac arrest and hemopneumothorax. Complications included hemoptysis, pneumothorax, hemothorax, pleural effusion, and pulmonary infection.

Ratko et al (2013) conducted a comparative effectiveness review on local nonsurgical therapies for stage I and symptomatic obstructive non-small-cell lung cancer for the Agency for Healthcare Research and Quality.¹⁹ Cryoablation was included as a potential therapy for airway obstruction due to an endoluminal non-small-cell lung cancer. Reviewers were unable to draw any conclusions about local nonsurgical therapies, including cryoablation, due to lack of quality evidence.

Nonrandomized Studies

The Evaluating Cryoablation of Metastatic Lung/Pleura Tumors in Patients-Safety and Efficacy (ECLIPSE) trial is prospective, multicenter trial of cryoablation for metastatic disease in the lungs; interim results at 1-year follow-up were published by de Baere et al (2015).²⁰ The trial enrolled 40 patients with 60 metastatic lung lesions who were treated with cryoablation and had at least 12 months of follow-up. Outcomes included survival, local tumor control, quality of life, and complications. Local tumor control was achieved in 94.2% (49/52) of treated lesions, and the 1-year OS rate was 97.5% (39/40). There were no significant changes in quality of life over the 12-month study. The most common adverse event was pneumothorax requiring chest tube intubation in 18.8% (9/48 procedures). No subsequent analyses have been identified.

Moore et al (2015) reported on a retrospective case review of 45 patients (47 tumors) managed with cryoablation during a 5-year period (2006-2011).²¹ All patients had biopsy-confirmed early-stage (T1a and T1b) primary lung tumors and had been assessed by a tumor board to be medically inoperable. Lesions were as small as 5 mm, with an average of 1.9 cm (range, 0.5-3 cm). Cryoablation was performed under general anesthesia. The primary endpoint was the completion of the freeze-thaw cycle. Mean follow-up was 51 months, with an observed 5-year survival rate of 67.8%, 5-year cancer-specific survival rate of 56.6%, and 5-year progression-free survival rate of 87.9%. There were 7 (14.8%) local recurrences; two had device failure and retreatment, and another had retreatment for a tumor recurrence at 1 year after initial treatment. The ablation zone was less than 5 mm outside the margin of the tumor in 5 of the 47 treatments, and 4 of these 5 had local recurrences. Complications primarily included 19 (40%) patients with hemoptysis, two of which required bronchoscopy, and 24 (51%) cases of pneumothorax, one of which required surgical chest intubation with prolonged placement and mechanical sclerosis. These 3 (6.4%) patients were considered major complications, but there were no reports of 30-day mortality.

Maiwand and Asimakopoulos (2004) reported on a large case series of 521 patients with symptomatic obstructive tracheobronchial malignant tumors who underwent cryosurgery with a mean of 2.4 treatments per patient.²² The patients were treated between 1995 and 2003, had a mean age of 67.9 years, and 72% were diagnosed with stage IIIB or IV disease. Improvement in one or more symptoms (hemoptysis, cough, dyspnea, chest pain) was demonstrated in 86.0% of patients. Postoperative complications were 9%, including 21 (4%) cases of hemoptysis, 12 (2%) cases of postoperative atrial fibrillation, and 16 (3%) patients developed respiratory distress and poor gas exchange that eventually resolved. There were 7 (1.2%) in-hospital deaths (cause of death was respiratory failure in all 7 patients).

Asimakopoulos et al (2005) reported on a subset of the same population of patients, analyzing outcomes from 2 groups of patients.²³ Group A consisted of 172 patients who underwent at least 2 sessions of cryoablation; group B consisted of 157 patients who underwent only 1 session of cryosurgery. The single treatment group (group B) was more diverse; it presented with a medical condition that did not permit patients to undergo a second session of cryosurgery. Group B was also more likely to have stage III or IV disease and less likely to have had prior palliative radiotherapy. Overall, there was a statistically significant chance ($p < 0.001$) that dyspnea would improve by at least 1 New York Heart Association functional class 2 weeks after the second session of cryosurgery. Patients in group B benefited to a lesser degree from cryosurgery. In group A, the chance of a patient experiencing improvement in cough by at least 1 class after 2

sessions of cryosurgery was statistically significant ($p < 0.001$). Group B patients benefited less with regard to improvement in cough. Only 78 (43.3%) of the 172 patients in group A reported episodes of hemoptysis before or after treatment. Overall, there was a statistically significant reduction in hemoptysis ($p < 0.001$). Group B had limited follow-up attendance.

