***Current Policy Effective Date: 5/1/22**

(See policy history boxes for previous effective dates)

Title: Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone

Description/Background

Cryosurgical ablation (hereafter referred to as cryosurgery or cryoablation) 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.

RENAL TUMORS

Localized kidney cancer 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.

LUNG TUMORS and LUNG METASTASES

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 from extrapulmonary primaries. 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.

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 presence and number of involved nodes, hormone receptor status, and other factors. Treatment of metastatic disease includes surgery to remove the primary lesion and combination chemotherapy.

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

PANCREATIC CANCER
Pancreatic cancer is a relatively rare solid tumor that occurs almost exclusively in adults and 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 advanced local or metastatic disease may undergo chemotherapy with radiation following resection. Treatment focuses on slowing tumor growth and palliation of symptoms.

BONE CANCER and BONE METASTASES
Primary bone cancers are extremely rare, accounting for less than 0.2% of all cancers. Bone metastases are more common, with clinical complications including debilitating bone pain. Treatment for bone metastases is performed to relieve local bone pain, provide stabilization, and prevent impending fracture or spinal cord compression.

Regulatory Status

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

- Cryocare® Surgical System (Endocare);
- CryoGen Cryosurgical System (Cryosurgical);
- CryoHit® (Galil Medical) for the treatment of breast fibroadenoma;
- IceSense3™, ProSense™, and MultiSense Systems (IceCure Medical);
- SeedNet™ System (Galil Medical); and
- Visica® System (Sanarus Medical).

Food and Drug Administration product code: GEH.

Medical Policy Statement

- The safety and effectiveness of cryosurgical ablation to treat localized renal cell carcinoma have been established. It may be considered a useful therapeutic option when indicated.
- The safety and effectiveness of cryosurgical ablation to treat lung cancer have been established. It may be considered a useful therapeutic option when indicated.
- The safety and effectiveness of cryosurgical ablation to palliate pain in patients with osteolytic bone metastases have been established. It may be considered a useful therapeutic option when indicated.
- The safety and effectiveness of cryosurgical ablation to treat osteoid osteoma have been established. It may be considered a useful therapeutic option when indicated.
- Cryosurgical ablation as a treatment of benign or malignant tumors of the breast, or pancreas is experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Renal cell carcinoma with no evidence of metastasis and when either of the following criteria is met:

- The tumor is no more than 4 cm in its greatest dimension, preservation of kidney function is necessary (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of less than 60 mL/min per m^2) and standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen kidney function; **OR**
- The tumor is no more than 4 cm in its greatest dimension and the patient is not considered a surgical candidate.

Cryosurgical ablation 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; or
- The patient requires palliation for a central airway obstructing lesion.

Cryosurgical ablation to palliate pain in patients with osteolytic bone metastases when **ALL** of the following criteria are met:

1. Patient ≥ age 18 years.
2. 1 or 2 painful bone metastasis lesions, 1-11 cm in size
3. Patient has failed or is a poor candidate for standard treatments such as radiation or opioids
4. Patient has pain score ≥ 4 on scale 0-10.
5. Life expectancy > 2 months
6. The lesion is > 1 cm away from the spinal cord, brain, other critical nerve structure, large abdominal vessel such as the aorta or inferior vena cava, bowel, or bladder
7. The coagulation profile is normal (platelets > 50,000 and INR < 1.5)
8. The site of the lesion is not at imminent risk of fracture.
9. Patient must not have a primary musculoskeletal malignancy, lymphoma, or leukemia.

Cryosurgical ablation to treat osteoid osteoma when any of the following criteria are met:

1. Those who have failed medical therapy
2. Those being considered for surgical resection
3. Those who have failed previous surgical therapy and have recurrent symptoms and/or pain

Exclusions:

Other indications not noted in the policy inclusions.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

20983	32994	50250	50542	50593

Other codes (investigational, not medically necessary, etc.):

19105	32999	48999	0581T

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a 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.

Cryoablation for Early Stage Kidney Cancer

Clinical Context and Therapy Purpose

The purpose of cryoablation in patients who have early stage kidney cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does cryoablation of early stage kidney tumors 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 early stage kidney tumors.

The review of evidence addresses the use of cryoablation in 2 populations of patients who have early stage renal cancer:
1. Patients who are candidates for surgery;
2. Patients who are not surgical candidates. Patients with 1 kidney or with renal insufficiency are likely to be deemed poor surgical candidates because a standard surgical approach (i.e., resection of renal tissue) is likely to worsen kidney function substantially.

Interventions
The therapy being considered is cryoablation, also referred as cryosurgery.

Cryoablation 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.

Comparators
For patients with stage 1 kidney cancer who are surgical candidates, the comparator of interest is surgical resection. Surgery by partial nephrectomy, whenever feasible, or by radical nephrectomy is the standard of care for stage 1 kidney cancer.

For select patients, including those with small renal masses <2 cm or significant competing risks of death or morbidity from intervention, active surveillance is an option. Active surveillance entails serial abdominal imaging and periodic metastatic survey including blood work and chest imaging.

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).

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

Review of Evidence

Patients Who are Surgical Candidates

Randomized Controlled Trials

There are no randomized controlled trials of cryoablation compared to surgery for kidney cancer.

