| 7.01.92 | Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors | | |
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| **Original Policy Date:** | March 1, 2006 | **Effective Date:** | September 1, 2020 |
| **Section:** | 7.0 Surgery | **Page:** | Page 1 of 37 |

## Policy Statement

Cryosurgical ablation may be considered **medically necessary** to treat localized renal cell carcinoma that is no more than 4 centimeters (cm) in size 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/$m^2$), and standard surgical approach (i.e., resection of renal tissue) is likely to worsen kidney function substantially
- The patient is not considered a surgical candidate

Cryosurgical ablation may be considered **medically necessary** to treat lung cancer when **either** of the following criteria is met:

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

Cryosurgical ablation is considered **investigational** when used to treat **any** of the following:

- Benign or malignant tumors of the breast, lung (other than defined above), pancreas, or bone
- Other solid tumors or metastases outside the liver and prostate
- Renal cell carcinomas in patients who are surgical candidates

## Policy Guidelines

### Coding

***Effective January 1, 2020,*** there is a new Category III code to report cryoablation of a cancerous tumor in the breast:

- **0581T**: Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral

There are specific CPT codes for cryosurgical ablation of renal mass lesions:

- **50250**: Ablation, open, 1 or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound guidance and monitoring, if performed
- **50593**: Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy

There is also a CPT code for laparoscopic ablation that is not specific to cryosurgical ablation:

- **50542**: Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed

There is a CPT code for cryosurgical ablation of fibroadenoma:

- **19105**: Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma

There is a CPT code for cryosurgical ablation of bone tumors:

- **20983**: Ablation therapy for reduction or eradication of 1 or more bone tumors (e.g., metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation

- **32994**: Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation

There are no other specific CPT codes describing cryosurgical ablation of solid tumors other than liver or prostate tumors.

## Description

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

## Related Policies

- Cryosurgical Ablation of Primary or Metastatic Liver Tumors
- Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors
- Whole Gland Cryoablation of Prostate Cancer

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

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

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

Food and Drug Administration product code: GEH.

## Rationale

### Background

**Breast Tumors**

Early-stage primary breast cancers are treated surgically. The selection of lumpectomy, modified radical mastectomy, or another approach is balanced against the patient's desire for breast conservation, the need for tumor-free margins in resected tissue, and the patient's age, hormone receptor status, and other factors. Adjuvant radiotherapy decreases local recurrences, particularly for those who select lumpectomy. Adjuvant hormonal therapy and/or chemotherapy are added, depending on the 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 a 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 a more advanced local disease or metastatic disease may undergo chemotherapy with radiation following resection. Treatment focuses on slowing tumor growth and palliation of symptoms.

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

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

**Literature Review**
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### Cryosurgical Treatment

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

### Clinical Context and Therapy Purpose

The purpose of cryosurgical ablation is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical resection, other ablative techniques, or no intervention, in patients with solid tumors (located in the breast, lung, pancreas, kidney, or bone).

The question addressed in this evidence review is: Will cryoablation (CRA) of miscellaneous solid tumors (located in areas such as the breast, lung, pancreas, kidney, or bone) improve the net health outcome?

The following PICO was used to select literature to inform this review.

#### *Patients*

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

Regarding tumors located in the breast, 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.

#### *Interventions*

The therapy being considered is cryosurgical ablation.
Cryosurgical ablation involves freezing of target tissues; this is most often performed by inserting a coolant-carrying probe into the tumor. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

Cryosurgical ablation is performed by oncologists in an inpatient clinical setting.

#### *Comparators*

Comparators of interest include surgical resection, and other ablative techniques such as laser surgery, radiofrequency ablation (RFA), irreversible electroporation, and argon beam coagulation.

Surgical resection and other ablative techniques are performed by surgical oncologists in an inpatient clinical setting.

#### *Outcomes*

The general outcomes of interest are overall survival (OS), disease-specific survival, quality of life, and treatment-related morbidity.

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).

**Table 1. Outcomes of Interest for Individuals with Solid Tumors (Located in The Breast, Lung, Pancreas, Kidney, or Bone)**

| Outcomes | Details |
|---|---|
| Disease-specific survival | Outcomes of interest include residual disease, and disease-free survival [Timing: 1-10 years] |
| Overall survival | Outcome of interest is death from any cause [Timing: 1-10 years] |
| Treatment-related morbidity | Outcomes of interest include complications such as ecchymosis and hematoma, pain, tenderness, and edema for breast cancers and hemoptysis, pneumothorax, hemothorax, pleural effusion, and pulmonary infection for lung cancer [Timing: ≥1 week] |

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.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, prefer larger sample size studies and longer duration studies.
- Studies with duplicative or overlapping populations were excluded.

### Breast Diseases
### Breast Cancer

### Review of Evidence
### Systematic Reviews

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

### Randomized Controlled Trials

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

### Nonrandomized Studies

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

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

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

**Breast Fibroadenomas**

A variety of case series has focused on the role of cryosurgery as an alternative to surgical excision of benign fibroadenomas. Kaufman et al (2002-2005) have published several case series on office-based ultrasound-guided CRA as a treatment of breast fibroadenomas.[11,12,13,14,15] These case series reported on a range of 29 to 68 patients followed for 6 months to 2.6 years. It is likely that these case series included overlapping patients. At 1 year, patients reported 91% patient satisfaction and fibroadenomas became nonpalpable in 75% of cases. At follow-up averaging 2.6 years in 37 patients, the authors noted only 16% of 84% palpable fibroadenomas remained palpable after treatment and, of the fibroadenomas initially 2 cm or less in diameter, only 6% remained palpable.[15] In this series, the authors also noted that CRA did not produce artifacts that could interfere with the interpretation of mammograms. These small case series, which were done by the same group of investigators, are inadequate to permit scientific conclusions.

Nurko et al (2005) reported on outcomes at 6 and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment registry by 55 different practice settings.[16] In these patients, before CRA, 75% of fibroadenomas were palpable by the patient. Follow-up at 6- and 12-month intervals showed palpable masses in 46% and 35%, respectively. When fibroadenomas were grouped by size, for lesions 2 cm or less in diameter, the treatment area was palpable in 28% of subjects at 12 months. For lesions more than 2 cm, the treatment area was palpable in 59% at 12 months.

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

**Section Summary: Breast Diseases**

For the treatment of primary and recurrent breast cancer, available evidence has shown that complete ablation can be achieved in most cases for variably defined small tumors, but studies have not included control groups or compared outcomes of cryosurgery with alternative strategies for managing similar patients. Therefore, no conclusions can be made on the net health outcome of cryosurgery for breast cancer. For the treatment of fibroadenomas, there is a small body of evidence. This evidence has demonstrated that most fibroadenomas become "nonpalpable" following CRA. 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 CRA).

**Lung Cancer**
**Review of Evidence**

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

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

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

**Nonrandomized Studies**
The Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE) study assessed the safety and local recurrence-free survival after CRA for treatment of pulmonary metastases. Callstrom et al (2020) performed this multicenter, prospective, single-arm, phase 2 study in 128 patients with 224 lung metastases ≤3.5 cm.[20] Median tumor size was 1.0 cm. Local recurrence-free response was 85.1% at 12 months and 77.2% at 24 months. Secondary local recurrence-free response after retreatment with CRA for recurrent tumors was 91.1% at 12 months and 84.4% at 24 months. Overall survival at 12 and 24 months was 97.6% and 86.6%, respectively.

The Evaluating Cryoablation of Metastatic Lung/Pleura Tumors in Patients-Safety and Efficacy trial is a prospective, multicenter trial of CRA for metastatic disease in the lungs; interim results at 1-year follow-up were published by de Baere et al (2015).[21] The trial enrolled 40 patients with 60 metastatic lung lesions who were treated with CRA and had at least 12 months of follow-up. Outcomes included survival, local tumor control, quality of life, and complications. Local tumor control was achieved in 94.2% (49/52) of treated lesions, and the 1-year OS rate was 97.5% (39/40). There were no significant changes in quality of life over the 12-month study. The most common adverse event was pneumothorax requiring chest tube intubation in 18.8% (9/48 procedures). No subsequent analyses have been identified.

Moore et al (2015) reported on a retrospective case review of 45 patients (47 tumors) managed with CRA during a 5-year period (2006-2011).[22] All patients had biopsy-confirmed early-stage

(T1a and T1b) primary lung tumors and had been assessed by a tumor board to be medically inoperable. Lesions were as small as 5 mm, with an average of 1.9 cm (range, 0.5-3 cm). CRA was performed under general anesthesia. The primary endpoint was the completion of the freeze-thaw cycle. Mean follow-up was 51 months, with an observed 5-year survival rate of 67.8%, 5-year cancer-specific survival rate of 56.6%, and 5-year progression-free survival rate of 87.9%. There were 7 (14.8%) local recurrences; 2 had device failure and retreatment, and another had retreatment for a tumor recurrence at 1 year after initial treatment. The ablation zone was less than 5 mm outside the margin of the tumor in 5 of the 47 treatments, and 4 of these 5 had local recurrences. Complications primarily included 19 (40%) patients with hemoptysis, 2 of which required bronchoscopy, and 24 (51%) cases of pneumothorax, 1 of which required surgical chest intubation with prolonged placement and mechanical sclerosis. These 3 (6.4%) patients were considered major complications but there were no reports of 30-day mortality.

Maiwand and Asimakopoulos (2004) reported on a large case series of 521 patients with symptomatic obstructive tracheobronchial malignant tumors who underwent cryosurgery with a mean of 2.4 treatments per patient.[23] The patients were treated between 1995 and 2003, had a mean age of 67.9 years, and 72% were diagnosed with stage IIIB or IV disease. Improvement in 1 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 a respiratory failure in all 7 patients).