Section Summary: Lung Cancer

The evidence on cryosurgery for lung cancer consists of studies that use cryosurgery for inoperable or metastatic disease. The available studies are small cohort studies and nonrandomized studies with relatively short-term follow-up as well as systematic reviews of these studies. Additionally, complications have frequently been reported and severe, but the true incidence of complications is uncertain and difficult to differentiate from manifestations of the underlying malignancy. Because available studies do not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients, no conclusions can be made on the net health outcome of cryosurgery for lung cancer.

Pancreatic Cancer

Systematic Reviews

Tao et al (2012) reported on a systematic review of cryoablation for pancreatic cancer.²⁴ Reviewers identified 29 studies and selected 5. All 5 were case series and considered of low quality. Adverse events, when mentioned, included delayed gastric emptying (0%-40.9% in 3 studies), pancreatic leak (0%-6.8% in 4 studies), biliary leak (0%-6.8% in 3 studies), and a single instance of upper gastrointestinal hemorrhage. Pain relief was reported in 3 studies and ranged from 66.7% to 100%. Median survival times reported in 3 studies ranged from 13.4 to 16 months. One-year total survival rates, as reported in 2 studies, were 57.5% and 63.6%. Keane et al (2014) reported on a systematic review of ablation therapy for locally advanced pancreatic cancer.²⁵ Reviewers noted that studies had demonstrated ablative therapies, including cryoablation, are feasible, but larger studies are needed. No conclusions could be made on whether ablation resulted in better outcomes than best supportive care.

Nonrandomized Trials

Li et al (2011) reported on a retrospective study of 142 patients with unresectable pancreatic cancer treated with palliative bypass with ($n=68$) or without cryoablation ($n=74$) from 1995 to 2002.²⁶ Median dominant tumor sizes decreased from 4.3 to 2.4 cm in 36 (65%) of 55 patients 3 months after cryoablation. Survival rates did not differ significantly between groups, with the cryoablation group surviving a median of 350 days vs 257 days in the group without cryoablation. Complications did not differ significantly between groups. However, a higher percentage of delayed gastric emptying occurred in the cryoablation group (36.8%) than in the group without cryoablation (16.2%).

A pilot study assessing combination cryosurgery plus iodine 125 seed implantation for treatment of locally advanced pancreatic cancer was reported by Xu et al (2008).²⁷ Forty-nine patients enrolled in the pilot study, and 12 had liver metastases; 20 patients received regional chemotherapy. At 3 months posttherapy, most patients showed tumor necrosis, with 20.4% having a complete response. Overall, the 6-, 12-, 24-, and 36-month survival rates were 94.9%, 63.1%, 22.8%, and 9.5%, respectively.

Kovach et al (2002) reported on 10 cryosurgical ablations in 9 patients with unresectable pancreatic cancer using intraoperative ultrasound guidance during laparotomy.²⁸ The authors reported adequate pain control in all patients postoperatively and no intraoperative morbidity or mortality. At publication, all patients had died at an average of 5 months postoperatively (range, 1-11 months).

Section Summary: Pancreatic Cancer

The available evidence on cryosurgery for pancreatic cancer consists of retrospective case series that used cryosurgery for palliation of inoperable disease and a systematic review of these studies. These studies reported that pain relief was achieved in most cases and that complications (eg, delayed gastric emptying) are common, but the true rate of complications is uncertain. Because these studies did not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients, no conclusions can be made on the net health outcome of cryosurgery for pancreatic cancer.

Renal Cell Carcinoma

There are a relatively large number of studies on cryoablation for renal cell carcinoma (RCC). However, there is also a lack of prospective controlled trials to determine comparative efficacy vs treatment alternatives. Numerous systematic reviews and meta-analyses have assessed these case series, some of which have indirectly compared cryosurgery outcomes with alternative strategies.