Systematic Reviews

Multiple systematic reviews of comparative observational studies have compared cryoablation to partial nephrectomy inpatients with early kidney cancer. This section summarizes the 3 most recent, relevant, and comprehensive reviews and meta-analyses, reported by Uhlig et al (2019), (1) Klatte et al (2014), (2) and Tang et al (2014). (3)

Table 1. Cryoablation Studies Included in Systematic Reviews and Meta-Analyses Comparing Cryoablation to Partial Nephrectomy

Study	Uhlig et al (2018)[1,])	Klatte et al (2014)[2,]	Tang et al (2014)[3,]
Atwell et al (2013)	●		
Bhindi et al (2017)	●		
Camacho et al (2016)	●		
Caputo et al (2017)	●		
Chehab et al (2016)	●		
Danzig et al (2015)	●		
Desai et al (2005)	●	●	●
Emara et al (2014)	●	●	●
Foyil et al (2008)	●		
Guillotreau et al (2012)	●	●	●
Haber et al (2012)	●	●	●
Haramis et al (2012)	●	●	●
Hegarty et al (2006)	●		
Hinshaw et al 2016)	●		
Hruby et al (2006)		●	●
Kim et al (2007)		●	
Kiriluk et al (2011)			●
Klatte et al (2011)	●		
Lian et al (2010)		●	
Lin et al (2008)		●	●
Lughezzani et al (2009)	●	●	
Mason et al (2017)	●		
Nisbett et al (2009)		●	

O'Malley et al (2007)	●	●	●
Panumatrassamee et al (2013)	●		
Tanagho et al (2013)	●		
Thompson et al (2015)	●		
Turna et al (2009)	●	●	
Weinberg et al (2015)	●		
Zechlinski et al (2016)	●		

Table 2. Systematic Reviews and Meta-Analyses Comparing Cryoablation to Partial Nephrectomy- Study Characteristics

Study	Search End Date	Study Inclusion Criteria	Studies Included	Mean Tumor size	Sample size	Follow-up Duration (months)
Uhlig et al (2018)[1]	December 2017	Evaluated PN, RFA, cryoablation, or MWA for treatment of renal masses; Comparative study design contrasting at least 2 different interventions; Assessed at least 1 of the following end points: all-cause mortality, cancer-specific mortality, local recurrence, complications or change in renal function. Retrospective and prospective studies were included.	Total = 47 (24,077 patients) 13 prospective, 34 retrospective Cryoablation: 24 studies (668 patients)	Cryoablation: 2.53 cm PN: 2.84 cm MWA: 2.74 cm RFA: 2.63 cm	Cryoablation: 6,618 PN: 15,238 MWA: 344 RFA: 1,877	Range 3 to 82
Klatte et al (2014)[2]	September 2013	Compared laparoscopic cryoablation with laparoscopic PN or robot-assisted laparoscopic PN for the treatment of small renal tumors; Reported perioperative outcomes or	Total = 13 (1191 patients) All retrospective	Cryoablation: 2.28 cm PN: 2.41 cm	Cryoablation: 627 PN: 564	Mean Cryoablation: 22.5 PN: 29.5

		data on histology and oncologic outcomes were provided.				
Tang et al (2014)[3.]	September 2013	Compared laparoscopic cryoablation and laparoscopic PN for small renal masses; Reported on at least 1 of the following outcomes: operating time, estimated blood loss, length of hospital stay, blood transfusion rate, conversions rate, postoperative serum creatinine increase, postoperative glomerular filtration rate decrease, catheterization time, local recurrence, distant metastasis, and overall complications, including both intraoperative and postoperative minor and major complications; Clearly documented indications for resection of the renal tumor.	Total = 92 prospective, 7 retrospective	Not reported	Cryoablation: 555 PN: 642	Range Cryoablation: 11.9 to 44.5 PN: 4.8 to 42.7

Uhlig et al (2019) published a systematic review and meta-analysis comparing partial nephrectomy, radiofrequency ablation (RFA), cryoablation, and microwave ablation for small renal masses. (1) Forty-seven studies published between 2005 and 2017, with a total of 24077 participants, were included. Of these, 24 studies conducted in 668 patients, compared cryoablation to partial or another ablative technique. Table 3 summarizes the results of the network meta-analysis for the comparison of cryoablation to partial nephrectomy.

No significant difference in cancer-specific mortality for partial nephrectomy (p=.8065), cryoablation (p=.5519), RFA(p=.3496), and microwave ablation (p=.2920) was found. Local recurrence was higher for cryoablation, RFA, and microwave ablation compared with partial nephrectomy (respectively, incidence rate ratio=4.13; incidence rate ratio=1.79;incidence rate ratio=2.52; p<.05). There was a less pronounced decline in renal function for RFA compared with partial nephrectomy, cryoablation, and microwave (respectively, mean difference in glomerular filtration rate 6.49; 5.82; 10.89;p<.05).

Tang et al (2014) reported on a systematic review and meta-analysis comparing renal laparoscopic renal cryoablation with laparoscopic partial nephrectomy in the treatment of small renal masses. (3) Reviewers identified 9 trials (2 prospective, 7retrospective) in which the 2 techniques were assessed (555 cases, 642 controls). Laparoscopic cryoablation was associated with statistically significant shorter surgical times, less blood loss, and fewer overall complications; however, it was estimated that laparoscopic partial nephrectomy might have a significantly lower local recurrence rate (odds ratio[OR]=13.03; 95% confidence interval [CI], 4.20 to 40.39; p<.001) and lower distant metastasis rate (OR=9.05; 95% CI,2.31 to 35.51; p=.002).

Klatte et al (2014) also reported on a systematic review and meta-analysis comparing laparoscopic renal cryoablation with laparoscopic partial nephrectomy for small renal tumors. (2) Thirteen nonrandomized studies were selected for analysis, which found cryoablation was associated with better perioperative outcomes than laparoscopic partial nephrectomy. Oncologic outcomes, however, were inferior with cryoablation, which was significantly associated with greater risk of local(relative risk, 9.39) and metastatic (relative risk, 4.68) tumor progression.

