



Kansas City

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

**Policy Number:** 7.01.92  
**Origination:** 2/2006

**Last Review:** 9/2014  
**Next Review:** 9/2015

### **Policy**

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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**

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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  $<60\text{mL}/\text{min}/\text{m}^2$ ) 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**

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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**

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Cryosurgical ablation (hereafter referred to as cryosurgery) 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.

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. Adjuvant radiation therapy 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 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**

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This policy was originally created in 2003 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period of May 2013 through June 20, 2014. The following is a summary of the key literature to date. The literature review identified publications discussing applications of cryosurgery for primary and metastatic tumors outside the liver and prostate. All were uncontrolled case series with varied criteria to select patients for cryosurgery and reported limited data on long-term outcomes.

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 (1) discussed cryosurgery in 429 patients with a wide variety of primary and recurrent solid tumors (eg, head and neck, lung, genital organs, sarcomas). Although the author reported survival for some patient subsets with certain of these malignancies, the article only reported baseline tumor and patient characteristics for those with breast cancer (see next).

### **Breast Cancer**

In 2010, Zhao and Wu reported on a systematic review of minimally-invasive ablative techniques of early stage breast cancer. (2) The review 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 of 36% to 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 either chemotherapy (n=29) or cryoablation (n=91,35 of whom also received immunotherapy). (3) After a 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 ( $p < 0.0001$ ). 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 described the outcome of cryosurgery for advanced primary or recurrent breast cancer in 72 patients. (1, 4, 5) 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 reported on a retrospective series of 9 patients with advanced primary tumors and 40 with recurrent disease. (1) The author reported 44% survival of primary breast cancer patients (n=9) 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 those enrolled in the study, details of the procedure, and procedure-related adverse events. The other studies (4-6) were smaller series of patients and also were inadequate with respect to study design, analysis, and reporting of results. Furthermore, the study by Pfleiderer et al (4) was a pilot trial to evaluate technical limitations of the procedure. Tumors were excised and evaluated by pathology days to weeks after cryosurgery, and the authors reported incomplete necrosis in tumors greater than 23 mm in diameter.

One 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. (7) This Phase I study included 29 patients who underwent cryoablation of primary breast cancers measuring less than 2 cm in diameter, followed up 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, Pusztaszeri et al found residual tumor present in 6 cases when follow-up lumpectomy was performed approximately 4 weeks after cryoablation. (8) In a case series of 15 patients with breast cancer lesions that were  $8 \pm 4$  mm in diameter, percutaneous cryoablation was performed 30 to 45 days before surgical resection. (9) Resection of the lesions confirmed complete necrosis occurred in 14 patients, but 1 lesion had residual disease considered to be probably due to incorrect probe placement.

Because available evidence 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 breast cancer. Therefore, cryosurgery for breast cancer is considered investigational.

## **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 reports on office-based ultrasound-guided cryoablation as a treatment of breast fibroadenomas. (10-14) These case series reported on a range of 29 to 68 patients followed for periods of 6 months to up to 2.6 years. It is likely that these case series include 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% out of 84% of palpable fibroadenomas remained palpable after treatment and of the fibroadenomas that were initially 2 cm or less in size, only 6% remained palpable. (14) In this series of patients, the authors also noted that cryoablation did not produce artifact that might interfere with interpretation of mammograms. These small case series from the same group of investigators is inadequate to permit scientific conclusions. In addition, 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 regarding harboring a palpable lesion.

Nurko et al 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. (15) 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, 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. The authors noted they would continue to follow up these patients to better define resolution of the treatment-induced physical and radiographic findings. 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 several years' time).

## **Lung Cancer**

Lee et al conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors. (16) 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 that would not be considered surgical candidates. Complications occurred in 11.1% of patients from 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. Improvements in pulmonary function and clinical symptoms occurred in studies reporting these outcomes.

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. (17) Included in the study population were stage IIIB+IV lung cancer patients. OS rates at 1, 2, and 3 years were 64%, 45% and 32%, respectively. The 30-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 1 and symptomatic obstructive NSCLC was published in 2014. (18) Cryoablation was included in the review 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.

Available studies are limited to primarily small cohort and nonrandomized studies with relatively short-term follow-up. Complications are also reported frequently and can be severe. 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. Therefore, cryosurgery for lung cancer is considered investigational.

## **Pancreatic Cancer**

In 2012, Tao et al reported on a systematic review of cryoablation for pancreatic cancer. (19) The authors identified 29 studies from the literature search and included 5 of these studies in the review. The 5 studies were all case series and considered to be of low quality. Adverse events, when mentioned in the studies, included delayed gastric emptying (0% to 40.9% in 3 studies), pancreatic leak (0% to 6.8% in 4 studies), biliary leak (0% to 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. (20) 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 oncologic outcomes than best supportive care.