Asimakopoulos et al (2005) reported on a subset of the same population of patients, analyzing outcomes from 2 groups of patients.[24] Group A consisted of 172 patients who underwent at least 2 sessions of CRA; group B consisted of 157 patients who underwent only 1 session of cryosurgery. The single treatment group (group B) was more diverse; it presented with a medical condition that did not permit patients to undergo a second session of cryosurgery. Group B was also more likely to have stage III or IV disease and less likely to have had prior palliative radiotherapy. Overall, there was a statistically significant chance ($p<0.001$) that dyspnea would improve by at least 1 New York Heart Association functional class, 2 weeks after the second session of cryosurgery. Patients in group B benefited to a lesser degree from cryosurgery. In group A, the chance of a patient experiencing improvement in cough by at least 1 class after 2 sessions of cryosurgery was statistically significant ($p<0.001$). Group B patients benefited less with regard to improvement in cough. Only 78 (43.3%) of the 172 patients in group A reported episodes of hemoptysis before or after treatment. Overall, there was a statistically significant reduction in hemoptysis ($p<0.001$). Group B had limited follow-up attendance.

**Section Summary: Lung Cancer**

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

## Pancreatic Cancer

### Review of Evidence

#### Systematic Reviews

Tao et al (2012) reported on a systematic review of CRA for pancreatic cancer.[25] Reviewers identified 29 studies and selected 5. All 5 were case series and considered of low quality. Adverse events, when mentioned, included delayed gastric emptying (0%-40.9% in 3 studies), pancreatic leak (0%-6.8% in 4 studies), biliary leak (0%-6.8% in 3 studies), and a single instance of upper gastrointestinal hemorrhage. Pain relief was reported in 3 studies and ranged from 66.7% to 100%. Median survival times reported in 3 studies ranged from 13.4 to 16 months. One-year total survival rates, as reported in 2 studies, were 57.5% and 63.6%. Keane et al (2014) reported on a systematic review of ablation therapy for locally advanced pancreatic cancer.26, Reviewers noted that studies had demonstrated ablative therapies, including CRA, are feasible, but larger studies are needed. No conclusions could be made on whether ablation resulted in better outcomes than best supportive care.

**Nonrandomized Trials**
Li et al (2011) reported on a retrospective study of 142 patients with unresectable pancreatic cancer treated with a palliative bypass with (n=68) or without CRA (n=74) from 1995 to 2002.[27.] Median dominant tumor sizes decreased from 4.3 to 2.4 cm in 36 (65%) of 55 patients 3 months after CRA. Survival rates did not differ significantly between groups, with the CRA group surviving a median of 350 days vs 257 days in the group without CRA. Complications did not differ significantly between groups. However, a higher percentage of delayed gastric emptying occurred in the CRA group (36.8%) than in the group without CRA (16.2%).

A pilot study assessing combination cryosurgery plus iodine 125 seed implantation for treatment of locally advanced pancreatic cancer was reported by Xu et al (2008).[28.] Forty-nine patients enrolled in the pilot study, and 12 had liver metastases; 20 patients received regional chemotherapy. At 3 months posttherapy, most patients showed tumor necrosis, with 20.4% having a complete response. Overall, the 6-, 12-, 24-, and 36-month survival rates were 94.9%, 63.1%, 22.8%, and 9.5%, respectively.

Kovach et al (2002) reported on 10 cryosurgical ablations in 9 patients with unresectable pancreatic cancer using intraoperative ultrasound guidance during laparotomy.[29.]The authors reported adequate pain control in all patients postoperatively and no intraoperative morbidity or mortality. At publication, all patients had died at an average of 5 months postoperatively (range, 1-11 months).

**Section Summary: Pancreatic Cancer**
The available evidence on cryosurgery for pancreatic cancer consists of retrospective case series that used cryosurgery for palliation of inoperable disease and a systematic review of these studies. These studies reported that pain relief was achieved in most cases and that complications (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 outcome of cryosurgery for pancreatic cancer.

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

**Review of Evidence**
**Systematic Reviews**
Uhlig et al (2018) published a systematic review and meta-analysis comparing partial nephrectomy (PN), RFA, CRA, and microwave ablation (MWA) for small renal masses.[30.] Forty-seven studies published between 2005 and 2017, with a total of 24077 participants, were included. No significant difference in cancer-specific mortality for PN (p=0.8065), CRA (p=0.5519), RFA (p=0.3496), and MWA (p=0.2920) was found. Local recurrence was higher for CRA, RFA, and MWA compared with PN (respectively, incidence rate ratio=4.13; incidence rate ratio=1.79; incidence rate ratio=2.52; $p<0.05$). There was a less pronounced decline in renal

function for RFA compared with PN, CRA, and MWA (respectively, mean difference in glomerular filtration rate =6.49; mean difference=5.82; mean difference MD=10.89; p<0.05). The study was limited by the following[30]:

- Most studies included were retrospective;
- 7 abstracts were included in the meta-analysis;
- statistical adjustments for confounders such as patient age and comorbidities were missing;
- few studies evaluated renal function; and
- follow-up periods were inconsistent.

Pessoa et al (2017) reported on the results of a systematic review of studies comparing the use of laparoscopic cryoablation (LCA) with PCA for the treatment of small renal masses.[31] Eleven studies were identified through March 2016 and represented a total of 1725 kidney CRA cases: 921 (53.4%) LCA and 804 (46.6%) PCA. All cases were obtained from observational retrospective case-control studies. No significant differences were found for baseline population characteristics including rates of premalignant histology and tumor sizes. Moreover, PCA was performed more frequently for posterior renal tumors. The rate of successful biopsies obtained did not differ significantly between techniques (88.5% for LCA vs 76.3% for PCA; p=0.59). The interventions were also comparable in operating times as well as intraoperative and postoperative complications.

Pessoa et al defined residual disease as a persistent imaging study enhancement in 7 of 8 studies, and only 1 study relied on histopathology to confirm the residual disease. Recurrent disease was defined as imaging enhancement after initial negative imaging in 4 of 7 studies. Imaging and confirmatory biopsy to confirm recurrence was reported in 3 studies. A PCA approach resulted in a higher likelihood of residual disease (odds ratio [OR], 2.6; 95% CI, 1.31 to 3.57; p=0.003) and a seemingly paradoxical lower likelihood of tumor recurrence (OR=0.62; 95% CI, 0.41 to 0.94; p=0.02). This systematic review provided some evidence, albeit low level, of the minimally invasive interventions emerging in clinical practice. The lack of pathologic confirmation of residual and recurrent lesions is a significant limitation.

Tang et al (2014) reported on a systematic review and meta-analysis comparing renal LCA with laparoscopic PN in the treatment of small renal masses.[32] Reviewers identified 9 trials (2 prospective, 7 retrospective) in which the 2 techniques were assessed (555 cases, 642 controls). LCA was associated with statistically significant shorter surgical times, less blood loss, and fewer overall complications; however, it was estimated that laparoscopic PN might have a significantly lower local recurrence rate (OR=13.03; 95% CI, 4.20 to 40.39; p<0.001) and lower distant metastasis rate (OR=9.05; 95% CI, 2.31 to 35.51; p=0.002).

Klatte et al (2014) also reported on a systematic review and meta-analysis comparing LCA with laparoscopic PN for small renal tumors.[33] Thirteen nonrandomized studies were selected for analysis, which found LCA was associated with better perioperative outcomes than laparoscopic PN. Oncologic outcomes, however, were inferior with CRA, which was significantly associated with greater risk of local (relative risk, 9.39) and metastatic (relative risk, 4.68) tumor progression.

Martin and Athreya (2013) reported on a meta-analysis that compared CRA with MWA for small renal tumors.[34] Analysis of 51 studies did not reveal any significant differences between MWA and CRA 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 MWA group, the mean tumor size was significantly larger (p=0.03). Open access was used more often in the MWA group (12.20% vs 1.04%, respectively; p<0.001) and percutaneous access was used more often in the CRA group (88.64% vs 37.20%, respectively; p=0.002).

El Dib et al (2012) conducted a meta-analysis evaluating CRA and RFA for small renal masses.[35.] Twenty CRA (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 CRA group and 2.7 cm (range, 2-4.3 cm) in the RFA group. Mean follow-up times for the CRA 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 CRA was 89% (95% CI, 0.83% to 0.94%) and 90% (95% CI, 0.86% to 0.93%) for RFA.

In another systematic review, Klatte et al (2011) reviewed 98 studies published through December 2010 to compare the treatment of small renal masses with LCA or PN.[36.] PN was performed in 5347 patients, and LCA was performed in 1295 patients. RCC was confirmed in 159 (2.9%) of patients. After CRA, local tumor progression of RCC occurred at a rate of 8.5% (70/821;range, 0%-17.7%). After PN, 1.9% (89/4689; range, 0%-4.8%) of patients experienced local tumor progression. Distant metastasis occurred more frequently in PN patients (n=91) than in CRA patients (n=9), although not significantly (p=0.126). However, mean tumor size for CRA patients (2.4 cm) was smaller than in the PN patients (3.0 cm; p<0.001). Fewer patients receiving CRA (17%; range, 0% to 42%) experienced perioperative complications than PN patients (23.5%; range, 8% to 66%; p<0.001).

Long et al (2011) also reported on a systematic review comparing PCA with surgical CRA of small renal masses.[37.] Forty-two studies treating small renal masses (totaln=1447 lesions) were reviewed, including 28 articles on surgical CRA and 14 articles on PCA. Reviewers concluded percutaneous and surgical CRA for small renal masses have similar, acceptable short-term oncologic outcomes, and each technique is relatively equivalent for rates of residual and recurrent tumors.

Van Poppel et al (2011) reviewed the literature on localized RCC treatment published between 2004 and May 2011.[38.] They concluded CRA is a reasonable treatment option for low-grade renal tumors less than 4 cm in diameter (mostly <3 cm) in patients not candidates for surgical resection or active surveillance.