Table 3. Systematic Reviews and Meta-Analyses Comparing Cryoablation to Partial Nephrectomy- Study Results

Study	All-Cause Mortality	Cancer-Specific Mortality	Local Recurrence	Metastases	Complications	Decline in Renal Function
Uhlig et al (2019)[1]						
Network meta-analysis Cryoablation vs PN IRR (95% CI) P	2.58 (1.92 to 3.46) <.001	2.27 (0.79 to 6.49) .126	4.13 (2.28 to 7.47) .001	Not assessed	0.67 (0.48 to 0.92) .013	0.66 (-3.18 to 4.51) .736
I^2 (P-value)	0% (.968)	0% (.8283)	29.4% (.6784)		59.9% (.003)	91.8% (.9001)
Klatte et al (2014)[2]						
Relative Risk (95% CI); P-value	Not assessed	Not assessed	Local Progression: 9.39 (3.83 to 22.98); <.0001	Metastatic Progression: 4.68 (1.88 to 11.64); <.001	Complications Total: 1.82 (1.22 to 2.72) Urological: 1.99 (1.10 to 3.63) Non-urological: 2.33	Not assessed

					(1.42 to 3.84)	
					Favors cryoablation	
Tang et al (2014)[3]						
Odds Ratio/Weighted Mean Difference (95% CI); P-value	Not assessed	Not assessed	13.03 (4.20 to 40.39); <.001	9.05 (2.31 to 35.51);.002	Overall: 0.53 (0.29 to 0.98);.04 Major: 0.45 (0.25 to 0.81);.008 Minor: 0.65 (0.33 to 1.28);.21 Postoperative: 0.61 (0.32 to 1.15);.13 Intraoperative: 0.20 (0.07 to 0.58);.003	SCr % increase: -6.77 (-13.79 to 0.24);.06 GFR decrease: -1.83 (-7.61, 3.96);.44
I^2 (P-value)			5% (.38)	0% (.79)	Overall: 61% (.009) Major: 0% (.48) Minor: 53% (.03) Postoperative: 60% (.01) Intraoperative: 0% (.89)	SCr % increase: 61% (.08) GFR decrease: 79% (.002)

CI: confidence interval; GFR: glomerular filtration rate; IRR: incidence rate ratio; PN: partial nephrectomy; SCr: serum creatinine

Comparative Observational Studies

This section summarizes recent comparative studies of cryoablation and partial nephrectomy not included in any of the systematic reviews discussed above.

Andrews et al (2019) reported on 1798 patients with primary stage 1 renal masses treated with partial nephrectomy, percutaneous RFA, or percutaneous cryoablation between 2000 and 2011 at Mayo Clinic. (4) A total of 1422 patients were treated with partial nephrectomy (n=1055), RFA (n=180), or cryoablation (n=187) for stage 1a renal masses, and 376 patients were treated with partial nephrectomy (n=324) or cryoablation (n=52) for stage 1b renal masses. Comparisons of cryoablation to partial nephrectomy among 1422 patients with stage 1a masses resulted in hazard ratios (HRs) of 1.88(95% CI 0.76 to 4.66, p=.18), 0.23 (95% CI, 0.03 to 1.72, p=.15), and 0.29 (95% CI, 0.01 to 6.11, p=.40) for local recurrence, metastases, and death from renal cell carcinoma. Five-year cancer-specific survival was 99%, 96%, and100% for partial nephrectomy, RFA, and cryoablation, respectively. Among 376 stage 1b patients, 324 and 52 underwent partial nephrectomy and cryoablation with median clinical follow-up of 8.7 and 6.0 years, respectively. Comparisons of cryoablation with partial nephrectomy resulted in HRs of 1.22 (95% CI, 0.33 to 4.48, p=.80), 0.95 (95% CI, 0.21 to 4.38, p>.90), and 1.94 (95% CI, 0.42 to 8.96, p=.40) for local recurrence, metastases, and death from renal cell carcinoma, respectively. Five-year cancer specific survival was 98% and 91% for partial nephrectomy and cryoablation, respectively.

A retrospective, nonrandomized analysis of prospectively collected data compared robot-assisted partial nephrectomy with percutaneous ablation in patients with T1b renal cell carcinoma. Rembeyo et al (2020) compared patients treated with robot-assisted partial nephrectomy (n=36), cryoablation (n=55), and RFA (n=11). (5) 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 partial nephrectomy, local recurrence-free survival was significantly shorter with cryoablation (adjusted HR, 4.3; 95% CI,1.78 to 10.37). Two-year local recurrence-free survival rates for the partial nephrectomy, cryoablation, and RFA groups were 89.1%, 73.5%, and 81.8%, respectively (p<.001).

A retrospective, nonrandomized study also compared partial nephrectomy with cryoablation 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 partial nephrectomy (n=15,395), cryoablation (n=1,381), and RFA (n=457). (6) Median follow-up was 30 months in all groups. Overall survival was significantly improved with partial nephrectomy compared with cryoablation (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 partial nephrectomy compared with cryoablation (HR, 3.562, 95% CI, 1.399 to 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 partial nephrectomy versus cryoablation (HR 1.958; 95% CI, 1.204 to 3.184) and RFA (HR, 2.841; 95% CI, 1.211 to6.662); however, cancer-specific survival was not different. In patients with tumor size 2 to 4 cm, OS was significantly improved with partial nephrectomy versus cryoablation (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 (partial nephrectomy vs. cryoablation: HR, 3.536; 95% CI, 2.006to 6.234; partial nephrectomy vs RFA: HR, 4.339; 95% CI, 1.573 to 11.971).
Another analysis of Medicare SEER data retrospectively compared partial nephrectomy with cryoablation in patients withT1b nonmetastatic renal cell carcinoma. Pecoraro et al (2019) compared patients undergoing cryoablation (n=434) with propensity score-matched patients undergoing partial nephrectomy (n=228). (7) In patients treated with cryoablation versus partial nephrectomy at 5 years, cancer-specific mortality rates were 7.6% versus 2.8%, respectively (p=.02), and other-cause mortality rates were 17.9% versus 11.8% (p=.1). Findings were consistent in multivariable analyses, where other-cause mortality remained nonsignificant, and cryoablation was associated with higher risk of mortality (adjusted HR,2.50).