Kovach et al (21) reported 10 cryosurgical ablations in 9 patients with unresectable pancreatic cancer using intraoperative ultrasound guidance during laparotomy. The authors report no intraoperative morbidity or mortality and adequate pain control in all patients postoperatively. 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 (125) iodine seed implantation for treatment of locally advanced pancreatic cancer was reported by Xu et al. (22) Forty-nine patients were enrolled, 12 with liver metastases. Twenty patients received regional chemotherapy. At 3 months after therapy, most patients showed tumor necrosis, with 20.4% of patients 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 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. (23) Median dominant tumor sizes decreased from 4.3 cm to 2.4 cm in 36 of 55 patients (65%) 3 months after cryoablation. Survival rates were not significantly different between groups, with the cryoablation group surviving a median of 350 days versus 257 days in the group that did not receive cryoablation. Complications overall were not significantly different between the 2 groups. However, a higher percentage of delayed gastric emptying occurred in the cryoablation group compared with the group that did not receive cryoablation (36.8% vs 16.2%, respectively).

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. Therefore, cryosurgery for pancreatic cancer is considered investigational.

## **Renal Cell Carcinoma**

In 2014, Klatter et al reported on a systematic review and meta-analysis of laparoscopic cryoablation versus laparoscopic partial nephrectomy for small renal tumors. (24) Thirteen nonrandomized studies were included in the 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 and metastatic tumor progression with relative risks of 9.39 and 4.68, respectively. Tang et al also reported on a systematic review and meta-analysis of laparoscopic cryoablation versus laparoscopic partial nephrectomy for small renal tumors in 2014. (25) This review included 2 prospective and 7 retrospective studies. Similar results to the Klatter analysis were found including better perioperative outcomes and inferior oncologic outcomes occurring with laparoscopic cryoablation than laparoscopic partial nephrectomy. Local recurrence and distant metastasis rates were significantly lower with laparoscopic partial nephrectomy (odds ratio [OR]=13.03; 95% confidence interval [CI], 4.20 to 40.39;  $p < 0.001$  and OR=9.05; 95% CI, 2.31 to 35.51;  $p = 0.002$ , respectively).

In an earlier 2011 systematic review, Klatter et al reviewed 98 studies published through December 2010 to compare treatment of small renal masses with laparoscopic cryoablation or partial nephrectomy. (26) Partial nephrectomy was performed in 5347 patients and laparoscopic cryoablation was performed in 1295 patients. Renal cell carcinoma (RCC) was proven in 159 (2.9%) of patients. After cryoablation, local tumor progression of the RCC occurred at a rate of 8.5% (70 of 821; range, 0% to 17.7%). After partial nephrectomy, 1.9% (89 of 4689; range, 0% to 4.8%), experienced local tumor progression. Distant metastasis occurred more frequently in partial nephrectomy patients than cryoablation patients, although not significantly (91 vs 9 patients, respectively;  $p = 0.126$ ). However, mean tumor size for cryoablation patients was smaller than the partial nephrectomy patients (2.4 vs 3.0

cm;  $p < 0.001$ ). Fewer patients receiving cryoablation experienced perioperative complications than partial nephrectomy patients (17% [range, 0% to 42%] vs. 23.5% [range, 8% to 66%];  $p < 0.001$ ).

Long et al reported on a 2011 systematic review comparing percutaneous cryoablation with surgical cryoablation of small renal masses. (27) A total of 42 studies treating small renal masses (pooled total of 1447 lesions) were reviewed including 28 articles on surgical cryoablation and 14 articles on percutaneous cryoablation. The authors 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 ultimately compare ablation techniques to the criterion standard of partial or radical nephrectomy.

In 2011, Van Poppel et al conducted a review of the literature on localized RCC treatment published between 2004 and May 2011. (28) In this review, the authors concluded cryoablation is a reasonable treatment option for low-grade renal tumors less than 4 cm (mostly less than 3 cm) in patients who are not candidates for surgical resection or active surveillance. The authors noted the need for 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 of cryoablation versus microwave ablation for small renal tumors in 2013. (29) The analysis included 51 studies and did not reveal any significant differences between microwave ablation and cryoablation in primary effectiveness (93.75% vs 91.27%, respectively;  $p = 0.4$ ), cancer-specific survival (98.27% vs 96.8%, respectively;  $p = 0.47$ ), local tumor progression (4.07% vs 2.53%, respectively;  $p = 0.46$ ), or progression to metastases (0.8% vs 0%, respectively;  $p = 0.12$ ). In the microwave ablation group, the mean tumor size was significantly larger ( $p = 0.03$ ) and open access was used more often than in the cryoablation group (12.20% vs 1.04%, respectively;  $p < 0.001$ ). In the cryoablation group, percutaneous access was used more often than in the microwave ablation group (88.64% vs 37.20%, respectively;  $p = 0.0021$ ).