In a Cochrane review, Nabi et al (2010) assessed evidence on the management of localized RCC.[39.] No randomized trials comparing CRA with open radical or PN were identified. One nonrandomized study, comparing laparoscopic PN with LCA using a matched-paired analysis,[40.] and 3 retrospective studies were selected. Reviewers noted PCA can successfully destroy small RCC and may be considered a treatment option in patients with serious comorbidities that pose surgical risks. Reviewers concluded that high-quality RCTs are required for the management of localized RCC and that an area of emphasis should be the comparative efficacy of renal surgery with minimally invasive techniques for small tumors (<4 cm). This review was withdrawn and replaced by another with a narrower scope. The Cochrane review replacement by Kunath et al (2017) focused on PN and radical nephrectomy as the relevant surgical therapy options for localized RCC.[41.] Only 1 RCT was identified (n=541 participants) that compared PN 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 PN (hazard ratio [HR], 1.50; 95% CI, 1.03 to 2.18). No other analyses were performed. Study limitations included lack of blinding and imprecision (a substantial proportion of patients were ultimately found not to have a malignant lesion).

Kunkle and Uzzo (2008) conducted a comparative meta-analysis of CRA and RFA as primary treatment for small renal masses.[42.] Forty-seven case series representing 1375 renal tumors were analyzed. Of 600 lesions treated with CRA, 494 underwent biopsy before treatment vs 482 of 775 treated with RFA. The incidence of RCC with known pathology was 72% in the CRA group and 90% in the RFA group. The mean duration of follow-up after CRA 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 CRA and in 100 (13%) of 775 lesions after RFA. Progression to metastatic disease was described in 6 (1%) of 600 lesions after CRA and 19 (2.5%) of 775 after RFA. Reviewers cautioned that minimally invasive ablation had generally been performed selectively on older patients with smaller tumors, possibly resulting in selection bias; case series of ablated lesions tend to have shorter posttreatment follow-up compared with tumors managed by surgical excision or active surveillance, and treatment efficacy may be overestimated in series that include tumors with unknown pathology.

Matin and Ahrar (2008) reviewed studies evaluating CRA and RFA with at least a 12-month follow-up and found that 3- and 5-year outcomes showed 93% to 98% cancer-specific survival in small cohorts.[43] They cautioned that, while selected studies suggested satisfactory outcomes, given the limitations of imaging and the indolent nature of the tumors, stringent selection criteria and rigorous follow-up were required.

**Nonrandomized Comparative Studies**

A retrospective, nonrandomized analysis of prospectively collected data compared robot-assisted PN with percutaneous ablation in patients with T1b renal cell carcinoma. Rembeyo et al (2020) compared patients treated with robot-assisted PN (n=36), CRA (n=55), and RFA (n=11).[44] Median tumor sizes in each group were 4.5, 4.6, and 4.2 cm, respectively, and median follow-up times were 23.7, 19.9, and 51.3 months. Compared with PN, local recurrence-free survival was significantly shorter with CRA (adjusted HR, 4.3; 95% CI, 1.78-10.37). Two-year local recurrence-free survival rates for the PN, CRA, and RFA groups were 89.1%, 73.5%, and 81.8%, respectively (p<0001).

Another retrospective, nonrandomized study also compared PN with CRA and RFA, specifically in patients with T1aN0M0 renal cell carcinoma with tumor size ≤4 cm. Yan et al (2019), using Medicare Surveillance, Epidemiology, and End Results (SEER) data, compared OS and cancer-specific survival in patients treated with PN (n=15,395), CRA (n=1,381), and RFA (n=457).45, Median follow-up was 30 months in all groups. Overall survival was significantly improved with PN compared with CRA (HR, 2.995; 95% CI, 2.363 to 3.794) and RFA (HR, 4.085; 95% CI, 2.683 to 6.220). Similarly, cancer-specific survival was significantly improved with PN compared with CRA (HR, 3.562, 95% CI, 1.399–6.220) and RFA (HR, 3.457; 95% CI, 2.043 to 5.850). In subgroup analyses of patients with tumor size ≤2 cm, OS was again significantly improved with PN versus CRA (HR 1.958; 95% CI, 1.204 to 3.184) and RFA (HR, 2.841; 95% CI, 1.211 to 6.662); however, cancer-specific survival was not different. In patients with tumor size 2 to 4 cm, OS was significantly improved with PN versus CRA (HR 3.284; 95% CI, 2.513 to 4.292) and versus RFA (HR, 4.497; 95% CI, 2.782 to 7.269), as was cancer-specific survival (PN vs. CRA: HR, 3.536; 95% CI, 2.006 to 6.234; PN vs RFA: HR, 4.339; 95% CI, 1.573 to 11.971).

Another analysis of Medicare SEER data retrospectively compared PN with CRA in patients with T1b nonmetastatic renal cell carcinoma. Pecoraro et al (2019) compared patients undergoing CRA (n=434) with propensity score-matched patients undergoing PN (n=228).[46] In patients treated with CRA versus PN at 5 years, cancer-specific mortality rates were 7.6% versus 2.8%, respectively (p=0.02), and other-cause mortality rates were 17.9% versus 11.8% (p=0.1). Findings were consistent in multivariable analyses, where other-cause mortality remained nonsignificant, and CRA was associated with higher risk of mortality (adjusted HR, 2.50).

A retrospective, nonrandomized study compared CRA with heat-based thermal ablation for treatment of T1a renal cell carcinoma. Wu et al (2019) analyzed data from the National Cancer Database including patients with renal cell carcinoma treated between 2004 and 2014 with CRA (n=3,936) or heat-based thermal ablation (n=2,322).[47] Mean tumor sizes in each group were 2.5 cm in each group. After propensity score matching, and with a median follow-up of 4 years, OS was longer in patients treated with CRA compared with heat-based thermal ablation (median, 11.3 vs. 10.4 years; HR, 1.175; 95% CI, 1.03–1.341). However, in the subgroup of patients with tumors ≤2 cm (n=755 in each group), propensity score–matched analyses demonstrated no

significant difference between groups. The 3-, 5-, and 10-year survival rates were, respectively, 91%, 82%, and 62% for CRA and 89%, 81%, and 55% for heat-based thermal ablation.
One retrospective, nonrandomized comparative study of different CRA techniques was identified. Strom et al (2011) reported on a retrospective comparison of 145 patients who underwent laparoscopic (n=84) or percutaneous (n=61) CRA of small renal masses at 5 U.S. academic medical centers.[48] Patients were offered CRA because they were considered to be at higher risk for complications from PN or were not surgical candidates due to comorbidities. Mean tumor sizes were 2.7 cm in the laparoscopic group and 2.5 cm in the percutaneous group.

Patients were followed longer in the laparoscopic group (mean, 42.3 months) than in the percutaneous group (31.0 months; p=0.008). Complications in both treatment groups were similar and did not occur with any significant difference in frequency. At a mean intermediate follow-up of 37.6 months, local tumor recurrence was significantly higher in the percutaneous group (16.4%; [10/61]) than in the laparoscopic group (5.9%; [5/84]). However, disease-free survival and OS did not differ significantly at the last follow-up in the laparoscopic group (91.7% and 89.3%) compared with the percutaneous group (93.7% and 88.9%), respectively.

### Nonrandomized Studies

A retrospective analysis of prospectively collected data evaluated outcomes in patients with T1 renal cell carcinoma treated with CRA (n=180) was performed by Lim et al (2020).[49] Median tumor size was 2.7 cm. Technical success was achieved in 183 of the 185 lesions treated (98.9%), and local tumor progression-free survival at 3 and 5 years was 98.3% and 94.9%, 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 CRA with RCC. Murray et al (2019) reported outcomes of 47 patients with renal cancer treated with CRA at a mean of 56 months.[50] Overall, 87% of all tumors (n=49) were recurrence-free at 56 months, and major complications occurred in 10% of procedures. Five of 6 local recurrences were successfully treated with repeat CRA.

Caputo et al (2015) reported on long-term outcomes on 138 patients with 142 tumors, with a mean follow-up of 98.8 months.[51] Perioperative complications occurred in 15 patients, for a rate of 10.6%. Recurrence-free survival was 91.4% at 3 years, 86.5% at 5 years, and 86.5% at 10 years. The latest reported recurrence occurred 4.4 years posttreatment.

Weld et al (2007) reported on 3-year follow-up for 36 (22 malignant) renal tumors treated with LCA.[52] In this series, the 3-year cancer-specific survival rate was 100%, and no patient developed metastatic disease. The authors concluded that these intermediate-term data seemed equivalent to results obtained with extirpative therapy. Hegarty et al (2006) reported on results for 164 LCAs and 82 percutaneous RFAs for localized renal tumors.[53] 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 PN for the treatment of renal masses.[40]
In a prospective, single-institution study, Rodriguez et al (2011) reported on 113 patients consecutively treated with PCA for 117 renal lesions.[54] The average renal lesion size in the study was 2.7 cm (83 [71%] were RCC). Patients were selected for CRA 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.[55] Recurrence rates at their center were 13 (7%) of 175 after CRA and 26 (25%) of 104 after RFA. Extensive perinephric scarring was encountered in all salvage operations following

CRA, leading authors to conclude that CRA, in particular, can lead to extensive perinephric fibrosis, which can complicate salvage attempts.

**Section Summary: Renal Cancer**

There is a large body of single-arm studies and systematic reviews of these studies reporting on CRA outcomes for small renal tumors, most of which involved patients who are inoperable or at high surgical risk. The success rate for CRA 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 CRA with surgery, but they had a selection bias and did not definitively provide evidence of comparative effectiveness. Some recent retrospective, nonrandomized comparative studies suggest improved survival outcomes with PN versus CRA at up to 5 years; however, p rospective controlled trials are needed to determine whether CRA achieves equivalent outcomes and/or reduced complications, compared with surgical treatment.