Section Summary: Patients Who Are Surgical Candidates
Multiple comparative observational studies and systematic reviews of these studies have compared cryoablation to partial nephrectomy for early stage renal cancer. These studies have consistently found that partial nephrectomy is associated with better oncological outcomes than cryosurgery.

Patients who Are Not Surgical Candidates
There are no RCTs or comparative observational studies comparing cryoablation to active surveillance in patients with kidney cancer.

Systematic Reviews

Although there are no systematic reviews directly comparing cryoablation with active surveillance in patients who are not surgical candidates, multiple systematic reviews of cryoablation compared to surgery or other ablative strategies have reported on outcomes in patients who received cryoablation for kidney tumors. These reviews consistently found that although oncological outcomes were better with surgery, cryoablation was associated with better perioperative outcomes, lower incidence of complications, and less decline in kidney function (see Table 2).

Case Series

In a review of strategies for treating stage 1 renal cell carcinoma, Cronan et al (2019) identified 17 articles published since2010 describing 2,320 lesions treated with cryoablation. (8) Mean tumor size was 2.6 cm. The overall recurrence rate was8.1% in studies with overall median follow-up of 41.4 months, and the technical success rate was 94.3%. Five-year OSand cancer-specific survival rates were 77.1% to 97.8% and 88% to 100%, respectively. Of the 568 lesions treated since2016, the local recurrence rate was 3.0%. Renal function was not assessed in this review.

Recent case series have shown cryoablation associated with good oncological outcomes and preservation of renal function (Table 4).

In a single-center series reported by Morkos et al (2020), 5 of 132 patients (3.8%) transitioned to hemodialysis. (9) The dialysis-free probability was 98% (95% CI, 0.95 to 1) at 5 years, and 95% (95% CI, 0.89 to 1) at 10 years.

In a series of 338 patients treated at 4 centers in Italy, Stacul et al (2021) reported that 93.3% of patients treated with cryoablation did not experience a significant decrease in renal function. (10)

Table 4. Renal Function Outcomes in Longer-Term Observational Studies and Case Series of Cryoablation for Kidney Tumors

Study	Setting	N	Mean Tumor Size	Follow-up Duration	Oncological Outcomes	Renal Function Outcomes
Morkos et al (2020)[9]	Single center	134	2.8 cm (SD±1.4 cm); range, 0.5 to 7.0 cm	10 years	Survival: 87% (95% CI, 80% to 93%) at 5 years; 72% (95% CI, 62% to 83%) at 10 years RFS: 85% (95% CI, 79% to 91%) at 5 years; 69% (95% CI, 59% to 79%) at 10 years Disease-specific survival: 94% (95% CI, 90% to 98%) at both 5 years and 10 years.	5 of 132 (3.8%) transitioned to hemodialysis Dialysis-free probability (95% CI): At 5 years: 98% (95% to 100%) At 10 years: 95% (89% to 100%)

Stacul et al (2021)[10]	4 centers in North-Eastern Italy	338	2.53 cm	5 years	RFS: 90.5% (95% CI ,83.0% to 94.9%) at 3 years and 82.4% (95% CI, 72.0% to 89.4%) at 5 years OS: 96.0% (95% CI, 90.6% to 98.3%) at 3 years and 91.0% (95% CI, 81.7% to 95.7%) at 5 years	Cryoablation was not associated with a significant decrease in renal function after treatment in 93.3%

CI: confidence interval; OS: overall survival; RFS: recurrence-free survival

Section Summary: Patients who Are Not Surgical Candidates

The evidence on cryoablation in patients with kidney cancer who are not surgical candidates consists of comparative observational studies of cryoablation compared to partial nephrectomy or other ablative techniques, systematic reviews of these studies, and case series. Although oncological outcomes were better with surgery, cryoablation was associated with less decline in kidney function. Recent case series totaling more than 400 patients showed cryoablation was associated with good oncological outcomes and preservation of renal function.

Non-Small Cell Lung Cancer

Clinical Context and Therapy Purpose

The purpose of cryoablation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with non-small cell lung cancer (NSCLC).

The question addressed in this evidence review is: Does cryoablation of lung tumors improve the net health outcome in patients with NSCLC?

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

Population

The relevant population of interest is individuals with NSCLC.
The review of evidence addresses the use of cryoablation in 2 populations of patients who have NSCLC:

Patients with NSCLC who are not surgical candidates;

Patients with NSCLC who require palliation for a central airway obstructing lesion.

Interventions

The therapy being considered is cryoablation, also referred to as cryosurgery. Cryoablation 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.

Comparators

For medically operable NSCLC, surgery is preferred. For patients who are medically inoperable, who refuse surgery, or who are high-risk surgical candidates, radiation therapy has a potential role, as either definitive or palliative therapy.

