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

Policy #: 429       Latest Review Date: July 2014
Category: Surgery       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
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 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.

Policy:
Cryosurgical ablation of localized renal cell carcinoma that is no more than 4 cm in size meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when performed as open, laparoscopically, or percutaneously when either of the following criteria is met:

- Preservation of kidney function is necessary (i.e., the patient has 1 kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of less than 60 mL/min/m²) and standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen kidney function; OR
- Patient is not considered a surgical candidate.

Cryosurgical ablation does not meet Blue Cross and Blue Shield of Alabama’s medical criteria as a treatment of benign or malignant tumors of the breast, lung, pancreatic cancer, or other solid tumors or metastases outside the liver and prostate, and to treat renal cell carcinomas in patients who are surgical candidates and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
This policy is updated regularly with searches of the MEDLINE database. 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 eight or more patients with the same diagnosis, or eight or more procedures on the same malignancy. One article discussed cryosurgery in 429 patients with a wide variety of primary and recurrent solid tumors (e.g., 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. 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 36-83%. Since 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 clinical trials become available.

Niu and colleagues 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). After a 10-year follow-up, median overall survival of all study participants was 55 months in the cryoablation group versus 27 months in the chemotherapy group (p<0.0001). Median overall survival 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 one week to one month.

Three studies described the outcome of cryosurgery for advanced primary or recurrent breast cancer in 72 patients. 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 the largest retrospective series: nine patients with advanced primary tumors and 40 with recurrent disease. The author reported 44% survival of primary breast cancer patients (n=9) at three and five 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 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. 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 and colleagues explored the role of cryoablation as an alternative to surgical excision as a primary treatment of early stage breast cancer. This Phase I study included 29 patients who underwent cryoablation of primary breast cancers measuring less than 2 cm in diameter, followed up one to four 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 six cases when follow-up lumpectomy was performed approximately four weeks after cryoablation. In a case series of 15 patients with breast cancer lesions that were 8 ± 4 mm in diameter, percutaneous cryoablation was performed 30-45 days prior to surgical resection. Resection of the lesions confirmed complete necrosis occurred in 14 patients, but one lesion had residual disease considered to be probably due to incorrect probe placement.
Since available evidence did not include control groups or compare outcomes of cryosurgery to 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. These case series reported on a range of 29-68 patients followed for periods of six months to up to 2.6 years. It is likely that these case series include overlapping patients. At one 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 2cm or less in size, only 6% remained palpable. 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 conclusion. 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 and colleagues reported on outcomes at six and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment (FACT) registry involving 55 different practice settings. In these patients, before cryoablation, 75% of fibroadenomas were palpable by the patient. Follow-up at six 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 and colleagues conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors. Included in the review were 15 case studies and one comparative, observational study. Cryoablation was performed for inoperable, advanced lung and bronchial cancers in most studies. Some studies included patients with co-morbid 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. Included in the study population were stage IIIB+IV lung cancer patients. Overall survival rates at one, two, and three 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 I and symptomatic obstructive NSCLC was published in 2014. 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 to 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 and colleagues reported on a systematic review of cryoablation for pancreatic cancer. The authors identified 29 studies from the literature search and included five of these studies in the review. The five 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 three studies), pancreatic leak (0% to 6.8% in four studies), biliary leak (0% to 6.8% in three studies), and one instance of upper gastrointestinal hemorrhage. Pain relief was reported in three studies and ranged from 66.7% to 100%. Median survival times reported in three studies ranged from 13.4 to 16 months. One-year total survival rates reported in two 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. 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 reported 10 cryosurgical ablations in nine 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 were dead at an average of five months postoperatively (range: 1–11 months).

