



Louisiana

Cryosurgery Ablation of Miscellaneous Solid Tumors other than Liver or Prostate Tumors or Breast Fibroadenomas

Policy # 00023

Original Effective Date: 01/26/2004

Current Effective Date: 12/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Whole Gland Cryoablation of Prostate Cancer is addressed separately in medical policy 00022.

Note: Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors is addressed separately in medical policy 00175.

Note: Radiofrequency Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.

Note: Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220.

Note: Cryosurgery Ablation of Breast Fibroadenomas is addressed separately in medical policy 00235.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider cryosurgery ablation as a treatment of localized renal cell carcinoma (RCC) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for the use of cryosurgery ablation to treat localized renal cell carcinoma [RCC] (no more than 4 cm in size) may be considered 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 $< 60 \text{ mL/min/m}^2$) and standard surgical approaches would compromise kidney function; or
- The patient is not considered a surgical candidate.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

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Based on review of available data, the Company may consider cryosurgical ablation to treat lung cancer to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for cryosurgical ablation to treat lung cancer may be considered when either of the following criteria is met:

- The patient has early-stage non-small cell lung cancer (NSCLC) and is a poor surgical candidate; or
- The patient requires palliation for a central airway obstructing lesion.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of cryosurgery ablation to treat localized renal cell carcinoma (RCC) when patient selection criteria are not met to be **investigational**.*

Based on review of available data, the Company considers the use of cryosurgery ablation to treat lung cancer when patient selection criteria are not met to be **investigational**.*

Based on review of available data, the Company considers cryosurgical ablation as a treatment for benign or malignant tumors of the breast, pancreas, or bone and other solid tumors or metastases outside the liver, prostate and breast fibroadenomas to be **investigational**.*

Background/Overview

CRYOSURGICAL TREATMENT

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 malignant and benign breast disease, lung cancer, pancreatic cancer, and RCC 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 is balanced against the patient's desire for breast conservation, the need for tumor-free margins in resected tissue, and the patient's age, hormone receptor status, and other factors. Adjuvant radiotherapy decreases local recurrences, particularly for those who select lumpectomy. Adjuvant

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hormonal therapy and/or chemotherapy are added, depending on presence and number of involved nodes, hormone receptor status, and other factors. Treatment of metastatic disease includes surgery to remove the lesion and combination chemotherapy.

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

LUNG TUMORS

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

PANCREATIC CANCER

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

RENAL CELL CARCINOMA

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Several cryoablation devices have been cleared for marketing by the U.S. 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 (Endocare [Irvine, CA]);
- CryoGen Cryosurgical System (Cryosurgical);
- CryoHit^{®†} (Galil Medical [Arden Hills, MN]) for the treatment of breast fibroadenoma;
- SeedNet^{™†} System (Galil Medical); and
- Visica^{®†} System (Sanarus Medical [Pleasanton, CA]).

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Food and Drug Administration product code: GEH.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes; however, these studies are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

CRYOSURGICAL TREATMENT

The following sections summarize studies that adequately described baseline characteristics of the patient populations and the methods used for cryosurgery; these studies report outcomes of treatment for 8 or more patients with the same diagnosis or 8 or more procedures on the same malignancy. One 1995 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 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. This trial enrolled 86 evaluable patients from 19 institutions with invasive ductal breast carcinoma that was 2 cm or less in size. The primary end point was complete ablation, defined as no residual evidence of tumor on magnetic resonance imaging. The investigators assigned a priori the success rates indicating that cryoablation would be a potentially efficacious treatment (>90%) or that the results of cryoablation would be unsatisfactory (<70%). Following cryoablation and determination of complete ablation, all patients underwent surgery according to standard protocols for treatment of early breast cancer. Of 87 cancers in 86 patients, complete ablation was achieved in 66 (75.9%; 95% confidence interval [CI], 67.1% to 83.2%). Most cases without complete ablation were the result of multifocal disease outside the targeted lesion. Success rates were intermediate, indicating that cryoablation is *not* potentially efficacious, nor are the results of cryoablation satisfactory.

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In 2010, Zhao and Wu reported on a systematic review of minimally invasive ablative techniques of early-stage breast cancer. They noted that studies on cryoablation for breast cancer were 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%). 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 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). At 10-year follow-up, the median overall survival of all study participants was 55 months in the cryoablation group vs 27 months in the chemotherapy group ($p < 0.001$). Moreover, the median overall survival was greater in patients receiving multiple cryoablations and in those receiving immunotherapy. Complications with cryotherapy to the breast included ecchymosis and hematoma, pain, tenderness, and edema—all these complications resolved within 1 week to 1 month.