For patients who require palliation for a central airway obstructing lesion, standard symptom palliative care is radiation. Chemotherapy, stent placement, and other ablative bronchoscopic therapies are also options.

Outcomes

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

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

Potential complications of cryosurgery include those caused by hypothermic damage to normal tissue adjacent to the tumor, structural damage along the probe track, and secondary tumors if cancerous cells are seeded during probe removal.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Patients with Non-Small Cell Lung Cancer who are not Surgical Candidates

Systematic Reviews

Lee et al (2011) conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors.(11) Included in the review were 15 case studies and a comparative observational study. Cryoablation was performed for inoperable, advanced lung and bronchial cancers in most studies. Some studies included patients with comorbid conditions and poor general health who would not be considered surgical candidates. Complications occurred in 11.1% of patients (10studies) 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 cryoablation and reported on their own experience with percutaneous cryoablation in 150 patients with NSCLC followed for 12 to 38 months.(12) The study population had stage IIIB or IV lung cancer. Overall survival rates at 1, 2, and 3 years were 64%, 45%, and 32%, respectively. Thirty-day mortality was 2.6% and included cardiac arrest and hemopneumothorax. Complications included hemoptysis, pneumothorax, hemothorax, pleural effusion, and pulmonary infection.

Nonrandomized Studies
The Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE) assessed the safety and local recurrence-free survival after cryoablation 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. (13) 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 cryoablation for recurrent tumors was 91.1% at 12months 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 was a prospective, multicenter trial of cryoablation for metastatic disease in the lungs; interim results at 1-year follow-up were published by de Baere et al (2015). (14) The trial enrolled 40 patients with 60 metastatic lung lesions who were treated with cryoablation and had at least 12 months of follow-up. Outcomes included survival, local tumor control, quality of life, and complications. Local tumor control was achieved in 94.2% (49/52) of treated lesions, and 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 prospective consecutive series of 45 patients (47 tumors) managed with cryoablation during a 5-year period (2006-2011). (15) 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 of1.9 cm (range, 0.5-3 cm). Cryoablation 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.

Section Summary: Patients With Non-Small Cell Lung Cancer who are not Surgical Candidates

Medically inoperable patients with early stage primary lung tumors were treated with cryoablation in a consecutive series of 45 patients. Five year survival was 68%; the main complications were hemoptypsis in 40% of patients and pneumothorax in 51%. A prospective single arm Phase 2 study of 128 patients reported on cryoablation for treatment of metastases to the lung. Cryoablation for metastatic lung cancer was studied in a single arm trial in 40 patients.

Patients with Non-Small Cell Lung Cancer who Require Palliation for a Central Airway Obstructing Lesion Systematic Review

Ratko et al (2013) conducted a comparative effectiveness review on local nonsurgical therapies for stage I and symptomatic obstructive NSCLC for the Agency for Healthcare Research and Quality. (16) Cryoablation was included as a potential therapy for airway obstruction due to endoluminal NSCLC. The reviewers identified 1 RCT that randomly allocated patients to external beam radiation therapy or endobronchial treatment (clinician choice of any one endobronchial treatment: brachytherapy, laser therapy or cryotherapy). The trial was discontinued before completion due to lack of patient accrual, and therefore the reviewers did not include the trial in their report. Reviewers were unable to draw any conclusions about local nonsurgical therapies, including cryoablation, due to lack of quality evidence.

Consecutive Case Series

Maiwand and Asimakopoulos (2004) reported on a consecutive series of 521 patients with symptomatic obstructive tracheobronchial malignant tumors who underwent cryosurgery with a mean of 2.4 treatments per patient. (17) 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). This study has several limitations, which are summarized in Tables 5 and 6.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Maiwand and Asimakopoulos (2004)[17.]	3. Patients were treated 20 to 30 years ago	1. Patients were treated 20 to 30 years ago; replicable across other institutions.	2. No comparator; radiation is standard of care and other treatment options are available.	5. No description of what size improvement is important	1,2. The duration of follow-up was not described for the 521 patients (it was described for the 15 with cryosurgery at exploratory thoracotomy but those are not relevant here). The timing of the outcome measures is unclear. It is unclear if patients were evaluated on a standard schedule and at what time point improvements were seen.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.d

Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Maiwand and Asimakopoulos (2004)[17.]	4. No comparator, not randomized. Not clear why these patients were chosen for cryosurgery versus one of the other procedures that are available for these patients (selection bias) at this institution.	3. No blinding. All of these measures are subjective. Although these symptoms would likely not improve without treatment, the symptom reports and physician assessment of performance status are potentially biased which is complicated by the fact that there is no comparator.		1. No description of patient flow or the amount of available data for any of the outcome measures.		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias. b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician. c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication. d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals a

Section Summary: Patients with Non-Small Cell Lung Cancer who Require Palliation for a Central Airway Obstructing Lesion

There are no comparative studies. A case series of 521 consecutive patients reported improvement in symptoms in 86%of patients, but multiple study design, conduct, and relevance limitations preclude drawing conclusions about efficacy or safety of cryoablation in this population.

Solid Tumors Located in the Breast, Pancreas, or Bone

Clinical Context and Therapy Purpose

The purpose of cryoablation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with solid tumors in the breast, pancreas, or bone.

The question addressed in this evidence review is: Will cryoablation of tumors in the breast, pancreas, or bone improve the net health outcome?

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

Population
The relevant population of interest is individuals with tumors in the breast, pancreas, or bone.

Interventions
The therapy being considered is cryoablation, also referred to as cryosurgery.
Cryoablation 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.