**Bone Cancers**

**Review of Evidence**

Meller et al (2008) retrospectively analyzed a single-center experience with 440 bone tumor cryosurgery procedures performed between 1988 and 2002, two-thirds of them for primary benign-aggressive and low-grade malignant lesions, and one-third for primary high-grade and metastatic bone tumors.[56.] At a median follow-up of 7 years (range, 3-18 years), the overall recurrence rate was 8%. Based on their data, the authors suggested that the ideal case for cryosurgery is a young adult with involvement of long bone, a benign-aggressive or low-grade malignant bone tumor, a good cavity with greater than 75%-thick surrounding walls, no or minimal soft-tissue component, and at least ±1 cm of subchondral bone left near a joint surface after curettage and burr drilling.

Callstrom et al (2013) reported on 61 patients treated with CRA for pain from 69 tumors (size, 1-11 cm) metastatic to the bone.[57.] 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 CRA 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 CRA 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 CRA for bone cancers. This evidence base consists of case series and is inadequate to determine efficacy for any of the indications studied.

**Summary of Evidence**

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

There is a lack of randomized controlled trials and high-quality comparative studies to determine the efficacy and comparative effectiveness of CRA. The largest amount of evidence assesses renal cell carcinoma 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). CRA 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 CRA improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

## CLINICAL INPUT

### CI - Objective

Clinical input is sought to help determine whether the use of cryosurgical ablation in clinical practice for the management of solid tumors of the breast, lung, pancreas, kidney, or bone results in a meaningful clinical benefit in improved net health outcome and whether this use is consistent with generally accepted medical practice.

### Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Society of Breast Surgeons[a]
- Society of Interventional Radiology[b]
- Gareth Morris-Stiff, MBBCh, MD, MCh, PhD, FRCS, Hepato-Pancreato-Biliary Surgery; identified by American College of Gastroenterology
- Anonymous, MD, Gastroenterology, Interventional Endoscopy; identified by American Gastroenterological Association
- Haritha Pabbathi, MD, Medical Oncology; identified by Cancer Treatment Centers of America (CTCA)
- Joana Bonta, MD, Medical Oncology; identified by CTCA
- Anonymous, DO, Pulmonology; identified by CTCA
- Anonymous, MD, Medical Oncology; identified by CTCA
- Daniel J. Canter, MD, Urologic Oncology; identified by American Society of Clinical Oncology

Indicates that conflicts of interest related to the topic where clinical input is being sought were reported by this respondent (see Appendix).

Note that American College of Radiology also identified one of the physicians who assisted in developing the Society of Interventional Radiology response.

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by the specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a special society and/or physician member designated by the specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

## Clinical Input Responses

**Figure 1:**

| | | | | Confidence Level That Clinical Use Expected to Provide Meaningful Clinical Benefit | | | | | | | | | | | Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | NO | | | | | YES | | | | | | NO | | | | | YES | | | | |
| | | | | High | | Intermediate | | Low | Low | | Intermediate | | High | | High | | Intermediate | | Low | Low | | Intermediate | | High |
| Clinical Indication | Respondent | Identified by | Yes or No | 5 | 4 | 3 | 2 | 1 | 1 | 2 | 3 | 4 | 5 | Yes or No | 5 | 4 | 3 | 2 | 1 | 1 | 2 | 3 | 4 | 5 |
| Breast cancer | ASBrS | | YES | | | | | | | ■ | | | | NO | ■ | | | | | | | | | |
| | SIR | | NO | | | | ■ | | | | | | | NO | | | | ■ | | | | | | |
| | Dr. Bonta | CTCA | YES | | | | | | | | | ■ | | YES | | | | | | | | ■ | | |
| | Anonymous | CTCA | NO | ■ | | | | | | | | | | NO | ■ | | | | | | | | | |
| | Dr. Pabbathi | CTCA | YES | | | | | | | | ■ | | | YES | | | | | | | | ■ | | |
| Breast tumor, benign / fibroadenoma | ASBrS | | YES | | | | | | | | | ■ | | YES | | | | | | | | | ■ | |
| | SIR | | NO | | | | ■ | | | | | | | NO | | | | ■ | | | | | | |
| | Anonymous | CTCA | YES | | | | | | | | ■ | | | YES | | | | | | | | | | ■ |
| | Dr. Bonta | CTCA | NO | ░ | ░ | ░ | ░ | ░ | | | | | | NO | ░ | ░ | ░ | ░ | ░ | | | | | |
| Lung cancer | SIR | | YES | | | | | | | | | | ■ | YES | | | | | | | | | ■ | |
| | Dr. Bonta | CTCA | YES | | | | | | | | | | ■ | YES | | | | | | | | | | ■ |
| | Anonymous | CTCA | NO | | ■ | | | | | | | | | NO | | ■ | | | | | | | | |
| | Anonymous | CTCA | YES | | | | | | | | | | ■ | YES | | | | | | | | | | ■ |
| Pancreatic cancer | SIR | | NO | | | | ■ | | | | | | | NO | | | | ■ | | | | | | |
| | Dr. Morris-Stiff | ACG | NO | | | | | ■ | | | | | | NO | | | | | ■ | | | | | |
| | Anonymous | AGA | NO | | | | | ■ | | | | | | NO | | | | ■ | | | | | | |
| | Anonymous | CTCA | NO | | ■ | | | | | | | | | NO | | ■ | | | | | | | | |
| | Dr. Bonta | CTCA | YES | | | | | | | | | | ■ | YES | | | | | | | | | | ■ |
| Renal cell carcinoma | SIR | | YES | | | | | | | | | | ■ | YES | | | | | | | | | | ■ |
| | Dr. Bonta | CTCA | YES | | | | | | | | | | ■ | YES | | | | | | | | | | ■ |
| | Anonymous | CTCA | YES | | | | | | | | | ■ | | YES | | | | | | | | | | ■ |
| | Dr. Canter | ASCO | YES | | | | | | | | | ■ | | YES | | | | | | | | | | ■ |
| Bone cancer | SIR | | YES | | | | | | | | | | ■ | YES | | | | | | | | | | ■ |
| | Anonymous | CTCA | NO | | ■ | | | | | | | | | NO | | ■ | | | | | | | | |
| | Dr. Bonta | CTCA | NO | ░ | ░ | ░ | ░ | ░ | | | | | | NO | ░ | ░ | ░ | ░ | ░ | | | | | |

Grey shaded cells denote that a 1 through 5 confidence rating was not provided.
ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; ASBrS: American Society of Breast Surgeons; ASCO: American Society for Clinical Oncology; CTCA: Cancer Treatment Centers of America; SIR: Society of Interventional Radiology.

### Additional Comments

- "In accordance with the American Society of Breast Surgeons Consensus Guideline on the Use of Transcutaneous and Percutaneous Methods for the Treatment of Benign and Malignant Tumors of the Breast (Approved June 22, 2017): While several prospective studies have shown that percutaneous cryoablation of small breast cancers may be technically feasible, success rates are <100%, and imaging, including MRI, is not sensitive or specific enough to assess treatment effect. The outcome of leaving residual or cryoablated tumor in the breast remains unknown. Therefore, cryoablative treatment of breast cancer is investigational and should not be performed outside the realm of a clinical trial such as NCT02200705 or NCT01992250." (American Society of Breast Surgeons)
- "Cryoablation interventions for early-stage breast cancer and fibroadenomas remains in an investigational stage." (Society for Interventional Radiology/American College of Radiology)
- "While fibroadenomas do not routinely require intervention after diagnostic confirmation, treatment may be desired due to discomfort or the presence of a bothersome mass. Percutaneous cryoablation under ultrasound guidance has been shown to be a safe and efficacious treatment of fibroadenomas and is an alternative to surgical excision for those desiring treatment. The diagnosis of fibroadenoma should be established prior to performing cryoablation with percutaneous biopsy." (American Society of Breast Surgeons)

- "In sum, surgery is still the gold standard to maximize oncologic outcome for stage I lung cancer, with surgery having different outcomes than thermal ablation (cryo, microwave, RFA). Studies show similar rate of local control compared to sublobar resection, but not lobectomy. Local ablative techniques play an important role for the management of unresectable early lung cancer, and in the management of multifocal lung cancer, as well as in the management of oligo progressive lung cancer on targeted therapy, and for the management of local recurrence after radiation therapy. There are some advantages of cryoablation over microwave, but the reverse is also true. The best tool is determined by the exact clinical context." (Society for Interventional Radiology / American College of Radiology)
- "Patients with central airway obstructions or endobronchial tumors may benefit from cryoablative techniques to restore airway patency. A patient must be a candidate to undergo general anesthesia for bronchoscopy. Patients should not have a coagulopathy, require uninterrupted anticoagulation or severe thrombocytopenia (less than 5OK platelets) as this would put them at increased risk of morbidity and mortality due to bleeding in the airway." (Anonymous, MD, Pulmonology; identified by CTCA)
- "Ablative procedures in early stage disease (Clinical stage IA(Tla-b,N0,M0) are considered an option for inoperable patients or in patients who refuse surgery. It is not currently clear that cryosurgery is equivalent in outcomes or safety to other ablative therapies (i.e. SBRT). Additional studies are needed. Based on the Eclipse trial, which was a small nonrandomized trial, there was good local control with cryotherapy. Additionally, there were few adverse events. Again it is unclear that this is equivalent to other ablative therapies." (Anonymous, MD, Medical Oncology; identified by CTCA)
- "Despite being a potentially attractive modality for the treatment of advanced pancreatic cancer, the data is limited to small retrospective observational studies. One such study comparing bypass to bypass and cryoablation that revealed no survival benefit from the addition of cryotherapy. Furthermore, complication rates of cryoablation are not insignificant including bleeding, pancreatic and biliary, leaks, and delayed gastric emptying. There has been no data comparing cryoablation to other therapies such as resection or thermal ablation with radiofrequency or microwave options. Cryotherapy has not been used as a potentially curative therapy. Clinical practice guidelines have just been published which will hopefully lead to further and better studies to determine the precise role of cryoablation in pancreatic cancer, and I would anticipate numerous of these to emanate from China over the coming years."
- "The literature for cryoablation for pancreatic or cholangiocarcinoma remains investigational." (Society for Interventional Radiology/American College of Radiology)
- "For renal cell carcinoma (RCC), literature suggests about 30% of patients diagnosed with local RCC show metastatic disease at presentation, and about a third of RCC patients at diagnosis develop metastatic RCC (mRCC). Surgical and chemotherapy options are available to these patients, but for RCC patients, long-term data confirms that cryoablation is a safe and highly efficacious alternative for the treatment of RCC with similar local and distant outcomes as partial nephrectomy, but with near-complete preservation of renal function. Cryoablation of renal tumors has become well established, with multiple papers confirming reproducibility with appropriate technique." (Society for Interventional Radiology/American College of Radiology)
- "There is a significant and robust literature surrounding the use of cryoablation for the treatment of renal tumors, specifically renal cell carcinomas. Based on the published experience, there is strong evidence to support the use of cryoablation for renal tumors less than 3 cm. Tumors less than 3 cm appear to achieve relatively equivalent responses to the treatment gold standard, which is surgical excision. This size cut-off is irrespective of patient age and medical co-morbidities. Furthermore, it does also appear that in terms of patient comfort and need for hospitalization, percutaneous cryoablation is superior to laparoscopic cryoablation. Thus, it stands to reason that tumors less than 3 cm that are not amenable to a percutaneous approach should be excised surgically. For tumors greater than 3 cm, surgical excision is the optimal treatment modality, however for patients with significant medical co-morbidities who may not be able to withstand the