Systematic Reviews

Pessoa et al (2017) reported on the results of a systematic review of studies comparing the use of laparoscopic cryoablation (LCA) with PCA for the treatment of small renal masses.²⁹ Eleven studies were identified through March 2016 and represented a total of 1725 kidney cryoablation cases: 921 (53.4%) LCA and 804 (46.6%) PCA. All cases were obtained from observational retrospective case-control studies. No significant differences were found for baseline population characteristics including rates of premalignant histology and tumor sizes. Moreover, PCA was performed more frequently for posterior renal tumors. The rate of successful biopsies obtained did not differ significantly between techniques (88.5% for LCA vs 76.3% for PCA; $p=0.59$). The interventions were also comparable in operating times as well as intraoperative and postoperative complications.

Residual disease was defined as a persistent imaging study enhancement in seven of eight studies, and only one study relied on histopathology to confirm residual disease. Recurrent disease was defined as imaging enhancement after an initial negative imaging in 4 of 7 studies. Imaging and confirmatory biopsy to confirm recurrence was reported in 3 studies. A PCA approach resulted in a higher likelihood of residual disease (odds ratio OR., 2.6; 95% CI, 1.31 to 3.57; $p=0.003$) and a seemingly paradoxical lower likelihood of tumor recurrence (OR=0.62; 95% CI, 0.41 to 0.94; $p=0.02$). This systematic review provided some evidence, albeit low level, of the minimally invasive interventions emerging in clinical practice. The lack of pathologic confirmation of residual and recurrent lesions is a significant limitation.

Tang et al (2014) reported on a systematic review and meta-analysis comparing laparoscopic renal cryoablation with laparoscopic partial nephrectomy in the treatment of small renal masses.³⁰ Reviewers identified 9 trials (2 prospective, 7 retrospective) in which the 2 techniques

were assessed (555 cases, 642 controls). LCA was associated with statistically significant shorter surgical times, less blood loss, and fewer overall complications; however, it was estimated that laparoscopic partial nephrectomy might have a significantly lower local recurrence rate (OR=13.03; 95% CI, 4.20 to 40.39; $p<0.001$) and lower distant metastasis rate (OR=9.05; 95% CI, 2.31 to 35.51; $p=0.002$).

Klatte et al (2014) also reported on a systematic review and meta-analysis comparing LCA with laparoscopic partial nephrectomy for small renal tumors.³¹ Thirteen nonrandomized studies were selected for analysis, which found LCA was associated with better perioperative outcomes than laparoscopic partial nephrectomy. Oncologic outcomes, however, were inferior with cryoablation, which was significantly associated with greater risk of local (relative risk, 9.39) and metastatic (relative risk, 4.68) tumor progression.

Martin and Athreya (2013) reported on a meta-analysis that compared cryoablation with microwave ablation for small renal tumors.³² Analysis of 51 studies did not reveal any significant differences between microwave ablation and cryoablation in primary effectiveness (93.75% vs 91.27%; $p=0.4$), cancer-specific survival (98.27% vs 96.8%; $p=0.47$), local tumor progression (4.07% vs 2.53%; $p=0.46$), or progression to metastases (0.8% vs 0%; $p=0.12$), all respectively. In the microwave ablation group, the mean tumor size was significantly larger ($p=0.03$). Open access was used more often in the microwave ablation group (12.20% vs 1.04%, respectively; $p<0.001$) and percutaneous access was used more often in the cryoablation group (88.64% vs 37.20%, respectively; $p=0.002$).

El Dib et al (2012) conducted a meta-analysis evaluating cryoablation and radiofrequency ablation (RFA) for small renal masses.³³ Twenty cryoablation ($n=457$ patients) and 11 RFA ($n=426$ patients) case series, published through January 2011, were selected. Mean tumor size was 2.5 cm in diameter (range, 2-4.2 cm) in the cryoablation group and 2.7 cm (range, 2-4.3 cm) in the RFA group. Mean follow-up times for the cryoablation group and RFA group were 17.9 months and 18.1 months, respectively. Clinical efficacy measures, defined as rates of cancer-specific survival, radiographic success, no evidence of local tumor progression, or distant metastases, did not differ significantly between groups. The pooled proportion of clinical efficacy for cryoablation was 89% (95% CI, 0.83% to 0.94%) and 90% (95% CI, 0.86% to 0.93%) for RFA.