Comparators
Comparators of interest include surgical resection, other ablative techniques such as laser surgery, RFA, irreversible electroporation, and argon beam coagulation.
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. Palliative treatments for bone metastases include analgesics, opioids, osteoclast inhibitors, and radiation therapy.

Outcomes
The general outcomes of interest are 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 (eg, preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

Potential complications of cryosurgery include those caused by hypothermic damage to normal tissue adjacent to the tumor, structural damage along the probe track, and secondary tumors if cancerous cells are seeded during probe removal.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Breast Tumors

<u>*Systematic Reviews*</u>

Zhao and Wu (2010) reported on a systematic review of minimally invasive ablative techniques of early-stage breast cancer.(18) They noted that studies assessing cryoablation 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 cryoablation, be limited until results from prospective, RCTs become available.

<u>*Randomized Controlled Trials*</u>

A prospective, single-arm, phase 2 trial was published by Simmons et al (2016) for the American College of Surgeons Oncology Group Z1072.(19) This trial enrolled 86 evaluable patients from 19 institutions with invasive ductal breast carcinoma that was 2 cm or less in size. The primary end point was complete ablation, defined as no residual evidence of tumor on magnetic resonance imaging. The investigators assigned a priori the success rates indicating that cryoablation would be a potentially efficacious treatment (>90%) or that the results of cryoablation would be unsatisfactory (<70%). Following cryoablation and determination of complete ablation, all patients underwent surgery according to standard protocols for treatment of early breast cancer. Of 87 cancers in 86 patients, complete ablation was achieved in 66 (75.9%; 95% confidence interval [CI], 67.1% to 83.2%). Most cases without complete ablation were the result of multifocal disease outside the targeted lesion. Success rates were intermediate, indicating that cryoablation is *not* potentially efficacious, nor are the results of cryoablation satisfactory.

<u>*Nonrandomized Studies*</u>

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 who were treated with either chemotherapy (n=29) or cryoablation (n=91,35 of whom also received immunotherapy).(20) At 10-year follow-up, median overall survival (OS) of all study participants was 55 months in the cryoablation group vs 27 months in the chemotherapy group (p<0.001). Median OS was also greater in patients receiving multiple cryoablations and in those receiving immunotherapy. Complications with cryotherapy to the breast were ecchymosis and hematoma, pain, tenderness and edema, all of which resolved within one week to one 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.(21) 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 cryoablation.(5) A case series by Sabel et al (2004) explored the role of cryoablation as an alternative to surgical excision as a primary treatment for early-stage breast cancer.(23) This phase 1 study included 29 patients who underwent cryoablation of primary breast cancers measuring less than 2 cm in diameter, followed 1 to 4 weeks later by standard surgical excision. Cryoablation was successful in patients with invasive ductal carcinoma less than 1.5 cm in diameter, and with less than 25% ductal carcinoma in situ identified in a prior biopsy specimen.

Other studies have described outcomes from cryosurgery for advanced primary or recurrent breast cancer.(25-27) 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 have focused on the role of cryosurgery as an alternative to surgical excision of benign fibroadenomas. Kaufman et al have published several case series reports on office-based ultrasound-guided cryoablation as a treatment of breast fibroadenomas.(28-32) 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 include overlapping patients. At 1 year, patients reported 91% patient satisfaction and fibroadenomas became nonpalpable in 75% of cases. At follow-up averaging 2.6 years in 37 patients, the authors noted only 16% out of 84% palpable fibroadenomas remained palpable after treatment and of the fibroadenomas that were initially 2 cm or less in size, only 6% remained palpable.(32) In this series, the authors also noted that cryoablation did not produce artifacts that could interfere with interpretation of mammograms. These small case series from the same group of investigators is 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 involving 55 different practice settings.(33) In these patients, before cryoablation, 75% of fibroadenomas were palpable by the patient. Follow-up at 6- and 12-month intervals showed palpable masses in 46% and 35%, respectively. When fibroadenomas were grouped by size, for lesions 2 cm or less, the treatment area was palpable in 28% at 12 months. For lesions more than 2 cm, the treatment area was palpable in 59% at 12 months.

It is unclear whether “non-palpability” is the most appropriate medical outcome. Fibroadenomas are benign lesions with only a very remote chance of malignant conversion, and thus complete surgical excision may be recommended primarily to allay patients’ concerns about harboring a palpable lesion.

Section Summary: Breast Tumors

For the treatment of breast cancer, available evidence has shown that complete ablation can be achieved in most cases for variably defined small tumors, but studies do not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients. Therefore, no conclusions can be made on the net health outcomes of cryosurgery for breast cancer. For treatment of fibroadenomas, there is a small amount of evidence. This evidence has demonstrated that most fibroadenomas become “nonpalpable” following cryoablation. However, there is a lack of comparative trials. Comparative trials with adequate long-term follow-up are needed to assess this technology and determine how this approach compares with surgery, as well as with vacuum-assisted excision and with observation (approximately one-third of fibroadenomas regress over time after cryoablation).

Pancreatic Cancer

Systematic Reviews

Tao et al (2012) reported on a systematic review of cryoablation for pancreatic cancer.(34) 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% to 40.9% in 3 studies), pancreatic leak (0% to 6.8% in 4 studies), biliary leak (0% to 6.8% in 3 studies), and 1 instance of upper gastrointestinal hemorrhage. Pain relief was reported in 3 studies and ranged from 66.7% to 100%. Median survival times reported in 3 studies ranged from 13.4 to 16 months. One-year total survival rates reported in 2 studies were 57.5% and 63.6%. Keane et al reported on a systematic review of ablation therapy for locally advanced pancreatic cancer in 2014.(35) Reviewers noted that studies have demonstrated ablative therapies, including cryoablation, are feasible but larger studies are needed. No conclusions could be made on whether ablation resulted in better oncologic outcomes than best supportive care.