In 2012, El Dib et al conducted a meta-analysis evaluating cryoablation and RFA for small renal masses. (30) Included in the review were 20 cryoablation (totaling 457 patients) and 11 RFA (totaling 426 patients) case series studies published through January 2011. Mean tumor size was 2.5 cm (range from 2 to 4.2 cm) in the cryoablation group and 2.7 cm (range from 2 to 4.3 cm) in the RFA group. Mean follow-up times for the cryoablation group and RFA group were 17.9 and 18.1 months, respectively. Clinical efficacy, defined as cancer-specific survival rate, radiographic success, no evidence of local tumor progression, or distant metastases, was not significantly different 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 a 2010 Cochrane review, Nabi et al reviewed evidence on the management of localized RCC. (31) No randomized trials comparing cryoablation to open radical or partial nephrectomy were identified. One nonrandomized study compared laparoscopic partial nephrectomy with laparoscopic cryoablation using a matched paired-analysis (32) and 3 retrospective studies. The review notes percutaneous cryoablation can successfully destroy small RCC and may be considered a treatment option in patients with serious comorbidities that pose surgical risks. The review concluded that high-quality, RCTs are required in the management of localized RCC and that 1 area of emphasis should be the role of renal surgery compared with minimally invasive techniques for small tumors (<4 cm).

Kunkle and Uzzo (33) conducted a comparative meta-analysis evaluating cryoablation and RFA as primary treatment for small renal masses in 2008. 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 of 600 (5%) lesions after cryoablation and in 100 of 775 (13%) lesions after RFA. Progression to metastatic disease was described in 6 of 600 (1%) lesions after cryoablation

versus 19 of 775 (2.5%) after RFA. The authors caution that minimally invasive ablation generally has been performed selectively on older patients with smaller tumors, possibly resulting in selection bias; series of ablated lesions tend to have shorter post-treatment 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.

A number of studies reported intermediate-term outcomes for cryoablation with RCC. Weld et al reported on 3-year follow-up of 36 renal tumors (22 were malignant) treated with laparoscopic cryoablation. (34) 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 reported results on 164 laparoscopic cryoablations and 82 percutaneous RFAs for localized renal tumors. (35) 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. The authors noted that cryoablation and RFA are developmental nephron-sparing options and that early results are encouraging in terms of early oncologic control, preservation of renal function, and low complication rates. Studies are also reporting results with small numbers of patients comparing laparoscopic cryoablation with laparoscopic partial nephrectomy for treatment of renal masses. (32)

Matin and Ahrar (36) reviewed studies of cryoablation and RFA with at least 12-month follow-up and found that recently published 3- and 5-year outcomes show 93% to 98% cancer-specific survival in small cohorts. 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 is required.

Strom et al reported on a retrospective comparison of 145 patients who underwent laparoscopic (n=84) or percutaneous (n=61) cryoablation of small renal masses at 5 academic medical centers in the United States. (37) 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 size was 2.7 cm in the laparoscopic group versus 2.5 cm in the percutaneous group. Patients were followed for a longer period of time in the laparoscopic group (mean of 42.3 + 21.2 months) compared with the percutaneous group (31.0 + 15.9 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 more frequent in the percutaneous group at 16.4% (10/61) compared with 5.9% (5/84) in the laparoscopic group. However, disease-free survival and OS were not significantly different at last follow-up in the laparoscopic group compared with the percutaneous group (91.7% and 89.3% vs 93.7% and 88.9%, respectively).

In a prospective, single-institution study, Rodriguez et al reported on 113 patients consecutively treated with percutaneous cryoablation for 117 renal lesions. (38) The average size of renal lesions in the study was 2.7 + 2.4 cm (83 or 71% were RCC). Patients were selected for cryoablation over surgery when tumors were 4 cm or less and percutaneously approachable or if the patient could not tolerate surgery when tumors were greater than 4 to 7 cm. Technical success was reported to be 100%, with 93% of patients having no complications or only mild complications. At a median follow-up of 2 years with 59 patients, efficacy was 98.3% and 92.3% at 3 years with 13 patients. Metastatic disease did not occur in any of the patients during the follow-up period, and cancer-specific survival was 100%.