A pilot study on the combination of cryosurgery and iodine seed implantation for treatment of locally advanced pancreatic cancer was reported by Xu et al. Forty-nine patients were enrolled, 12 with liver metastases. Twenty patients received regional chemotherapy. At three 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 and colleagues 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 cm to 2.4 cm in 36 of 55 patients (65%) three 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 two groups. However, a higher percentage of delayed gastric emptying occurred in the cryoablation group compared to 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 to 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, Klatte et al reported on a systematic review and meta-analysis of laparoscopic cryoablation versus laparoscopic partial nephrectomy for small renal tumors. 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. This review included two prospective and seven retrospective studies. Similar results to the Klatte 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, Klatte et al reviewed 98 studies published through December 2010 to compare treatment of small renal masses with laparoscopic cryoablation or partial nephrectomy. 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% (70/821; 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 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%-42%] vs. 23.5% [range, 8%-66%]; p<0.001).
Long et al reported on a 2011 systematic review comparing percutaneous cryoablation with surgical cryoablation of small renal masses. 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. In this review, the authors concluded cryoablation is a reasonable treatment option for low-grade renal tumors less than 4 cm (mostly <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. 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=0.002).

In 2012, El Dib et al conducted a meta-analysis evaluating cryoablation and RFA for small renal masses. 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, 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 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. 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 and three 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 one area of emphasis should be the role of renal surgery compared with minimally invasive techniques for small tumors (<4 cm).
Kunkle and Uzzo 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 three-year follow-up of 36 renal tumors (22 were malignant) treated with laparoscopic cryoablation. In this series, the three-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. Mean tumor size was 2.5 cm. Cancer-specific survival following cryotherapy was 98% at a median follow-up of three years and 100% for RFA at just one-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.

Matin and Ahrar reviewed studies of cryoablation and RFA with at least 12-month follow-up and found that recently published three- and five-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 five academic medical centers in the United States. 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, 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. The average size of renal lesions in the study was 2.7±2.4 cm (83 [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 two years with 59 patients, efficacy was 98.3% and 92.3% at three 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 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 reported on a retrospective analysis of a single center experience of 440 bone tumor cryosurgery procedures performed between 1998 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 seven 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. Before treatment, patients rated their pain with a four or more on a 1-10 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 one 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.
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 or less) 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 non-comparative, 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. 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.

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. 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 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 indicate surgical resection is the preferred local treatment but cryotherapy and other approaches are listed as treatment options.

**U.S. Preventive Services Task Force Recommendations**

**Cryoablation/cryosurgery is not a preventive service.**

**Key Words:**
Renal cell carcinoma, RCC, cryoablation, cryosurgery, cryotherapy, breast cancer, pancreatic cancer, breast fibroadenoma, lung cancer

**Approved by Governing Bodies:**
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.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0340T</td>
<td>Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance</td>
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19105 Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma

19499 Unlisted procedure, breast

48999 Unlisted procedure, pancreas

50250 Ablation, open, one or more renal mass lesion(s), cryosurgical, including intra-operative ultrasound guidance and monitoring, if performed

50542 Laparoscopy, surgical; ablation of renal mass lesion(s), including intra-operative ultrasound guidance and monitoring, when performed.

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

References:
63. Simmons RM. Freezing breast cancers to enhance complete resection, Annals of Surgical Oncology, November 2003; 10(9): 999.
64. Simmons RM. Ultrasound in the changing approaches to breast cancer diagnosis and treatment, January 2004; 10 Suppl 1; S13-14.

**Policy History:**

Medical Policy Group, June 2010 (1)
Medical Policy Administration Committee, July 2010
Available for comment July 2-August 16, 2010
Medical Policy Group, November 2010 CPT Code update
Medical Policy Group, July 2011 (1): Update to Key Points, Approved by Governing Bodies and References; Key Points reformatted
Medical Policy Panel, July 2012
Medical Policy Group, April 2013 (1): Update to policy with addition of lung cancer to non-covered/investigational indications; update to Key Points and References; policies #236 and #294 removed due to duplicate information that is contained and maintained on this policy
Medical Policy Administration Committee, April 2013
Available for comment April 18 through June 5, 2013
Medical Policy Panel, July 2013
Medical Policy Group, September 2013 (1): Update to Policy statement with addition of “other metastases” to investigational section, other policy statements unchanged; update to Key Points and References
Medical Policy Administration Committee, October 2013
Available for comment September 24 through November 7, 2013
Medical Policy Group, December 2013 (1) 2014 Coding Update: added new code 0340T, effective 01/01/2014
Medical Policy Panel, July 2014
Medical Policy Group, July 2014 (1): Policy statement criteria consolidated in more current concise verbiage; update to Key Points and References; no change in intent or coverage of policy statement

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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.