Cryosurgical Ablation of Miscellaneous Solid Tumors Other than Liver, Prostate, or Dermatologic Tumors

Policy Number: 7.01.92  Last Review: 9/2017
Origination: 2/2006  Next Review: 9/2018

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

When Policy Topic is covered
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:
- Preservation of kidney function is necessary (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of <60mL/min/m²) and standard surgical approaches (i.e., resection of renal tissue) is likely to substantially worsen kidney function; or
- Patient is not considered a surgical candidate due to co-morbid disease.

When Policy Topic is not covered
Cryosurgical ablation is considered investigational as a treatment of benign or malignant tumors of the breast, lung, pancreas, or other solid tumors or metastases outside the liver and prostate, and to treat renal cell carcinomas in patients who are surgical candidates.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: With solid tumors of the breast, lung, pancreas, kidney, or bone</td>
<td>Interventions of interest are: ▪ Cryosurgical ablation</td>
<td>Comparators of interest are: ▪ Surgical resection ▪ Other ablative techniques ▪ No intervention</td>
<td>Relevant outcomes include: ▪ Overall survival ▪ Disease-specific survival ▪ Quality of life ▪ Treatment-related morbidity</td>
</tr>
</tbody>
</table>
Cryosurgical ablation (hereafter cryosurgery or cryoablation) involves freezing of target tissues, most often by inserting into the tumor a probe through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

For individuals who have solid tumors 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 is for renal cell carcinoma in select patients, ie, those with small tumors who are not surgical candidates or who have baseline renal insufficiency such 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 draw conclusions whether cryoablation improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

There was strong clinical support for cryoablation in patients with small renal cell cancers who are either poor surgical candidates or whose kidney function is likely to be substantially impaired by surgery. Contextual factors contributing to this support include the lack of treatment alternatives and the potential for reduced harm compared to surgery.

**Background**

The hypothesized advantages of cryosurgery include improved local control and benefits common to any minimally invasive procedure (e.g., preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization). 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.

Cryosurgical treatment of various tumors including renal cell carcinomas, malignant and benign breast disease, pancreatic cancer, and lung cancer has been reported in the literature.

**Breast tumors.** Early stage primary breast cancers are treated surgically. The selection of lumpectomy, modified radical mastectomy, or another approach balances 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. Adjutant radiation therapy decreases local recurrences, particularly for those who select lumpectomy. Adjutant 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 primary lesion and combination chemotherapy.

Fibroadenomas are common, benign tumors of the breast that can either 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 radiation treatment 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. This is rarely curative but rather 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 is almost always fatal. 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. This is rarely curative but rather seeks to retard tumor growth or palliate symptoms.

**Renal cell carcinoma.** Localized renal cell carcinoma (RCC) is treated by radical nephrectomy or nephron-sparing surgery. Prognosis drops precipitously if the tumor extends outside the kidney capsule, since chemotherapy is relatively ineffective against metastatic RCC.

**Regulatory Status**
There are several cryoablation devices cleared for marketing by the U.S. Food and Drug Administration (FDA) 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 by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit by Galil Medical for the treatment of breast fibroadenoma;
- SeedNet System by Galil Medical; and
- Visica System by Sanarus Medical.

**Rationale**
This evidence review was originally created in October 2003 and has been updated regularly with searches of the MEDLINE database. The most recent literature search was performed through June 14, 2017.
The following sections summarize those studies that adequately described baseline characteristics of the patient populations and the methods used for cryosurgery and also reported outcomes of treatment for 8 or more patients with the same diagnosis, or 8 or more procedures on the same malignancy. One article discussed cryosurgery in 429 patients with a wide variety of primary and recurrent solid tumors (eg, head and neck, lung, genital organs, sarcomas). (1) Although the author reported survival for some patient subsets with some of these malignancies, the article only reported baseline tumor and patient characteristics for those with breast cancer (see next section).

**BREAST DISEASE**

**Breast Cancer**

A prospective, single-arm, phase 2 trial was published by the American College of Surgeons Oncology Group Z1072 in 2016. (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 neither that cryoablation is potentially efficacious, nor that the results of cryoablation were unsatisfactory.