In another systematic review, Klatte et al (2011) reviewed 98 studies published through December 2010 to compare the treatment of small renal masses with LCA or partial nephrectomy.³⁴ Partial nephrectomy was performed in 5347 patients, and LCA was performed in 1295 patients. RCC was confirmed in 159 (2.9%) of patients. After cryoablation, local tumor progression of RCC occurred at a rate of 8.5% (70/821; range, 0%-17.7%). After partial nephrectomy, 1.9% (89/4689; range, 0%-4.8%) of patients experienced local tumor progression. Distant metastasis occurred more frequently in partial nephrectomy patients ($n=91$) than in cryoablation patients ($n=9$), although not significantly ($p=0.126$). However, mean tumor size for cryoablation patients (2.4 cm) was smaller than in the partial nephrectomy patients (3.0 cm; $p<0.001$). Fewer patients receiving cryoablation (17%; range, 0%-42%) experienced perioperative complications than partial nephrectomy patients (23.5%; range, 8%-66%; $p<0.001$).

Long et al also (2011) reported on a systematic review comparing PCA with surgical cryoablation of small renal masses.³⁵ Forty-two studies treating small renal masses (total N=1447 lesions) were reviewed, including 28 articles on surgical cryoablation and 14 articles on PCA. Reviewers concluded percutaneous and surgical cryoablation for small renal masses have similar, acceptable short-term oncologic outcomes, and each technique is relatively equivalent for rates of residual and recurrent tumors.

Van Poppel et al (2011) reviewed the literature on localized RCC treatment published between 2004 and May 2011.³⁶ They concluded cryoablation is a reasonable treatment option for low-grade renal tumors less than 4 cm in diameter (mostly <3 cm) in patients not candidates for surgical resection or active surveillance.

In a Cochrane review, Nabi et al (2010) assessed evidence on the management of localized RCC.³⁷ No randomized trials comparing cryoablation with open radical or partial nephrectomy were identified. One nonrandomized study, comparing laparoscopic partial nephrectomy with LCA using a matched-paired analysis,³⁸ and 3 retrospective studies were selected. Reviewers noted PCA can successfully destroy small RCC and may be considered a treatment option in patients with serious comorbidities that pose surgical risks. Reviewers concluded that high-quality RCTs are required for the management of localized RCC and that an area of emphasis should be the comparative efficacy of renal surgery with minimally invasive techniques for small tumors (<4 cm). This review was withdrawn and replaced by another with a narrower scope. The Cochrane review replacement by Kunath et al (2017) focused on partial nephrectomy and radical nephrectomy as the relevant surgical therapy options for localized RCC.³⁹ Only 1 RCT was identified (n=541 participants) that compared partial nephrectomy with radical nephrectomy. The median follow-up was 9.3 years. The trial was judged to demonstrate a time-to-death of any cause, that favored using partial nephrectomy (hazard ratio, 1.50; 95% CI, 1.03 to 2.18). No other analyses were performed. Study limitations included lack of blinding and imprecision (a substantial proportion of patients were ultimately found not to have a malignant lesion).

Kunkle and Uzzo (2008) conducted a comparative meta-analysis of cryoablation and RFA as primary treatment for small renal masses.⁴⁰ Forty-seven case series representing 1375 renal tumors were analyzed. Of 600 lesions treated with cryoablation, 494 underwent biopsy before treatment vs 482 of 775 treated with RFA. The incidence of RCC with known pathology was 72% in the cryoablation group and 90% in the RFA group. The mean duration of follow-up after cryoablation was 22.5 months. Most studies used contrast-enhanced imaging to determine treatment effect. Local tumor progression was reported in 31 (5%) of 600 lesions after cryoablation and in 100 (13%) of 775 lesions after RFA. Progression to metastatic disease was described in 6 (1%) of 600 lesions after cryoablation and 19 (2.5%) of 775 after RFA. Reviewers cautioned that minimally invasive ablation had generally been performed selectively on older patients with smaller tumors, possibly resulting in selection bias; case series of ablated lesions tend to have shorter posttreatment follow-up compared with tumors managed by surgical excision or active surveillance, and treatment efficacy may be overestimated in series that include tumors with unknown pathology.