physiologic stress of surgery, percutaneous cryoablation may be considered. For larger tumors, it should be recognized that patients may require a repeat cryoablation in order to achieve a complete oncologic response." (Dr. Canter, Urologic Oncology; identified by ASCO)

- "The bony skeleton is the most common metastatic site from cancer after lungs and liver, with prostate, breast, lung, kidney, and thyroid malignancies accounting for approximately 80% of skeletal metastases. Of the patients who develop skeletal metastases, approximately 50% of patients will develop poorly controlled pain during the course of their disease. Surgical resection has been the care standard for local treatment of most newly diagnosed cancer cases. However, for patients with stage IV disease, resection of oligometastases in nonorgan locations produces quality-of-life concerns, and may limit most surgery to isolated resections of liver and pulmonary metastases. Chemotherapy is generally ineffective in treating pain in bone and recurrent soft-tissue metastases, and radiation therapy, although effective when used before surgery on small tumors, is limited for many sites. Cryosurgery has the advantage of lower morbidity, less neurological deficit, improved speed, and ease of surgical procedure, less potential blood loss, preservation of spinal and pelvic continuity, and lower tumor recurrence rates. In our patients with metastasis, treatment with cryotherapy allows local control with less extensive resection, allowing patient more rapid recovery and thus preserving the quality. A special note needs to be made regarding osteoid osteomas and other benign bone tumors in the pediatric population. Cryoablation is well-researched, and is an effective in treatment of many of these patients. In fact, cryoablation is usually preferred over Radiofrequency (RFA), as RFA has increased risk of permanent nerve injury, while nerve injuries from cryoablation, if they occur, are transient. Current research suggests that the recurrence rates of these tumors following cryoablation are about half of that encountered following heat-based ablation therapy." (Society for Interventional Radiology/American College of Radiology)
-

See Appendices 1 and 2 for details of the clinical input.

**Supplemental Information**
**Clinical Input From Physician Specialty Societies and Academic Medical Centers**
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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

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

- Use of cryosurgical ablation to manage individuals with localized renal cell cancer when either of the following criteria is met:
  - No more than 4 cm in size when preservation of kidney function is necessary (i.e., the patient has 1 kidney or renal insufficiency defined by a glomerular filtration rate <60 mL/min/m$^2$), and standard surgical approach (i.e., resection of renal tissue) is likely to worsen kidney function substantially; or
  - When the patient is not considered a surgical candidate.

- Use of cryosurgical ablation to manage individuals with lung cancer when either of the following criteria is met:
    - o Poor surgical candidates with early-stage non-small-cell lung cancer; or
    - o Palliation of a central airway obstructing lesion.

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

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

### 2009 Input

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

### Practice Guidelines and Position Statements

### American College of Radiology

The American College of Radiology Appropriateness Criteria (2009) for post-treatment follow-up and active surveillance of renal cell carcinoma, updated most recently in 2019 , indicated that "Ablative therapies, such as radiofrequency ablation, microwave ablation, and cryoablation, have been shown to be an effective and safe alternative [to surgical resection] for the treatment of small, localized RCCs."[58.] These recommendations are based on a review of the data and consensus.

### American Urological Association

The American Urological Association (2017) updated its guidelines on the evaluation and management of clinically localized sporadic renal masses suspicious for renal cell carcinoma.[59.] The guideline statements on thermal ablation (radiofrequency ablation, cryoablation) are listed in Table 2.

**Table 2. Guidelines on Localized Masses Suspicious for Renal Cell Carcinoma**

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

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

### National Comprehensive Cancer Network

The NCCN (v.2.2020) guidelines on kidney cancer state that "thermal ablation (cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions. Thermal ablation is an option for masses <3 cm, but may also be an option for larger masses in select patients. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications. Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies. Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes. NCCN guidelines also note that "ablative techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks." NCCN guidelines also note that "Randomized phase III comparison with surgical resection (i.e., radical or partial nephrectomy by open or laparoscopic techniques) has not been done" and "Ablative techniques are associated with a higher local recurrence rate than conventional surgery."[60.]

The NCCN (v. 5.2020) guidelines for non-small-cell lung cancer indicate surgical "resection is the preferred local treatment modality" and "other modalities include ... cryotherapy."[61.]

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

Not applicable.

### Medicare National Coverage

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.

### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| *Ongoing* | | | |
| *Renal cancer* | | | |
| NCT02399124[a] | ICESECRET PROSENSE™ Cryotherapy for Renal Cell Carcinoma Trial | 100 | Jan 2025 |
| NCT03390413 | Robot-assisted Surgical Resection vs Cryoablation of Localised Renal Cancer - a Randomised Trial of Functional, Oncological and Financial Aspects | 190 | Mar 2028 |

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

# Appendix

## Appendix 1: Clinical Input

### Appendix Table 1. Respondent Profile

| No. | Name of Organization | Clinical Specialty |
|---|---|---|
| | **Specialty Society** | |
| 1 | American Society of Breast Surgeons | Breast Surgery |
| 2 | Society of Interventional Radiology[a] | Interventional Radiology |

| No. | Name | Degree | Institutional Affiliation | Clinical Specialty | Board Certification and Fellowship Training |
|---|---|---|---|---|---|
| | **Physician** | | | | |
| **Identified by American College of Gastroenterology** | | | | | |
| 3 | Gareth Morris-Stiff | MBBCh, MD, MCh, PhD, FRCS, FACS | Cleveland Clinic | Hepato-Pancreato-Biliary Surgery | Fellowship of the Royal College of Surgeons (FRCS) England |
| **Identified by American Gastroenterological Association** | | | | | |
| 4 | Anonymous | MD | Yale University | Gastroenterology, Interventional Endoscopy | GI Board Certification, Gastroenterology, and Advanced Endoscopy Fellowship |
| **Identified by Cancer Treatment Centers of America** | | | | | |
| 5 | Haritha Pabbathi | MD | Cancer Treatment Centers of America | Medical Oncology | Internal Medicine; Hematology; Oncology Certified |
| 6 | Joana Bonta | MD | Cancer Treatment Centers of America | Medical Oncology | Internal Medicine; Medical Oncology |
| 7 | Anonymous | DO | Cancer Treatment Centers of America | Pulmonology | Internal Medicine and Pulmonology |
| 8 | Anonymous | MD | Cancer Treatment Centers of America | Medical Oncology | Medical Oncology, Hematology, East Carolina University |
| **Identified by American Society for Clinical Oncology** | | | | | |
| 9 | Daniel J. Canter | MD | American Society of Clinical Oncology | Urologic Oncology | American Board of Urology/Urologic Oncology, Fox Chase Cancer Center |

[a] Note that American College of Radiology also identified one of the physicians who assisted in developing Society of Interventional Radiology response.

### Appendix Table 2. Respondent Conflict of Interest Disclosure

| No. | 1. Research support related to the topic where clinical input is being sought | | 2. Positions, paid or unpaid, related to the topic where clinical input is being sought | | 3. Reportable, more than $1000, healthcare-related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought | | 4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought | |
|---|---|---|---|---|---|---|---|---|
| | Yes/No | Explanation | Yes/No | Explanation | Yes/No | Explanation | Yes/No | Explanation |
| 1 | 9 No | | 1 Yes<br>8 No | Served on scientific advisory board that designed IceSense3 | 9 No | | 9 No | |

| No. | 1. Research support related to the topic where clinical input is being sought | 2. Positions, paid or unpaid, related to the topic where clinical input is being sought | 3. Reportable, more than $1000, healthcare-related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought | 4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought |
|---|---|---|---|---|
| | | cryoablation protocol for breast cancer for IceCure in 2014. Unpaid Position. | | |
| 3 | No | No | No | No |
| 4 | No | No | No | No |
| 5 | No | No | No | No |
| 6 | No | No | No | No |
| 7 | No | No | No | No |
| 8 | No | No | No | No |
| 9 | No | No | No | No |

| No. | Conflict of Interest Policy Statement |
|---|---|
| 2 | The Society of Interventional Radiology (SIR) supports fair and unbiased participation of our volunteers in SIR activities. Any actual or potential conflicts of interest must be identified and managed. **All** direct financial relationships with a company that directly impact and/or might conflict with SIR activities must be disclosed, or you must disclose that you have no direct financial relationships. Other relationships that could cause private interests to conflict with professional interests must also be identified. This policy is intended to openly identify any potential conflict so that any potential bias may be identified and the risk thereof mitigated. **Failure or refusal to complete the disclosure form or disclose any potential conflicts of interest will result in disqualification to participate in the SIR specified committee or activity.**<br>Our full statement is publicly available on our website: https://www.sirweb.org/about-sir/governance/policies/<br>The physicians involved in preparing this clinical input response did not disclose any conflicts of interest related to the topic where clinical input is being sought. |

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.
NR: not reported.