In 2010, Zhao and Wu reported on a systematic review of minimally invasive ablative techniques of early-stage breast cancer. (3) They noted that studies on cryoablation for breast cancer are primarily limited to pilot and feasibility studies in the research setting. Complete ablation of tumors was found to be reported within a wide range (36%-83%). Because there are many outstanding issues, including patient selection criteria and the ability to precisely determine the size of tumors and achieve 100% tumor cell death, the reviewers noted minimally invasive thermal ablation techniques for breast cancer treatment, including cryoablation, should be limited until results from prospective, randomized controlled trials (RCTs) become available.

Niu et al reported on a 2013 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 who were treated with chemotherapy (n=29) or cryoablation (n=91, 35 of whom also received immunotherapy). (4) At 10-year follow-up, median overall survival (OS) of all study participants was 55 months in the cryoablation group versus 27 months in the chemotherapy group (p<0.001). Median OS was also greater in patients receiving multiple cryoablations and in those receiving immunotherapy. Complications with cryotherapy to the
breast were ecchymosis and hematoma, pain, tenderness, and edema, all of which resolved within 1 week to 1 month.

Three studies have described outcomes from cryosurgery for advanced primary or recurrent breast cancer in 72 patients.(1,5,6) Cryosurgery was performed percutaneously with ultrasound guidance (n=15) or during an open surgical procedure (n=57). Patients were treated for advanced primary disease (44%) or recurrent tumors (56%). Tanaka (1995) reported on a retrospective series of 9 patients with advanced primary tumors and 40 with recurrent disease.(1) The author reported 44% (n=9) survival of primary breast cancer patients at 3 and 5 years but did not report survival duration or other outcomes for those with recurrent or metastatic disease. The report also did not adequately describe selection criteria for trial enrollees, details of the procedure, and procedure-related adverse events. The other studies were smaller series of patients with inadequate study designs, analyses, and reporting of results.(5-7) Furthermore, the trial by Pfleiderer et al (2002) was a pilot to evaluate technical limitations of the procedure.(5) Tumors were excised and evaluated by pathology days to weeks after cryosurgery, and the authors reported incomplete necrosis in tumors more than 23 mm in diameter.

One 2004 case series by Sabel et al explored the role of cryoablation as an alternative to surgical excision as a primary treatment of early-stage breast cancer.(8) 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. 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.(9) In a case series of 15 breast cancer patients, percutaneous cryoablation was performed 30 to 45 days before surgical resection.(10) 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.

**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 have published several case series on office-based ultrasound-guided cryoablation as a treatment of breast fibroadenomas.(11-15) These case series reported on a range of 29 to 68 patients followed for 6 months to 2.6 years. It is likely that these case series included overlapping patients. At 1 year, patients reported 91% patient satisfaction and fibroadenomas became nonpalpable in 75% of cases. At follow-up averaging 2.6 years in 37 patients, the authors noted only 16% of 84% palpable fibroadenomas remained palpable after treatment and, of the fibroadenomas initially 2 cm or less in diameter, only 6% remained palpable.(15) In this series, the authors also noted that cryoablation did not produce artifacts that could
Nurko et al (2005) reported on outcomes at 6 and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment (FACT) registry involving 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% 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 chance of malignant conversion, and thus complete surgical excision may be recommended primarily to allay patients’ concerns about harboring a palpable lesion.

Section Summary: Breast Disease
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 do not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients. Therefore, no conclusions can be made on the net health outcomes of cryosurgery for breast cancer. For treatment of fibroadenomas, there is a small amount 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 regress over time after cryoablation).

LUNG CANCER
The ECLIPSE trial is prospective, multicenter trial of cryoablation for metastatic disease in the lungs, interim results at 1-year follow-up were published in 2015. (17) 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 1-year OS 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 insertion in 18.8% (9/48 procedures). No subsequent analyses were identified.

Lee et al (2011) conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors. (18) Included in the review were 15 case studies and 1 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.

In 2012, Niu et al reviewed the literature on lung cryoablation and reported on their own experience with percutaneous cryoablation in 150 patients with non-small-cell lung cancer (NSCLC) followed for 12 to 38 months.(19) 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.

An Agency for Healthcare Research and Quality comparative effectiveness review on local nonsurgical therapies for stage I and symptomatic obstructive NSCLC was published in 2013.(20) Cryoablation was included as a potential therapy for airway obstruction due to an endoluminal NSCLC. The reviewers were unable to draw any conclusions on local nonsurgical therapies, including cryoablation, due to lack of available quality evidence.