Matin and Ahrar (2008) reviewed studies evaluating cryoablation and RFA with at least a 12-month follow-up and found that 3- and 5-year outcomes showed 93% to 98% cancer-specific survival in small cohorts.⁴¹ They cautioned that, while selected studies suggested satisfactory

outcomes, given the limitations of imaging and the indolent nature of the tumors, stringent selection criteria and rigorous follow-up were required.

Nonrandomized Comparative Studies

One retrospective, nonrandomized comparative study of different cryoablation techniques was identified. Strom et al (2011) reported on a retrospective comparison of 145 patients who underwent laparoscopic (n=84) or percutaneous (n=61) cryoablation of small renal masses at 5 U.S. academic medical centers.⁴² Patients were offered cryoablation because they were considered to be at higher risk for complications from partial nephrectomy or were not surgical candidates due to comorbidities. Mean tumor sizes were 2.7 cm in the laparoscopic group and 2.5 cm in the percutaneous group. Patients were followed longer in the laparoscopic group (mean, 42.3 months) than in the percutaneous group (31.0 months; p=0.008). Complications in both treatment groups were similar and did not occur with any significant difference in frequency. At a mean intermediate follow-up of 37.6 months, local tumor recurrence was significantly higher in the percutaneous group (16.4%; 10/61.) than in the laparoscopic group (5.9%; 5/84.). However, disease-free survival and OS did not differ significantly at the last follow-up in the laparoscopic group (91.7% and 89.3%) compared with the percutaneous group (93.7% and 88.9%), respectively.

Case Series

The individual case series do not add substantially to the evidence on efficacy, but a number have reported intermediate or longer term outcomes for cryoablation with RCC. Caputo et al (2015) reported on long-term outcomes on 138 patients with 142 tumors, with a mean follow-up of 98.8 months.⁴³ Perioperative complications occurred in 15 patients, for a rate of 10.6%. Recurrence-free survival was 91.4% at 3 years, 86.5% at 5 years, and 86.5% at 10 years. The latest reported recurrence occurred 4.4 years posttreatment.

Weld et al (2007) reported on 3-year follow-up for 36 (22 malignant) renal tumors treated with LCA.⁴⁴ In this series, the 3-year cancer-specific survival rate was 100%, and no patient developed metastatic disease. The authors concluded that these intermediate-term data seemed equivalent to results obtained with extirpative therapy. Hegarty et al (2006) reported on results for 164 LCAs and 82 percutaneous RFAs for localized renal tumors.⁴⁵ Mean tumor size was 2.5 cm. Cancer-specific survival following cryotherapy was 98% at a median follow-up of 3 years and 100% for RFA at just 1-year median follow-up. Studies have also reported results for small numbers of patients who had LCA or laparoscopic partial nephrectomy for treatment of renal masses.³⁸

In a prospective, single-institution study, Rodriguez et al (2011) reported on 113 patients consecutively treated with PCA for 117 renal lesions.⁴⁶ The average renal lesion size in the study was 2.7 cm (83 71%. were RCC). Patients were selected for cryoablation over surgery when tumors were 4 cm or less in diameter and percutaneously approachable or if the patient could not tolerate surgery when tumors were greater than 4 to 7 cm. Technical success was reported as 100%, with 93% of patients having no or only mild complications. At a median follow-up of 2 years (59 patients), efficacy was 98.3% and 92.3% at 3 years (13 patients). Metastatic disease did not occur in any patients during follow-up, and cancer-specific survival was 100%.