Three studies have described outcomes from 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 (1995) reported on a retrospective series of 9 patients with advanced primary tumors and 40 with recurrent disease. The author reported a 44% (n=9) survival rate among 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. Moreover, the report did not adequately describe selection criteria for trial enrollees, procedure details, or procedure-related adverse events. The other studies were smaller series with inadequate study designs, analyses, and reporting of results. Further, the trial by Pfleiderer et al (2002) was a pilot study to evaluate the 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 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 for early-stage breast cancer. 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. In a 2011 case series of 15 breast cancer patients, percutaneous cryoablation (PCA) was performed 30 to 45 days before surgical resection. 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.

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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. 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. In this series, the authors also noted that cryoablation did not produce artifacts that could interfere with interpretation of mammograms. These small case series, which were done by the same group of investigators, are inadequate to permit scientific conclusions.

Nurko et al (2005) reported on outcomes at 6 and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment registry by 55 different practice settings. In these patients, before cryoablation, 75% of fibroadenomas were palpable by the patient. Follow-up at 6- and 12-month intervals showed palpable masses in 46% and 35%, respectively. When fibroadenomas were grouped by size, for lesions 2 cm or less in diameter, the treatment area was palpable in 28% of subjects at 12 months. For lesions more than 2 cm, the treatment area was palpable in 59% at 12 months.

It is unclear whether “nonpalpability” is the most appropriate medical outcome. Fibroadenomas are benign lesions with only a very remote 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 of fibroadenomas 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. 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 overall survival was 97.5% (39/40). There were no significant changes

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

In 2012, Niu et al reviewed the literature on lung cryoablation and reported on their own experience with PCA in 150 patients with NSCLC followed for 12 to 38 months. The study population had stage IIIB or IV lung cancer. overall survival 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. Cryoablation was included as a potential therapy for airway obstruction due to an endoluminal NSCLC. Reviewers were unable to draw any conclusions on local nonsurgical therapies, including cryoablation, due to lack of quality evidence.

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

In 2004, Maiwand and Asimakopoulos reported on a large case series of 521 patients with symptomatic obstructive tracheobronchial malignant tumors who underwent cryosurgery with a mean of 2.4 treatments per patient. The patients were treated between 1995 and 2003, had a mean age of 67.9 years, and 72%

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were diagnosed with stage IIIb or IV disease. Improvement in one or more symptoms (hemoptysis, cough, dyspnea, chest pain) was demonstrated in 86.0% of patients. Postoperative complications were 9%, including 21 (4%) cases of hemoptysis, 12 (2%) cases of postoperative atrial fibrillation, and 16 (3%) patients developed respiratory distress and poor gas exchange that eventually resolved. There were 7 (1.2%) in-hospital deaths (cause of death was respiratory failure in all of these patients).

In 2005, Asimakopoulos et al reported on a subset of the same population of patients, analyzing outcomes from 2 groups of patients. Group A consisted of 172 patients who underwent at least 2 sessions of cryoablation; group B consisted of 157 patients who underwent only 1 session of cryosurgery. The single treatment group (group B) was a more diverse patient group; it presented with a medical condition that did not permit them to undergo a second session of cryosurgery. Group B was also more likely to have stage III or IV disease and less likely to have had prior palliative radiotherapy. Overall, there was a statistically significant chance ($p < 0.001$) that dyspnea would improve by at least 1 New York Heart Association functional class 2 weeks after the second session of cryosurgery. Patients in group B benefited to a lesser degree from cryosurgery. In group A, the chance of a patient experiencing improvement in cough by at least 1 class after 2 sessions of cryosurgery was statistically significant ($p < 0.001$). Group B patients benefited less with regard to improvement in cough. Only 78 (43.3%) of the 172 patients in group A reported episodes of hemoptysis before or after treatment. Overall, there was a statistically significant reduction in hemoptysis ($p < 0.001$). Group B remained had limited follow-up attendance.