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 and nonrandomized studies with relatively short-term follow-up. In addition, complications are reported frequently and can be 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 outcomes of cryosurgery for lung cancer.

PANCREATIC CANCER
In 2012, Tao et al reported on a systematic review of cryoablation for pancreatic cancer.(21) 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 1 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 reported in 2 studies were 57.5% and 63.6%. Keane et al reported on a systematic review of ablation therapy for locally advanced pancreatic cancer in 2014.(22) The review noted studies have 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.
Kovach et al (2002) reported 10 cryosurgical ablations in 9 patients with unresectable pancreatic cancer using intraoperative ultrasound guidance during laparotomy. The authors reported adequate pain control in all patients postoperatively and no intraoperative morbidity or mortality. At the time of publication, all patients had died at an average of 5 months postoperatively (range, 1-11 months).

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

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. 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 versus 257 days in the group without cryoablation. Complications did not differ significantly between the 2 groups. However, a higher percentage of delayed gastric emptying occurred in the cryoablation group (36.8%) than the group without cryoablation (16.2%).

**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. These studies reported that pain relief is 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 outcomes of cryosurgery for pancreatic cancer.

**RENAAL 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 versus alternatives. There are also numerous systematic reviews and meta-analyses of these case series, some of which have indirectly compared cryosurgery outcomes to alternative strategies.

**Systematic Reviews**
In 2017, Pessoa et al reported the results of a systematic review of the literature on studies comparing the use of laparoscopic cryoablation (LCA) to percutaneous cryoablation (PCA) for the treatment of small renal masses. 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 rate of premalignant histology and tumor size. 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 = .59). The interventions were also comparable in terms of operating time as well as intraoperative and postoperative complications.

Residual disease was defined as a persistent imaging study enhancement in 7 of 8 studies and only 1 study relied on histopathology to confirm residual disease. Recurrent disease was defined as imaging study 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 = .003) and a seemingly paradoxical lower likelihood of tumor recurrence (OR = 0.62; 95% CI, 0.41 to 0.94; p = .02). This study 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. (26)

In 2014, Tang et al reported on a systematic review and meta-analysis of laparoscopic renal cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal masses. (27) Reviewers identified 9 trials (2 prospective, 7 retrospective) in which the 2 techniques were assessed (555 cases, 642 controls). Laparoscopic cryoablation was associated with statistically significant shorter surgical time, less blood loss, and fewer overall complications; however, it was estimated that laparoscopic partial nephrectomy may still 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).

In 2014, Klatte et al reported on a systematic review and meta-analysis of laparoscopic cryoablation versus laparoscopic partial nephrectomy for small renal tumors. (28) Thirteen nonrandomized studies were selected for analysis, which found laparoscopic cryoablation 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 (RR = 9.39) and metastatic (RR = 4.68) tumor progression.

In a 2011 systematic review, Klatte et al reviewed 98 studies published through December 2010 to compare treatment of small renal masses with laparoscopic cryoablation or partial nephrectomy. (29) Partial nephrectomy was performed in 5347 patients and laparoscopic cryoablation 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%) experienced local tumor progression. Distant metastasis occurred more frequently in partial nephrectomy patients (91 patients) than in cryoablation patients (9 patients), 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 reported on a 2011 systematic review comparing percutaneous cryoablation with surgical cryoablation of small renal masses.(30) Forty-two studies treating small renal masses (pooled total of 1447 lesions) were reviewed, including 28 articles on surgical cryoablation and 14 articles on percutaneous cryoablation. Reviewers concluded percutaneous and surgical cryoablation for small renal masses have similar, acceptable short-term oncologic outcomes, and each technique is relatively equivalent. Long-term data are needed to compare ablation techniques to the criterion standard (partial or radical nephrectomy).

In 2011, Van Poppel et al reviewed the literature on localized RCC treatment published between 2004 and May 2011.(31) They concluded cryoablation is a reasonable treatment option for low-grade renal tumors less than 4 cm in diameter (mostly <3 cm) in patients who are not candidates for surgical resection or active surveillance. The authors recommended conducting long-term prospective studies to compare ablative techniques for renal ablation, such as radiofrequency ablation (RFA) versus cryoablation.