## Appendix 2: Clinical Input Responses

Clinical input is sought to help determine whether the use of cryosurgical ablation in clinical practice for the management of solid tumors of the breast, lung, pancreas, kidney, or bone results in a meaningful clinical benefit in improved net health outcome and whether this use is consistent with generally accepted medical practice.

### Responses

1. Based on the totality of the evidence and your clinical experience, describe the objective condition characteristics (i.e., patient selection criteria) and any management criteria (i.e., regarding prior trial of therapy) for clinical use of cryosurgical ablation for management of each of the solid tumors listed below. Please provide comments/rationale and any citations supporting your clinical input.
    a. Breast cancer

| No. | Response |
|---|---|
| 1 | In accordance with the American Society of Breast Surgeons. Consensus Guideline on the Use of Transcutaneous and Percutaneous Methods for the Treatment of Benign and Malignant Tumors of the Breast. 2017; https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/Transcutaneous_Percutaneous.pdf Accessed October 25, 2017. While several prospective studies have shown that percutaneous cryoablation of small breast cancers may be technically feasible, success rates are <100%, and imaging, including MRI, is not sensitive or specific enough to assess treatment effect. The outcome of leaving residual or cryoablated tumor in the breast remains unknown. Therefore, cryoablative treatment of breast cancer is investigational and should not be performed outside the realm of a clinical trial such as NCT02200705 or NCT01992250.<br>• Fornage BD, Hwang RF. Current status of imaging-guided percutaneous ablation of breast cancer. *AJR Am J Roentgenol.* Aug 2014;203(2):442-448. PMID 25055283.<br>• Simmons RM, Ballman KV, Cox C, et al. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. *Ann Surg Oncol.* Aug 2016;23(8):2438-2445. PMID 27221361. |
| 2 | Cryoablation interventions for early-stage breast cancer and fibroadenomas remain in an investigational stage. Early results on small tumor IBC appear promising, but more research is needed. The SIR agrees with the Evidence Street draft report. |
| 3 | Not my clinical realm. |
| 4 | NR |
| 5 | NR |
| 6 | NR |
| 7 | NR |
| 8 | Would consider cryotherapy for breast cancer to currently be an experimental treatment to be performed only on a clinical trial. This is supported by the lack of comparative trials (ie. Cryo vs surgery). |
| 9 | NR |

IBC: inflammatory breast cancer; NR: no response; SIR: Society of Interventional Radiology.

b. Breast tumor (benign/fibroadenoma)

| No. | Response |
|---|---|
| 1 | While fibroadenomas do not routinely require intervention after diagnostic confirmation, treatment may be desired due to discomfort or the presence of a bothersome mass. Percutaneous cryoablation under ultrasound guidance has been shown to be a safe and efficacious treatment of fibroadenomas and is an alternative to surgical excision for those desiring treatments. The diagnosis of fibroadenoma should be established prior to performing cryoablation with percutaneous biopsy.<br>Several studies have reported good efficacy without significant adverse events in those patients treated with cryoablation of their fibroadenoma. Most patients reported resolution of the palpable mass. There were low rates of recurrence and few incidences of chronic pain. Cosmesis is generally rated as good to excellent, compared with surgical excision.<br>Indications for cryoablation of fibroadenoma are as follows:<br>a. The lesion must be easily visualized on ultrasound.<br>b. The diagnosis of fibroadenoma must be confirmed histologically on core biopsy prior to treatment.<br>c. The diagnosis of fibroadenoma must be concordant with the imaging findings, patient history, and physical exam.<br>d. Lesions should be less than 4 cm in largest diameter<br>• Golatta M, Harcos A, Pavlista D, et al. Ultrasound-guided cryoablation of breast fibroadenoma: a pilot trial. *Arch Gynecol Obstet.* Jun 2015;291(6):1355-1360. PMID 25408274<br>• Kaufman CS, Littrup PJ, Freeman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas with long-term follow-up. *Breast J.* Sep-Oct 2005;11(5):344-350. PMID 16174156<br>• Kaufman CS, Littrup PJ, Freman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas: 12-month followup. *J Am Coll Surg.* Jun 2004;198(6):914-923. PMID 15194073<br>• Edwards MJ, Broadwater R, Tafra L, et al. Progressive adoption of cryoablative therapy for breast fibroadenoma in community practice. *Am J Surg.* Sep 2004;188(3):221-224. PMID 15450823 |

| No. | Response |
|---|---|
| 2 | Please see above Question 1a response. |
| 3 | Not my clinical realm. |
| 4 | NR |
| 5 | NR |
| 6 | NR |
| 7 | NR |
| 8 | There is some evidence available to demonstrate both short and long term outcomes in terms of efficacy, as indicated by lesion becoming nonpalpable, and safety for use of cryotherapy for fibroadenoma. This does require prior biopsy to confirm the lesion is, in fact, a benign fibroadenoma. Based on available evidence, I do feel this is a reasonable option for women who are considering surgical removal of a fibroadenoma which is biopsy-proven and <4cm.<br>• Nurko J, Mabry CD, Whitworth P, et al. Interim results from the FibroAdenoma Cryoablation Treatment Registry. *Am J Surg.* Oct 2005;190(4):647-651; discussion 651-642. PMID 16164941<br>• Kaufman CS, Bachman B, Littrup PJ, et al. Cryoablation treatment of benign breast lesions with 12-month follow-up. *Am J Surg.* Oct 2004;188(4):340-348. PMID 15474424<br>• Kaufman CS, Littrup PJ, Freeman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas with long-term follow-up. *Breast J.* Sep-Oct 2005;11(5):344-350. PMID 16174156 |
| 9 | NR |

NR: no response.

c. Lung cancer

| No. | Response |
|---|---|
| 1 | NR |
| 2 | While surgical interventions for early-stage non-small cell lung cancer (NSCLC) remain the standard of care, the use and supporting literature for cryoablation has advanced in recent years. In 2018, a new Category I CPT code for pulmonary cryoablation will go into effect. SIR was the lead specialty that presented the data on that procedure to the CPT Panel in an effort supported by the ACR, ARRS, and RSNA.<br>For those patients who are poor surgical candidates, cryoablation has shown its potential as a curative therapeutic option for early-stage NSCLC. In 2015, Moore et al (Moore W, Talati R, Bhattacharji P, et al. Five-year survival after cryoablation of stage I non-small cell lung cancer in medically inoperable patients. *J Vasc Interv Radiol.* Mar 2015;26(3):312-319. PMID 25735518) reported 5-year survival of cryoablation patients as 67.8%, ± 15.3, similar to 5-year survival seen with sublobar resection.<br>The literature surrounding cryoablation vs external beam radiation also seems to suggest better outcomes with cryoablation.<br>SIR is concerned that the draft Evidence Street report does not give sufficient import to the role that cryoablation can offer appropriate patients with stage I NSCLC and even treatment of locally recurrent mesothelioma.<br>In sum, surgery is still the gold standard to maximize oncologic outcome for stage I lung cancer, with surgery having different outcomes than thermal ablation (cryo, microwave, RFA). Studies show similar rate of local control compared to sublobar resection, but not lobectomy. Local ablative techniques play an important role for the management of unresectable early lung cancer, and in the management of multifocal lung cancer, as well as in the management of oligo progressive lung cancer on targeted therapy, and for the management of local recurrence after radiation therapy.<br>There are some advantages of cryoablation over microwave, but the reverse is also true. The best tool is determined by the exact clinical context. |
| 3 | Not my clinical realm. |
| 4 | NR |
| 5 | NR |
| 6 | For patients with early stage - we have not used cryoablation.<br>For advanced lung carcinoma - we use it in selected patients:<br>- Oligometastatic disease when most sites are under control, if 1-2 sites are progressing, will consider cryoablation for the progressive sites |

| No. | Response |
|---|---|
| | - Any NSCL that has a site that has an impending significant event |
| 7 | Patients with central airway obstructions or endobronchial tumors may benefit from cyroablative techniques to restore airway patency. A patient must be a candidate to undergo general anesthesia for bronchoscopy. Patients should not have a coagulopathy, require uninterrupted anticoagulation or severe thrombocytopenia (less than 5OK platelets) as this would put them at increased risk of morbidity and mortality due to bleeding in the airway. |
| 8 | Ablative procedures in early-stage disease (Clinical stage IA(Tla-b, N0, M0) are considered an option for inoperable patients or in patients who refuse surgery. It is not currently clear that cryosurgery is equivalent in outcomes or safety to other ablative therapies (ie SBRT). Additional studies are needed.<br>Based on the Eclipse trial (de Baere T, Tselikas L, Woodrum D, et al. Evaluating Cryoablation of Metastatic Lung Tumors in Patients--Safety and Efficacy: The ECLIPSE Trial--Interim Analysis at 1 Year. *J Thorac Oncol.* Oct 2015;10(10):1468-1474. PMID 26230972), which was a small nonrandomized trial, there was good local control with cryotherapy. Additionally, there were few adverse events. Again it is unclear that this is equivalent to other ablative therapies. |
| 9 | NR |

ACR: American College of Radiology; NR: no response; SIR: Society of Interventional Radiology.