Section Summary: Lung Cancer

The evidence on cryosurgery for lung cancer consists of studies that use cryosurgery for inoperable or metastatic disease. The available studies are small cohort studies and nonrandomized studies with relatively short-term follow-up. Additionally, complications are frequently reported 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. Reviewers identified 29 studies and selected five. All five were case series and considered of low quality. Adverse events, when mentioned, included delayed gastric emptying (0%-40.9% in 3 studies), pancreatic leak (0%-6.8% in 4 studies), biliary leak (0%-6.8% in 3 studies), and a single instance of upper gastrointestinal hemorrhage. Pain relief was reported in 3 studies and ranged from 66.7% to 100%. Median survival times reported in 3 studies ranged from 13.4 to 16 months. One-year total survival rates, as reported in 2 studies, were 57.5% and 63.6%. Keane et al reported on a systematic review of ablation therapy for locally advanced pancreatic cancer in 2014. Reviewers noted that studies had demonstrated ablative therapies, including cryoablation, are feasible, but larger studies are needed. No conclusions could be made on whether ablation resulted in better outcomes than best supportive care.

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Kovach et al (2002) reported on 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 publication, all patients had died at an average of 5 months postoperatively (range, 1-11 months).

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

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

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 (e.g., 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.

Renal Cell Carcinoma

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

Systematic Reviews

In 2017, Pessoa et al reported on the results of a systematic review of studies comparing the use of laparoscopic cryoablation (LCA) with PCA for the treatment of small renal masses. 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 the rate of premalignant histology and tumor size. Moreover, PCA was performed more frequently for posterior renal tumors. The rate of successful biopsies obtained did not differ significantly between techniques (88.5% for LCA vs

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76.3% for PCA; $p=0.59$). The interventions were also comparable in operating times as well as intraoperative and postoperative complications.

Residual disease was defined as a persistent imaging study enhancement in 7 of 8 studies, and only one study relied on histopathology to confirm residual disease. Recurrent disease was defined as imaging enhancement after an initial negative imaging in 4 of 7 studies. Imaging and confirmatory biopsy to confirm recurrence was reported in 3 studies. A PCA approach resulted in a higher likelihood of residual disease (odds ratio [OR], 2.6; 95% CI, 1.31 to 3.57; $p=0.003$) and a seemingly paradoxical lower likelihood of tumor recurrence (OR=0.62; 95% CI, 0.41 to 0.94; $p=0.02$). This systematic review provided some evidence, albeit low level, of the minimally invasive interventions emerging in clinical practice. The lack of pathologic confirmation of residual and recurrent lesions is a significant limitation.

In 2014, Tang et al reported on a systematic review and meta-analysis comparing laparoscopic renal cryoablation with laparoscopic partial nephrectomy in the treatment of small renal masses. Reviewers identified 9 trials (2 prospective, 7 retrospective) in which the 2 techniques were assessed (555 cases, 642 controls). LCA was associated with statistically significant shorter surgical 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, Klatter et al reported on a systematic review and meta-analysis comparing LCA with laparoscopic partial nephrectomy for small renal tumors. Thirteen nonrandomized studies were selected for analysis, which found LCA was associated with better perioperative outcomes than laparoscopic partial nephrectomy. Oncologic outcomes, however, were inferior with cryoablation, which was significantly associated with greater risk of local risk ratio (RR=9.39) and metastatic (RR=4.68) tumor progression.

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

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

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Louisiana

Cryosurgery Ablation of Miscellaneous Solid Tumors other than Liver or Prostate Tumors or Breast Fibroadenomas

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and each technique is relatively equivalent for rates of residual and recurrent tumor. Long-term data are needed to compare ablation techniques with 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. 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) with cryoablation.

Martin and Athreya reported on a meta-analysis that compared cryoablation with microwave ablation for small renal tumors in 2013. 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. 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. Forty-seven case series representing 1375 renal tumors were analyzed. Of 600 lesions treated with cryoablation, 494 underwent biopsy before treatment vs 482 of 775 treated with RFA. The incidence of RCC with known pathology was 72% in the cryoablation group and 90% in the RFA group. The mean duration of follow-up after cryoablation was 22.5 months. Most studies used contrast-enhanced imaging to determine treatment effect. Local tumor progression was reported in 31 (5%) of 600 lesions after cryoablation and in 100 (13%) of 775 lesions after RFA. Progression to metastatic disease was described in 6 (1%) of 600 lesions after cryoablation and 19 (2.5%) of 775 after RFA. Reviewers cautioned that minimally invasive ablation had generally been performed selectively on older patients with smaller tumors, possibly resulting in selection bias; case series of ablated lesions tend to have shorter posttreatment follow-up compared with tumors managed by surgical excision or active surveillance, and treatment efficacy may be overestimated in series that include tumors with unknown pathology.

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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. They cautioned that, while studies suggested satisfactory outcomes, given the limitations of imaging and the indolent nature of the tumors, stringent selection criteria and rigorous follow-up were required.