Martin and Athreya reported on a meta-analysis that compared cryoablation with microwave ablation for small renal tumors in 2013.(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).

In 2012, El Dib et al conducted a meta-analysis evaluating cryoablation and 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.

Kunkle and Uzzo conducted a comparative meta-analysis of cryoablation and RFA as primary treatment for small renal masses in 2008.(35) Forty-seven case series representing 1375 renal tumors were analyzed. Of 600 lesions treated with
cryoablation, 494 underwent biopsy before treatment versus 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. The authors cautioned that minimally invasive ablation generally has 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 of cryoablation and RFA with at least 12-month follow-up and found that 3- and 5-year outcomes showed 93% to 98% cancer-specific survival in small cohorts.(36) They caution that, while studies suggest satisfactory outcomes, given the limitations of imaging and the indolent nature of the tumors, stringent selection criteria and rigorous follow-up were required.

In a 2010 Cochrane review, Nabi et al assessed evidence on the management of localized RCC.(34) No randomized trials comparing cryoablation with open radical or partial nephrectomy were identified. One nonrandomized study, comparing laparoscopic partial nephrectomy with laparoscopic cryoablation using a matched-paired analysis,(37) and 3 retrospective studies were selected. Reviewers noted percutaneous cryoablation 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 on 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 2017 Cochrane review replacement focused on partial nephrectomy and radical nephrectomy as the relevant surgical therapy options for localized renal cell carcinoma. Only 1 RCT was identified with 541 participants that compared partial nephrectomy to radical nephrectomy. The median follow-up was 9.3 years. The study was judged to demonstrate a time-to-death of any cause that favored using partial nephrectomy (HR=1.50; 95% CI, 1.03 to 2.18). No other analyses were performed. Study limitations were lack of blinding and imprecision and indirectness; a substantial proportion of patients were ultimately found not to have a malignant lesion.(38)

**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.(39) These 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 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.\(^{(40)}\) 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 recurrence occurred 4.4 years posttreatment.

Weld et al (2007) reported on 3-year follow-up for 36 (22 malignant) renal tumors treated with laparoscopic cryoablation.\(^{(41)}\) 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 results on 164 laparoscopic cryoablations and 82 percutaneous RFAs for localized renal tumors.\(^{(42)}\) 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 laparoscopic cryoablation or laparoscopic partial nephrectomy for treatment of renal masses.\(^{37}\)

In a prospective, single-institution study, Rodriguez et al (2011) reported on 113 patients consecutively treated with percutaneous cryoablation for 117 renal lesions.\(^{(43)}\) 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.\(^{(4)}\) 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 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 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 to surgical treatment.

Bone Cancers
Meller et al (2008) retrospectively analyzed a single center experience of 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. At median follow-up of 7 years (range, 3-18 years), overall recurrence rate was 8%. Based on their experience, 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, none or minimal soft tissue component, and at least ±1 cm of subchondral bone left near a joint surface after curettage and burr drilling.

In 2013, Callstrom et al reported on 61 patients treated with cryoablation for pain from 69 tumors (size, 1-11 cm) metastatic to the bone. 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 miscellaneous solid tumors. The available evidence 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 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 is for renal cell carcinoma in select patients, ie, those with small tumors who are not surgical candidates or who have baseline renal insufficiency such 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 draw conclusions whether cryoablation improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 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 reviewer support for use of cryoablation in the treatment of select patients with renal tumors. There also was support for 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 Society of Breast Surgeons
The American Society of Breast Surgeons 2008 consensus statement on management of fibroadenomas of the breast indicated cryoablation would be appropriate for histologically confirmed fibroadenoma lesions that are less than 4 cm in largest diameter and sonographically visible.(47) Cryoablation of fibroadenoma of the breast would be contraindicated when ultrasound visualization is poor or core biopsy suggests a diagnosis of cystosarcoma phyllodes tumor or other malignancy or if physical examination or imaging is discordant with a biopsy diagnosis of fibroadenoma.