d. Pancreatic cancer

| No. | Response |
|---|---|
| 1 | NR |
| 2 | The literature for cryoablation for pancreatic or cholangiocarcinoma remains investigational. SIR has reviewed the draft Evidence Street report and concurs with the summation. |
| 3 | Despite being a potentially attractive modality for the treatment of advanced pancreatic cancer, the data is limited to small retrospective observational studies. One such study comparing bypass to bypass and cryoablation that revealed no survival benefit from the addition of cryotherapy. Furthermore, complication rates of cryoablation are not insignificant including bleeding, pancreatic and biliary, leaks, and delayed gastric emptying. There has been no data comparing cryoablation to other therapies such as resection or thermal ablation with radiofrequency or microwave options. Cryotherapy has not been used as a potentially curative therapy. Clinical practice guidelines have just been published which will hopefully lead to further and better studies to determine the precise role of cryoablation in pancreatic cancer, and I would anticipate numerous of these to emanate from China over the coming years. |
| 4 | Poor quality evidence to support a specific role for cryoablation in this area. |
| 5 | NR |
| 6 | NR |
| 7 | NR |
| 8 | There is insufficient evidence that cryotherapy is equivalent in efficacy and safety to other palliative therapies for patients with advanced pancreatic cancer. |
| 9 | NR |

NR: no response. SIR: Society of Interventional Radiology

e. Renal cell carcinoma

| No. | Response |
|---|---|
| 1 | NR |
| 2 | For renal cell carcinoma (RCC), literature suggests about 30% of patients diagnosed with local RCC show metastatic disease at presentation, and about a third of RCC patients at diagnosis develop metastatic RCC (mRCC). Surgical and chemotherapy options are available to these patients, but for RCC patients, long-term data confirms that cryoablation is a safe and highly efficacious alternative for the treatment of RCC with similar local and distant outcomes as partial nephrectomy, but with near-complete preservation of renal function. Cryoablation of renal tumors has become well established, with multiple papers confirming reproducibility with appropriate technique. |

| No. | Response |
|---|---|
| | Confirming much of the past research, a new study ( Aoun HD, Littrup PJ, Jaber M, et al. Percutaneous Cryoablation of Renal Tumors: Is It Time for a New Paradigm Shift? *J Vasc Interv Radiol.* Oct 2017;28(10):1363-1370. PMID 28844831) retrospectively evaluated 302 patients. Complication rates were low, and because of the ability to see ice margins (one of the advantages of cryoablation), adjacent vital structures are better able to be protected.<br>In general, recurrence rates seen with cryoablation are comparable to partial nephrectomy, but with near total preservation of renal function.<br>The SIR asserts that the Evidence Street draft report reexamine the literature on cryoablation vs surgical interventions. Cryoablation for RCC is in our view, safe and highly effective for appropriate patients. |
| 3 | Not my clinical realm. |
| 4 | NR |
| 5 | NR |
| 6 | NR |
| 7 | NR |
| 8 | Ablative procedures are appropriate for small lesions (Tla) in patients who are inoperable or who refuse surgery. Though there is a lack of randomized trials (versus surgery), there is enough evidence to support the use of cryotherapy based on efficacy and safety. It is understood that the local recurrence rate is higher with ablative procedures versus surgery.<br>• Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass: a meta-analysis. *Cancer.* Nov 15 2008;113(10):2671-2680. PMID 18816624<br>• O'Malley RL, Berger AD, Kanofsky JA, et al. A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. *BJU Int.* Feb 2007;99(2):395-398. PMID 17092288 |
| 9 | There is a significant and robust literature surrounding the use of cryoablation for the treatment of renal tumors, specifically renal cell carcinomas. Based on the published experience, there is strong evidence to support the use of cryoablation for renal tumors less than 3 cm. Tumors less than 3 cm appear to achieve relatively equivalent responses to the treatment gold standard, which is surgical excision. This size cut-off is irrespective of patient age and medical co-morbidities. Furthermore, it does also appear that in terms of patient comfort and need for hospitalization, percutaneous cryoablation is superior to laparoscopic cryoablation. Thus, it stands to reason that tumors less than 3 cm that are not amenable to a percutaneous approach should be excised surgically.<br>For tumors greater than 3 cm, surgical excision is the optimal treatment modality, however, for patients with significant medical co-morbidities who may not be able to withstand the physiologic stress of surgery, percutaneous cryoablation may be considered. For larger tumors, it should be recognized that patients may require repeat cryoablation in order to achieve a complete oncologic response. |

NR: no response. SIR: Society of Interventional Radiology

f. Bone cancer

| No. | Response |
|---|---|
| 1 | NR |
| 2 | The bony skeleton is the most common metastatic site from cancer after lungs and liver, with prostate, breast, lung, kidney, and thyroid malignancies accounting for approximately 80% of skeletal metastases. Of the patients who develop skeletal metastases, approximately 50% of patients will develop poorly controlled pain during the course of their disease.<br>Surgical resection has been the care standard for local treatment of most newly diagnosed cancer cases. However, for patients with stage IV disease, resection of oligometastases in nonorgan locations produces quality-of-life concerns and may limit most surgery to isolated resections of liver and pulmonary metastases. Chemotherapy is generally ineffective in treating pain in bone and recurrent soft-tissue metastases, and radiation therapy, although effective when used before surgery on small tumors, is limited for many sites.<br>Cryosurgery has the advantage of lower morbidity, less neurological deficit, improved speed, and ease of surgical procedure, less potential blood loss, preservation of spinal and pelvic continuity, and lower tumor recurrence rates. In our patients with metastasis, treatment with cryotherapy allows local control with less extensive resection, allowing patient more rapid recovery and thus preserving the quality.<br>A special note needs to be made regarding osteoid osteomas and other benign bone tumors in the pediatric population. Cryoablation is well-researched and is effective in treatment of many of these patients. In fact, cryoablation is usually preferred over Radiofrequency (RFA), as RFA |

| No. | Response |
|---|---|
| | has increased risk of permanent nerve injury, while nerve injuries from cryoablation, if they occur, is transient. Current research suggests that the recurrence rates of these tumors following cryoablation are about half of that encountered following heat-based ablation therapy. |
| 3 | Not my clinical realm. |
| 4 | NR |
| 5 | NR |
| 6 | Nothing listed |
| 7 | NR |
| 8 | Would consider cryotherapy for metastatic bone lesions to be experimental and should be performed only on a clinical trial.<br>For primary bone tumors lesions, benign or low-grade, there is a lack of randomized trials to compare efficacy and safety to alternative standard therapies. |
| 9 | NR |

NR: no response.

2. Based on the evidence and your clinical experience for the indications described in Question 1:
   a. Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful benefit in the net health outcome.
   b. Use the 1 to 5 scale outlined below to indicate your level of confidence that there is adequate evidence that supports your conclusions.

| No. | Indications | Yes/No | Low Confidence | | Intermediate Confidence | | High Confidence |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 |
| 1 | Breast cancer | Yes | | X | | | |
| | Breast tumor, benign / fibroadenoma | Yes | | | | X | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | NR | | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 2 | Breast cancer | No | | X | | | |
| | Breast tumor, benign / fibroadenoma | No | | X | | | |
| | Lung cancer | Yes | | | | | X |
| | Pancreatic cancer | No | | X | | | |
| | Renal cell carcinoma | Yes | | | | | X |
| | Bone cancer | Yes | | | | | X |
| 3 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | No | X | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 4 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | No | X | | | | |
| | Renal cell carcinoma | NR | | | | | |

| No. | Indications | Yes/No | Low Confidence | | Intermediate Confidence | | High Confidence |
|---|---|---|---|---|---|---|---|
| | Bone cancer | NR | | | | | |
| 5 | Breast cancer | Yes | | | X | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | NR | | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 6 | Breast cancer | Yes | | | | X | |
| | Breast tumor, benign / fibroadenoma | No | | | No rating provided | | |
| | Lung cancer | Yes | | | | | X |
| | Pancreatic cancer | Yes | | | | | X |
| | Renal cell carcinoma | Yes | | | | | X |
| | Bone cancer | No | | | No rating provided | | |
| 7 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | Yes | | | | | X |
| | Pancreatic cancer | NR | | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 8 | Breast cancer | No | | | | | X |
| | Breast tumor, benign / fibroadenoma | Yes | | | X | | |
| | Lung cancer | No | | | | X | |
| | Pancreatic cancer | No | | | | X | |
| | Renal cell carcinoma | Yes | | | | X | |
| | Bone cancer | No | | | | X | |
| 9 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | NR | | | | | |
| | Renal cell carcinoma | Yes | | | | X | |
| | Bone cancer | NR | | | | | |

NR: no response.

3. Based on the evidence and your clinical experience for the indications described in Question 1:
   a. Respond YES or NO for each indication whether this intervention is consistent with generally accepted medical practice.
   b. Use the 1 to 5 scale outlined below to indicate your level of confidence in your conclusions.

| No. | Indications | Yes/No | Low Confidence | | Intermediate Confidence | | High Confidence |
|---|---|---|---|---|---|---|---|
| | | | **1** | **2** | **3** | **4** | **5** |
| 1 | Breast cancer | No | | | | | X |
| | Breast tumor, benign / fibroadenoma | Yes | | | | X | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | NR | | | | | |

| No. | Indications | Yes/No | Low Confidence | | Intermediate Confidence | | High Confidence |
|---|---|---|---|---|---|---|---|
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 2 | Breast cancer | No | | X | | | |
| | Breast tumor, benign / fibroadenoma | No | | X | | | |
| | Lung cancer | Yes | | | | X | |
| | Pancreatic cancer | No | | X | | | |
| | Renal cell carcinoma | Yes | | | | | X |
| | Bone cancer | Yes | | | | | X |
| 3 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | No | X | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 4 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | No | | X | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 5 | Breast cancer | Yes | | | X | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | NR | | | | | |
| | Pancreatic cancer | NR | | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 6 | Breast cancer | Yes | | | X | | |
| | Breast tumor, benign / fibroadenoma | No | | | No rating provided | | |
| | Lung cancer | Yes | | | | | X |
| | Pancreatic cancer | Yes | | | | | X |
| | Renal cell carcinoma | Yes | | | | | X |
| | Bone cancer | No | | | No rating provided | | |
| 7 | Breast cancer | NR | | | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | | | |
| | Lung cancer | Yes | | | | | X |
| | Pancreatic cancer | NR | | | | | |
| | Renal cell carcinoma | NR | | | | | |
| | Bone cancer | NR | | | | | |
| 8 | Breast cancer | No | | | | | X |
| | Breast tumor, benign / fibroadenoma | Yes | | | | | X |
| | Lung cancer | No | | | | X | |
| | Pancreatic cancer | No | | | | X | |
| | Renal cell carcinoma | Yes | | | | | X |
| | Bone cancer | No | | | | X | |

| No. | Indications | Yes/No | Low Confidence | Intermediate Confidence | High Confidence |
|---|---|---|---|---|---|
| 9 | Breast cancer | NR | | | |
| | Breast tumor, benign / fibroadenoma | NR | | | |
| | Lung cancer | NR | | | |
| | Pancreatic cancer | NR | | | |
| | Renal cell carcinoma | Yes | | | X |
| | Bone cancer | NR | | | |

NR: no response.