Nguyen et al (2008) evaluated options for salvage of ipsilateral tumor recurrence after previous ablation.⁴⁷ Recurrence rates at their center were 13 (7%) of 175 after cryoablation and 26 (25%) of 104 after RFA. Extensive perinephric scarring was encountered in all salvage operations following cryoablation, leading authors to conclude that cryoablation, in particular, can lead to extensive perinephric fibrosis, which can complicate salvage attempts.

Section Summary: Renal Cancer

There is a large body of single-arm studies and systematic reviews of these studies reporting on cryoablation outcomes for small renal tumors, most of which involved patients who are inoperable or at high surgical risk. The success rate for cryoablation is high, likely greater than 95%, and the long-term disease-free survival is more than 90%. Some meta-analyses have performed indirect comparisons of cryoablation with surgery, but they had a selection bias and did not definitively provide evidence of comparative effectiveness. Prospective controlled trials are needed to determine whether cryoablation achieves equivalent outcomes and/or reduced complications, compared with surgical treatment.

Bone Cancers

Meller et al (2008) retrospectively analyzed a single-center experience with 440 bone tumor cryosurgery procedures performed between 1988 and 2002, two-thirds of them for primary benign-aggressive and low-grade malignant lesions, and one-third for primary high-grade and metastatic bone tumors.⁴⁸ At a median follow-up of 7 years (range, 3-18 years), the overall recurrence rate was 8%. Based on their data, the authors suggested that the ideal case for cryosurgery is a young adult with involvement of long bone, a benign-aggressive or low-grade malignant bone tumor, a good cavity with greater than 75%-thick surrounding walls, no or minimal soft-tissue component, and at least ± 1 cm of subchondral bone left near a joint surface after curettage and burr drilling.

Callstrom et al (2013) reported on 61 patients treated with cryoablation for pain from 69 tumors (size, 1-11 cm) metastatic to the bone.⁴⁹ Before treatment, patients rated their pain with a 4+ on a 1-to-10 scale using the Brief Pain Inventory, with a mean score of 7.1 for worst pain in a 24-hour period. The mean pain score gradually decreased after cryoablation to 1.4 ($p < 0.001$) at 24 weeks for worst pain in a 24-hour period. A major complication of osteomyelitis was experienced by 1 (2%) patient.

Other articles identified in the literature search related to use of cryoablation in other cancers either involved small numbers of patients or limited follow-up.

Section Summary: Bone Cancers

There is a small amount of literature on cryoablation for bone cancers. This evidence base consists of case series and is inadequate to determine efficacy for any of the indications studied.

SUMMARY OF EVIDENCE

For individuals who have solid tumors (located in areas of the breast, lung, pancreas, kidney, or bone) who receive cryosurgical ablation, the evidence includes nonrandomized comparative studies, case series, and systematic reviews of these nonrandomized studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. There is a lack of randomized controlled trials and high-quality comparative studies to determine

the efficacy and comparative effectiveness of cryoablation. The largest amount of evidence assesses renal cell carcinoma in select patients (ie, those with small tumors who are not surgical candidates, or those who have baseline renal insufficiency of such severity that standard surgical procedures would impair their kidney function). Cryoablation results in short-term tumor control and less morbidity than surgical resection, but long-term outcomes may be inferior to surgery. For other indications, there is less evidence, with single-arm series reporting high rates of local control. Due to the lack of prospective controlled trials, it is difficult to conclude that cryoablation improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

2017 Input

In response to requests, clinical input on use of cryosurgical ablation to manage individuals with localized renal cell cancer, use of cryosurgical ablation to manage individuals with lung cancer, and use of cryosurgical ablation to manage individuals with breast, pancreatic, or bone cancers was received from 9 respondents, including 2 specialty society-level responses, 3 physician-level responses identified by specialty societies, and 4 physicians identified by 1 health system, while this policy was under review in 2017.

Based on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice.

- Use of cryosurgical ablation to manage individuals with localized renal cell cancer when either of the following criteria is met:
- No more than 4 cm in size when preservation of kidney function is necessary (ie, the patient has 1 kidney or renal insufficiency defined by a glomerular filtration rate <60 mL/min/m²), and standard surgical approach (ie, resection of renal tissue) is likely to worsen kidney function substantially; or
- When the patient is not considered a surgical candidate.
- Use of cryosurgical ablation to manage individuals with lung cancer when either of the following criteria is met:
- Poor surgical candidates with early-stage non-small-cell lung cancer; or
- Palliation of a central airway obstructing lesion.