Nguyen et al (39) evaluated options for salvage of ipsilateral tumor recurrence after previous ablation. Recurrence rates at their center were 13 of 175 (7%) after cryoablation and 26 of 104 (25%) after RFA. Extensive perinephric scarring was encountered in all salvage operations following cryoablation, and the authors conclude that cryoablation in particular can lead to extensive perinephric fibrosis, which can complicate attempts at salvage.

The available evidence supports a role for cryoablation for patients with small renal tumors less than 4 cm in size. Because longer-term cancer-specific outcomes are unknown, cryoablation of renal tumors should be limited to patients considered to be poor candidates for the standard surgical approach.

## **Other Cancers**

Meller et al (40) report a retrospective analysis of 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 suggest 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. (41) Before treatment, patients rated their pain with a 4 or more on a 1 to 10 scale using the Brief Pain Inventory with a mean score of 7.1/10 for worst pain in a 24-hour period.

The mean pain score gradually decreased after cryoablation to 1.4/10 ( $p < 0.0001$ ) 24 weeks for worst pain in a 24-hour period. A major complication of osteomyelitis was experienced by 1 patient (2%).

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.

## **Ongoing and Unpublished Clinical Trials**

A search of online site ClinicalTrials.gov on June 20, 2014 found 1 randomized trial on cryoablation for lung lesions with focal pure ground-glass opacity (NCT01429649). This trial is scheduled for completion in December 2014. Several ongoing nonrandomized clinical trials addressing cryoablation in breast, bone, lung, pancreatic and renal tumors were identified.

## **Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers**

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 for February 2009. 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. 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 this was investigational in the treatment of pancreatic cancer.

## **Summary**

Cryosurgical ablation 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.

The literature on the use of cryosurgical ablation of tumors addressed in this policy consists primarily of reports of single-center case series; however, evidence is accumulating that cryoablation provides short-term tumor control and perhaps survival benefit for carefully selected patients with small renal cell carcinomas. Based on the scientific data (large numbers of patients treated with follow-up) and the

clinical input received, cryoablation of small (<4 cm) renal cancers may be considered medically necessary in those patients who are not surgical candidates due to comorbid conditions or who have baseline renal insufficiency such that standard surgical procedures would impair their kidney function.

The current evidence on cryoablation for all other indications consists largely of noncomparative, case series and is insufficient to permit conclusions concerning the effect of cryoablation on health outcomes. Therefore, cryoablation is considered investigational for all other indications. Comparative studies with larger numbers of subjects and longer follow-up are needed.

### **Practice Guidelines and Position Statements**

The American Society of Breast Surgeons 2008 Consensus Statement on Management of Fibroadenomas of the Breast indicates cryoablation is appropriate for histologically confirmed fibroadenoma lesions that are less than 4 cm in largest diameter and sonographically visible. (42) Cryoablation of fibroadenoma of the breast is 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.

The 2009 American College of Radiology Appropriateness Criteria for renal cell carcinoma indicates: "Energy ablative therapies, such as cryoablation..., are increasingly used in treating small renal cell carcinomas as an alternative to partial nephrectomy. These therapies have been shown to be effective and safe." These recommendations are based on review of the data and consensus."(38) The 2009 guidelines from the American Urological Association on stage 1 renal masses indicate 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." (43) The guidelines also indicate 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 are based on review of the data and "appreciable" majority consensus.

The National Comprehensive Cancer Network (NCCN) practice guidelines for kidney cancer (44) 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." The NCCN guidelines also note "rigorous comparison with surgical resection (i.e., total or partial nephrectomy by open or laparoscopic techniques) has not been done and [t]hermal ablative techniques are associated with a higher local recurrence rate than conventional surgery."

The NCCN practice guidelines for non small cell lung cancer (45) indicate surgical resection is the preferred local treatment but cryotherapy and other approaches are listed as treatment options.

Cryoablation/Cryosurgery is not a preventive service.

### **Medicare National Coverage**

No national coverage determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

### **References**

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### **Billing Coding/Physician Documentation Information**

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| <b>19105</b> | Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma  |
| <b>49203</b> | Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors; largest tumor 5 cm diameter or less |
| <b>49204</b> | Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors; largest tumor 5.1-10.0 cm diameter  |

- 49205** Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors; largest tumor greater than 10.0 cm diameter
- 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

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

**Additional Policy Key Words**

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N/A

**Policy Implementation/Update Information**

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- 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 statements.
  - 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.
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