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 RCCs [renal cell carcinomas]. These therapies have been
shown to be effective and safe.” These recommendations are based on review of the data and consensus.(48)

**American Urological Association**

The 2009 guidelines from the American Urological Association (AUA) on stage 1 renal masses indicated percutaneous or laparoscopic cryoablation “is an available treatment option for the patient at high surgical risk who wants active treatment and accepts the need for long-term radiographic surveillance after treatment.”(49) The guidelines also indicated cryoablation “should be discussed as a less-invasive treatment option” in healthy patients with a renal mass equal to or less than 4.0 cm and clinical stage T1a. Patients should be informed that “local tumor recurrence is more likely than with surgical excision, measures of success are not well defined, and surgical salvage may be difficult.” These recommendations were based on review of the data and “appreciable” majority consensus.

In 2017, AUA published an update on its evaluation and management of clinically localized sporadic renal masses suspicious for renal cell carcinoma. The guideline statements on thermal ablation (radiofrequency ablation and cryoablation) are listed in Table 1.(50)

<p>| <strong>Table 1. Guideline Statements on Localized Masses Suspicious for Renal Cell Carcinoma</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Recommendations</strong></th>
<th><strong>LOR</strong></th>
<th><strong>LOE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guideline statement 24</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physicians should consider thermal ablation (TA) as an alternate approach for the management of cT1a renal masses &lt;3 cm in size. For patients who elect TA, a percutaneous technique is preferred over a surgical approach whenever feasible to minimize morbidity.</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td><strong>Guideline statement 25</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both radiofrequency ablation and cryoablation are options for patients who elect thermal ablation</td>
<td>Conditional</td>
<td>C</td>
</tr>
<tr>
<td><strong>Guideline statement 27</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>Strong</td>
<td>B</td>
</tr>
</tbody>
</table>

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

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) guidelines on kidney cancer (v.2.2017)(51) 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.” 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.6.2017)(52) indicate surgical “resection is the preferred local treatment modality” and “other modalities include ... cryotherapy”.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02440334</td>
<td>Two and Three Dimensional Contrast-enhanced Ultrasound for Screening of Renal Cell Carcinoma Recurrence Following Cryoablation</td>
<td>100</td>
<td>May 2017</td>
</tr>
<tr>
<td>NCT02399124a</td>
<td>ICESECRET PROSENSE™ Cryotherapy For Renal Cell Carcinoma Trial</td>
<td>50</td>
<td>Jun 2017</td>
</tr>
<tr>
<td>NCT03189186</td>
<td>Phase-I Trial of Pembrolizumab and Percutaneous Cryoablation Combination Followed by Nephron-Sparing Surgery or Cytoreductive Nephrectomy in Locally Advanced and Metastatic Renal Cell Carcinomas</td>
<td>21</td>
<td>Jul 2022</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01608165</td>
<td>A Feasibility Study for a Multicentre Randomised Controlled Trial to Compare Surgery with Needle Ablation Techniques in People with Small Renal Masses</td>
<td>17</td>
<td>Jan 2015 (completed)</td>
</tr>
<tr>
<td></td>
<td>Lung Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01957787</td>
<td>Study of Cryoablation for Metastatic Lung Tumors (SOLSTICE)</td>
<td>134</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References:


37. American Society of Breast Surgeons. Consensus Statement: Management of Fibroadenomas of the Breast. 2008 (revised);
Billing Coding/Physician Documentation Information

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

50250  Ablation, open, one or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound, if performed

50542  Laparoscopy, surgical; ablation of renal mass lesion(s)

50593  Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy

0340T  Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance

ICD-10 Codes

C64.0- C65.9  Malignant neoplasm of kidney and renal pelvis, code range

There is no specific code for other lesions addressed in this policy, unlisted codes may be used.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

3/1/06  New policy added to the Surgery section.
9/1/06  No policy statement changes.
3/1/07  No policy statement changes.
9/1/07  No policy statement changes.
9/1/08  No policy statement changes.
2/12/09  Interim update. Policy statement added that treatment of renal cancers may be considered medically necessary when specific criteria are met; no other changes were made to the policy.
states.

9/1/09  No policy statement changes.
9/1/10  No policy statement changes.
9/1/11  No policy statement changes.
9/1/12  Lung cancer added to investigational policy statement.
9/1/13  Metastases added to investigational policy statement.
9/1/14  No policy statement changes.
9/1/15  No policy statement changes. Deleted CPT codes: 49203, 49204, 49205, 0340T.
9/1/16  No policy statement changes.
9/1/17  No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.