Based on the evidence and independent clinical input, the clinical input does not support whether the following indication provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice.

- Use of cryosurgical ablation to manage individuals with:
- Malignant or benign tumors of the breast;
- Pancreatic cancer; or
- Bone cancer.

2009 Input

In response to requests, input was received from 2 physician specialty societies (5 reviews) and from 2 academic medical centers (3 reviews) while this policy was under review in 2009. There was strong support for the use of cryoablation in the treatment of select patients with renal tumors. There also was support for its use in the treatment of benign breast disease. Reviewers generally agreed cryoablation was investigational in the treatment of pancreatic cancer.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Radiology

The 2009 American College of Radiology Appropriateness Criteria for renal cell carcinoma, updated most recently in 2014, indicated that “As an alternative to partial nephrectomy, energy-ablative therapies, such as cryoablation... are being used to treat small renal cell carcinomas. These therapies have been shown to be effective and safe.”⁵⁰ These recommendations are based on a review of the data and consensus.

American Urological Association

The American Urological Association (2017) updated its guidelines on evaluation and management of clinically localized sporadic renal masses suspicious for renal cell carcinoma.⁵¹ The guideline statements on thermal ablation (radiofrequency ablation, cryoablation) are listed in Table 1.

Table 1. Guidelines on Localized Masses Suspicious for Renal Cell Carcinoma

Recommendations	LOR	LOE
Guideline statement 24 Physicians should consider thermal ablation (TA) as an alternate approach for the management of cT1a renal masses <3 cm in size. For patients who elect TA, a percutaneous technique is preferred over a surgical approach whenever feasible to minimize morbidity.	Conditional	C
Guideline statement 25 Both radiofrequency ablation and cryoablation are options for patients who elect thermal ablation	Conditional	C
Guideline statement 27 Counseling about thermal ablation should include information regarding an increased likelihood of tumor persistence or local recurrence after primary thermal ablation relative to surgical extirpation, which may be addressed with repeat ablation if further intervention is elected	Strong	B

LOE: level of evidence; LOR: level of recommendation.

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines on kidney cancer (v.4.2018) state that, based on lower level evidence and uniform NCCN consensus, cryosurgery: “Can be considered for patients with clinical stage T1 renal lesions who are not surgical candidates. Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery ... and. ablation strategies.”⁵² NCCN guidelines also note that “Randomized phase III comparison with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been done” and “Ablative techniques are associated with a higher local recurrence rate than conventional surgery.”

NCCN guidelines for non-small-cell lung cancer (v.4.2018) indicate surgical “resection is the preferred local treatment modality” and “other modalities include ... cryotherapy.”⁵³

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Renal cancer			
NCT01957787 ^a	Study of Cryoablation for Metastatic Lung Tumors (SOLSTICE)	134	Sep 2018
NCT02399124 ^a	ICESECRET PROSENSE™ Cryotherapy for Renal Cell Carcinoma Trial	100	Jan 2022
NCT03390413	Robot-assisted Surgical Resection vs. Cryoablation of Localised Renal Cancer - a Randomised Trial of Functional, Oncological and Financial Aspects	190	Mar 2028

NCT: national clinical trial.

^aDenotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 19105 Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma
- 20983 Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation
- 32994 Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation
- 50250 Ablation, open, 1 or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound guidance and monitoring, if performed
- 50542 Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed
- 50593 Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy

ICD-10 Diagnoses

- C64.1 Malignant neoplasm of right kidney, except renal pelvis
- C64.2 Malignant neoplasm of left kidney, except renal pelvis
- C64.9 Malignant neoplasm of unspecified kidney, except renal pelvis
- C65.1 Malignant neoplasm of right renal pelvis
- C65.2 Malignant neoplasm of left renal pelvis

REVISIONS

03-04-2019	Policy added to the bcbsks.com web site on 02-01-2019 with an effective date of 03-04-2019.
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