Nonrandomized Trials

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

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).(37) 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 10 cryoablations in 9 patients with unresectable pancreatic cancer using intraoperative ultrasound guidance during laparotomy.(38) The authors reported adequate pain control in all patients postoperatively. At the time of publication, all patients had died at an average of 5 months postoperatively (range: 1–11 months).

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 is achieved in most cases, and that complications (e.g., delayed gastric emptying) are common, but the true rate of complications is uncertain. Because these studies did not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients, no conclusions can be made on the net health outcomes of cryosurgery for pancreatic cancer.

Bone Cancer and Bone Metastases

Review of Evidence

Meller et al (2008) retrospectively analyzed a single center experience of 440 bone tumor cryosurgery procedures performed between 1988 and 2002, two-thirds of them for primary benign-aggressive and low-grade malignant lesions, and one-third for primary high-grade and metastatic bone tumors.(39) At a median follow-up of 7 years (range 3–18 years), the overall recurrence rate was 8%. Based on their experience, the authors suggest that the ideal case for cryosurgery is a young adult with involvement of long bone, a benign-aggressive or low-grade malignant bone tumor, a good cavity with greater than 75% thick surrounding walls, none or minimal soft tissue component, and at least +/-1 cm of subchondral bone left near a joint surface after curettage and burr drilling. The functional outcome for the 372 patients with no evidence of disease was almost 100% ‘‘good’’ and ‘‘excellent’’. The authors concluded that “Bone cryosurgery is a safe and effective limb-, joint- and even epiphysis-sparing surgical technique in suitable types of bone tumors, temporarily or permanently obviating the need for resection surgery.”

Callstrom et al (2013) reported on 61 patients treated with cryoablation for pain from 69 tumors (size, 1- 11 cm) metastatic to the bone.(40) Before treatment, patients rated their pain with a 4+ on a 1-to-10 scale using the Brief Pain Inventory, with a mean score of 7.1 for worst pain in a 24-hour period. The mean pain score gradually decreased after cryoablation to 1.4 ($p<0.001$) at 24 weeks for worst pain in a 24-hour period. A major complication of osteomyelitis was experienced by 1 (2%) patient.

Jennings et al (2021) reported on a multicenter, single-arm prospective study of 66 patients with metastatic bone disease who were treated with cryoablation, all of whom were not candidates for or had not benefited from standard therapy. (41) The primary endpoint was the change in pain score from baseline to week 8 and patients were followed for 24 weeks. The mean decrease in pain score from baseline to week 8 was 2.61 points (95% CI 3.45 to 1.78). Pain scores decreased further after the primary endpoint and reached clinically meaningful levels (more than a 2-point decrease) after week 8.This study was limited by its lack of a comparator, potential for selection bias, and lack of blinding combined with subjective outcome measures.

Section Summary: Bone Cancers and Metastases

There is a small amount of literature on CRA for bone cancer and bone metastases. For bone metastases, the evidence base consists of 2 single arm nonrandomized studies (N = 61 and 66) and is inadequate to determine efficacy. Studies were limited by a lack of a comparator, potential for selection bias, and lack of blinding combined with subjective outcome measures.

SUMMARY OF EVIDENCE

For individuals with early stage kidney cancer who are surgical candidates treated with cryoablation, the evidence includes comparative observational studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. Multiple comparative observational studies and systematic reviews of these studies have compared cryoablation to partial nephrectomy for early stage renal cancer. These studies have consistently found that partial nephrectomy is associated with better oncological outcomes than cryosurgery, but cryosurgery was associated with better perioperative outcomes, lower incidence of complications, and less decline in kidney function.. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with early stage kidney cancer who are not surgical candidates and who are treated with cryoablation, the evidence includes comparative observational studies of cryoablation compared to partial nephrectomy or other ablative techniques, systematic reviews of these studies, and case series. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. Although oncological outcomes were better with surgery, in comparative observational studies, cryoablation was associated with less decline in kidney function. Recent case series totaling more than 400 patients showed cryoablation was associated with good oncological outcomes and preservation of renal function. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with NSCLC who are not surgical candidates, the evidence includes uncontrolled observational studies and case series. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. Medically inoperable patients with early stage primary lung tumors were treated with cryoablation in a consecutive series of 45 patients. Five year survival was 68%; the main complications were hemoptysis in 40% of patients and pneumothorax in 51%. A prospective single arm Phase 2 study of 128 patients reported on cryoablation for treatment of metastases to the lung. Cryoablation for metastatic lung cancer was studied in a single arm trial in 40 patients. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with NSCLC who require palliation for a central airway obstructing lesion who are treated with cryoablation, the evidence includes case series. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. There are no comparative studies. A series of 521 consecutive patients reported improvement in symptoms in 86% of patients, but multiple study design, conduct, and relevance limitations preclude drawing conclusions about efficacy or safety of cryoablation in this population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with solid tumors located in the breast, pancreas, or bone who are treated with cryoablation, the evidence includes uncontrolled observational studies and case series. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. Due to the lack of prospective controlled trials, it is not possible to conclude that cryoablation improves outcomes for any indication better than alternative treatments. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Clinical Input

OBJECTIVE

Clinical input is sought to help determine whether the use of cryoablation in clinical practice for 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, FACS, 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 Cancer Treatment Centers of America
- Joana Bonta, MD, Medical Oncology; identified Cancer Treatment Centers of America
- Anonymous, DO, Pulmonology; identified Cancer Treatment Centers of America
- Anonymous, MD, Medical Oncology; identified Cancer Treatment Centers of America
- Daniel J. Canter, MD, Urologic Oncology; identified by American Society of Clinical Oncology (ASCO)