4. Additional comments and/or any citations supporting your clinical input on this topic.

| No. | Additional Comments |
|---|---|
| 1 | NR |
| 2 | NR |
| 3 | NR |
| 4 | With respect to pancreatic tumors, there are two major types: adenocarcinoma and endocrine tumors. For endocrine tumors of the pancreas and specifically symptomatic insulinoma, there is a literature to support local ablative management. This has been done with either alcohol or more recently RFA. While cryoablation is just another type of ablation there is no efficacy or safety data for it in symptomatic endocrine tumors such as insulinomas. |
| 5 | NR |
| 6 | NR |
| 7 | Cryoprobe and Cryospray (TruFreeze) therapy is used in the treatment of central airway malignancies to restore patency of the airways and palliate symptoms.<br>• Maiwand MO, Asimakopoulos G. Cryosurgery for lung cancer: clinical results and technical aspects. *Technol Cancer Res Treat.* Apr 2004;3(2):143-150. PMID 15059020<br>• Asimakopoulos G, Beeson J, Evans J, et al. Cryosurgery for malignant endobronchial tumors: analysis of outcome. *Chest.* Jun 2005;127(6):2007-2014. PMID 15947313 |
| 8 | NR |
| 9 | NR |

NR: no response.

5. Is there any evidence missing from the attached draft review of evidence that demonstrates clinical benefit?

| No. | Yes/No | Citations of Missing Evidence |
|---|---|---|
| 1 | NR | |
| 2 | Yes | • Aoun HD, Littrup PJ, Jaber M, et al. Percutaneous Cryoablation of Renal Tumors: Is It Time for a New Paradigm Shift? *J Vasc Interv Radiol.* Oct 2017;28(10):1363-1370. PMID 28844831<br>For osteoid osteoma, see:<br>• Whitmore MJ, Hawkins CM, Prologo JD, et al. Cryoablation of Osteoid Osteoma in the Pediatric and Adolescent Population. *J Vasc Interv Radiol.* Feb 2016;27(2):232-237; quiz 238. PMID 26683456<br>• Wu B, Xiao YY, Zhang X, et al. CT-guided percutaneous cryoablation of osteoid osteoma in children: an initial study. *Skeletal Radiol.* Oct 2011;40(10):1303-1310. PMID 21311882<br>• Liu DM, Kee ST, Loh CT, et al. Cryoablation of osteoid osteoma: two case reports. *J Vasc Interv Radiol.* Apr 2010;21(4):586-589. PMID 20138545<br>Bone cryoablation bibliography |

| No. | Yes/No | Citations of Missing Evidence |
|---|---|---|
| | | • McMenomy BP, Kurup AN, Johnson GB, et al. Percutaneous cryoablation of musculoskeletal oligometastatic disease for complete remission. *J Vasc Interv Radiol.* Feb 2013;24(2):207-213. PMID 23265724<br><br>• Callstrom MR, Dupuy DE, Solomon SB, et al. Percutaneous image-guided cryoablation of painful metastases involving bone: multicenter trial. *Cancer.* Mar 01 2013;119(5):1033-1041. PMID 23065947<br><br>• Lim CT, Tan LB, Nathan SS. Prospective evaluation of argon gas probe delivery for cryotherapy of bone tumours. *Ann Acad Med Singapore.* Aug 2012;41(8):347-353. PMID 23010812<br><br>• Kurup AN, Woodrum DA, Morris JM, et al. Cryoablation of recurrent sacrococcygeal tumors. *J Vasc Interv Radiol.* Aug 2012;23(8):1070-1075. PMID 22840806<br><br>• Tutton S, Olson E, King D, et al. Successful treatment of tumor-induced osteomalacia with CT-guided percutaneous ethanol and cryoablation. *J Clin Endocrinol Metab.* Oct 2012;97(10):3421-3425. PMID 22837186<br><br>• Bang HJ, Littrup PJ, Currier BP, et al. Percutaneous cryoablation of metastatic lesions from non-small-cell lung carcinoma: initial survival, local control, and cost observations. *J Vasc Interv Radiol.* Jun 2012;23(6):761-769. PMID 22626267<br><br>• Duarte R, Pereira T, Pinto P, et al. [Percutaneous Image-guided cryoablation for localized bone plasmacytoma treatment]. *Radiologia.* Sep-Oct 2014;56(5):e1-4. PMID 22621822<br><br>• Abdel-Aal AK, Underwood ES, Saddekni S. Use of cryoablation and osteoplasty reinforced with Kirschner wires in the treatment of femoral metastasis. *Cardiovasc Intervent Radiol.* Oct 2012;35(5):1211-1215. PMID 22565529<br><br>• Ogunsalu C, West W, Lewis A, et al. Ameloblastoma in Jamaica--predominantly unicystic: analysis of 47 patients over a 16-year period and a case report on re-entry cryosurgery as a new modality of treatment for the prevention of recurrence. *West Indian Med J.* Mar 2011;60(2):240-246. PMID 21942138<br><br>• Saito T, Mitomi H, Suehara Y, et al. A case of de novo secondary malignant giant-cell tumor of bone with loss of heterozygosity of p53 gene that transformed within a short-term follow-up. *Pathol Res Pract.* Oct 15 2011;207(10):664-669. PMID 21924561<br>• Thacker PG, Callstrom MR, Curry TB, et al. Palliation of painful metastatic disease involving bone with imaging-guided treatment: comparison of patients' immediate response to radiofrequency ablation and cryoablation. *AJR Am J Roentgenol.* Aug 2011;197(2):510-515. PMID 21785102<br><br>• Castaneda Rodriguez WR, Callstrom MR. Effective pain palliation and prevention of fracture for axial-loading skeletal metastases using combined cryoablation and cementoplasty. *Tech Vasc Interv Radiol.* Sep 2011;14(3):160-169. PMID 21767783<br><br>• de Freitas RM, de Menezes MR, Cerri GG, et al. Sclerotic vertebral metastases: pain palliation using percutaneous image-guided cryoablation. *Cardiovasc Intervent Radiol.* Feb 2011;34 Suppl 2:S294-299. PMID 21170528<br><br>• Mohler DG, Chiu R, McCall DA, et al. Curettage and cryosurgery for low-grade cartilage tumors is associated with low recurrence and high function. *Clin Orthop Relat Res.* Oct 2010;468(10):2765-2773. PMID 20574801<br><br>• Abdelrahman M, Bassiony AA, Shalaby H, et al. Cryosurgery and impaction subchondral bone graft for the treatment of giant cell tumor around the knee. *HSS J.* Sep 2009;5(2):123-128. PMID 19590926 |

| No. | Yes/No | Citations of Missing Evidence |
|---|---|---|
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| 4 | No | Not as it pertains to cryoablation and pancreatic adenocarcinoma.<br>More data is now available for other ablative technologies in pancreatic disease. |
| 5 | NR | |
| 6 | NR | |
| 7 | No | |
| 8 | No | |
| 9 | No | |

NR: no response.

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55. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 7.01.92 (July 2020).

## Documentation for Clinical Review

**Please provide the following documentation:**

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., diagnosis of early-stage non-small cell lung cancer)
  - Tumor type and size
  - Laboratory renal function reports specifically glomerular filtration rate (GFR)
  - Prior treatment and response
  - Reason for cryosurgical ablation versus standard surgical approach
- Radiology report(s) and interpretation (i.e., MRI, CT, Chest x-ray)

**Post Service**

- Operative report(s) or procedure report(s)

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

***MN/IE***
**The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.**

| Type | Code | Description |
|---|---|---|
| CPT® | 0581T | Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral ***(Code effective 1/1/2020)*** |
| | 19105 | Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma |
| | 20983 | Ablation therapy for reduction or eradication of 1 or more bone tumors (e.g., metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation |
| | 32994 | Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation |
| | 50250 | Ablation, open, 1 or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound guidance and monitoring, if performed |
| | 50542 | Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed |
| | 50593 | Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy |
| HCPCS | None | |

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|---|---|
| 03/01/2006 | New Policy Adoption |
| 09/25/2009 | Policy title change from Cryoablation for the Treatment of Breast Fibroadenoma<br>Policy revision with position change |
| 01/04/2011 | Documentation required revised |
| 07/14/2014 | Policy title change from Cryosurgical Ablation of Miscellaneous Solid Tumors<br>Policy revision with position change |
| 09/30/2014 | Policy revision without position change |
| 01/01/2015 | Coding update |
| 10/01/2016 | Policy revision without position change |
| 10/01/2017 | Policy revision without position change |

| Effective Date | Action |
|---|---|
| 01/01/2018 | Coding update |
| 09/01/2018 | Policy revision without position change |
| 11/01/2019 | Policy revision without position change |
| 03/01/2020 | Coding update |
| 09/01/2020 | Annual review. No change to policy statement. Literature review updated. |

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*