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

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. 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 overall survival 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. Perioperative

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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 LCA. 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 LCAs 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 3 years and 100% for RFA at just 1-year median follow-up. Studies have also reported results for small numbers of patients who had LCA or laparoscopic partial nephrectomy for treatment of renal masses.

In a prospective, single-institution study, Rodriguez et al (2011) reported on 113 patients consecutively treated with PCA for 117 renal lesions. 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. 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 a selection bias and did not definitively provide evidence of comparative effectiveness. Prospective controlled trials are needed to determine whether cryoablation achieves equivalent outcomes and/or reduced complications, compared with surgical treatment.

Bone Cancers

Meller et al (2008) retrospectively analyzed a single-center experience 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 a median follow-up of 7 years (range, 3-18 years), the overall recurrence rate was 8%. Based on their experience, the

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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 (located in areas of the breast, lung, pancreas, kidney, or bone) who receive cryosurgical ablation, the evidence includes nonrandomized comparative studies, case series, and systematic reviews of these nonrandomized studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. There is a lack of randomized controlled trials and high-quality comparative studies to determine the efficacy and comparative effectiveness of cryoablation. The largest amount of evidence is for RCC in select patients (i.e., those with small tumors who are not surgical candidates, or those who have baseline renal insufficiency of such severity that standard surgical procedures would impair their kidney function). Cryoablation results in short-term tumor control and less morbidity than surgical resection, but long-term outcomes may be inferior to surgery. For other indications, there is less evidence, with single-arm series reporting high rates of local control. Due to the lack of prospective controlled trials, it is difficult to conclude that cryoablation improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

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10/21/2003 Medical Policy Committee review
 01/26/2004 Managed Care Advisory Committee approval
 12/07/2005 Medical Director review
 12/20/2005 Medical Policy Committee review. Format revision. FDA approval information added to policy.
 02/23/2006 Quality Care Advisory Council approval
 10/10/2007 Medical Director review
 10/17/2007 Medical Policy Committee approval. No change to coverage eligibility.
 03/04/2009 Medical Director review
 03/18/2009 Medical Policy Committee approval. Changed localized renal cell carcinoma from investigational to eligible for coverage with criteria. Breast fibroadenomas removed from this policy and made into a separate policy.

03/05/2010 Medical Policy Committee review
 03/19/2010 Medical Policy Implementation Committee approval. Added benign tumors of the breast to be investigational.

03/03/2011 Medical Policy Committee review
 03/16/2011 Medical Policy Implementation Committee approval. Renal cell carcinomas in patients who are surgical candidates was added as investigational.

03/01/2012 Medical Policy Committee review
 03/21/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 03/07/2013 Medical Policy Committee review
 03/20/2013 Medical Policy Implementation Committee approval. Title changed from "Cryosurgery Ablation of Miscellaneous Solid Tumors other than Liver or Prostate" to "Cryosurgery Ablation of Miscellaneous Solid Tumors Other than Liver or Prostate Tumors or Breast Fibroadenomas". Removed the second criteria bullet for treatment of renal cell carcinoma requiring that the patient not be considered as a surgical candidate due to co-morbid disease. Lung cancer added to investigational statement. The investigational statement was revised for clarification.

03/06/2014 Medical Policy Committee review
 03/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
 09/03/2015 Medical Policy Committee review
 09/23/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 09/08/2016 Medical Policy Committee review
 09/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 12/07/2017 Medical Policy Committee review
 12/20/2017 Medical Policy Implementation Committee approval. Added a criteria bullet to localized renal cell carcinoma that states "the patient is not considered a surgical candidate." Added that cryosurgical

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ablation to treat lung cancer may be considered eligible for coverage with criteria. Added an investigational statement for lung cancer when criteria are not met. Replaced the investigational statement regarding cryosurgical ablation for malignant tumors with an investigational statement indicating that cryosurgical ablation as a treatment for benign or malignant tumors of the breast, pancreas, or bone and other solid tumors or metastases outside the liver, prostate and breast fibroadenomas is considered to be investigational.

01/01/2018 Coding update
 08/31/2018 Coding update
 Next Scheduled Review Date: 12/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)[®]†, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	19105, 20983, 32994, 50250, 50542, 50593 Deleted code effective 1/1/2018: 0340T
HCPCS	C2618
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

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Louisiana

Cryosurgery Ablation of Miscellaneous Solid Tumors other than Liver or Prostate Tumors or Breast Fibroadenomas

Policy # 00023

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of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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