[a] *Indicates that conflicts of interest related to the topic where clinical input is being sought were reported by this respondent (see Appendix).*
[b] *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 a 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 review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a 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

			Confidence Level That Clinical Use Expected to Provide Meaningful Clinical Benefit											Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice										
				NO (High – Intermediate – Low)					YES (Low – Intermediate – High)						NO (High – Intermediate – Low)					YES (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 (e.g., 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 non-organ 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, 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." (Society for Interventional Radiology / American College of Radiology)

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

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH 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, Blue Cross Blue Shield Association received clinical input on use of cryoablation to manage individuals with localized renal cell cancer, use of cryoablation to manage individuals with lung cancer, and use of cryoablation 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, while this policy was under review 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 cryoablation 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 (e.g., the patient has 1 kidney or renal insufficiency defined by a glomerular filtration rate <60 mL/min/m2), and standard surgical approach (e.g., resection of renal tissue) is likely to worsen kidney function substantially; or
  - When the patient is not considered a surgical candidate.

- Use of cryoablation to manage individuals with lung cancer when either of the following criteria is met:
  - Poor surgical candidates with early-stage non-small-cell lung cancer; or
  - 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 cryoablation to manage individuals with:
  - Malignant or benign tumors of the breast;
  - Pancreatic cancer; or
  - Bone cancer.

2009 Input

In response to requests, Blue Cross Blue Shield Association received input from 2 Physician Specialty Societies (5 reviews) and from 2 Academic Medical Centers (3 reviews) while this policy was under review for February 2009. There was strong reviewer support for use of cryoablation in the treatment of select patients with renal tumors. There also was support for use in the treatment of benign breast disease. Reviewers generally agreed this was experimental/investigational in the treatment of pancreatic cancer.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Radiology

The American College of Radiology Appropriateness Criteria (2009, updated 2019) for post-treatment follow-up and active surveillance of renal cell carcinoma [RCC] 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."(42) 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.(43) The guideline statements on thermal ablation (radiofrequency ablation and cryoablation) are listed in Table 7.

Table 7. 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

Kidney Cancer

The NCCN (v.2.2021) 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 <3cm, 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 (e.g., 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."(44)

Non-Small Cell Lung Cancer

NCCN practice guidelines for non-small cell lung cancer (v.4.2021) made the following relevant recommendations. (45)

- Resection is the preferred local treatment modality for medically operable disease.
- Image-guided thermal ablation (IGTA) techniques include radiofrequency ablation, microwave ablation, and cryoablation.
- IGTA may be an option for select patients not receiving stereotactic ablative radiotherapy or definitive radiotherapy.
- IGTA may be considered for those patients who are deemed "high risk"- those with tumors that are for the most part surgically resectable but rendered medically inoperable due to comorbidities. In cases where IGTA is considered for high-risk or borderline operable patients, a multidisciplinary evaluation is recommended.
- IGTA is an option for the management of NSCLC lesions <3 cm. Ablation for NSCLC lesions >3 cm may be associated with higher rates of local recurrence and complications.
- The guidelines do not separate out recommendations by ablation technique and note that "each energy modality has advantages and disadvantages. Determination of energy modality to be used for ablation should take into consideration the size and location of the target tumor, risk of complication, as well as local expertise and/or operator familiarity."

Cancer Pain

The NCCN Guidelines on Adult Cancer Pain (v.2.2021) do not address cryoablation specifically for pain due to bone metastases, but note that "ablation techniques may...be helpful for pain management in patients who receive inadequate relief from pharmacological therapy. (46)

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 8.

Table 8. 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	120	Jan 2025
Unpublished			
NCT0111779[a]	Tracking Renal Tumors After Cryoablation Evaluation (TRACE) Registry		Mar 2028

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

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

Government Regulations

National:

There is no national coverage determination that addresses the indications listed in this policy.

Local:

There is a local coverage determination (L30312) titled "Ablative Therapy," Retired 09/30/2015

Primary carcinomas of the breast, lung, stomach, pancreas, adenocarcinoma of unknown origin and other primary cancers which are widely disseminated at the same time liver metastases are present are not appropriate for cryosurgical ablation.

Bone Tumors:
Percutaneous RFA of osteoid osteomas has become the preferred method of therapy for these benign lesions. RFA and cryotherapy have both been shown to be safe and effective in the palliation of metastatic bone tumors.

Renal Tumors:
Although open partial nephrectomy has been the gold standard for excision of renal tumors, minimally invasive approaches offer excellent results with lower morbidity and sparing renal function. The ablative techniques, cryoablation and radiofrequency ablation, have been relatively safe. At present, RF ablation is probably better suited for peripheral, exophytic masses in which higher blood flow and the collecting system are not problems.

Breast Tumors:
There is ongoing research into the use of ablation in both benign and malignant breast tumors. At present the research is too preliminary to determine the role of ablation in breast treatment. Ablation of breast lesions is not yet proven effective and therefore is not covered by WPS Medicare.

Lung Tumors:
Endobronchial cryosurgery is a palliative technique, with the aim of alleviating symptoms and improving the patient's performance status. Patients with lung cancers can develop endobronchial lesions that obstruct the major airways, causing symptoms such as dyspnea, cough, hemoptysis and post-obstructive pneumonia. Future randomized trials, comparing the results of endobronchial cryosurgery with other forms of palliative treatment for lung cancer are needed. At this time this procedure will not be covered outside of a Medicare- approved clinical trial.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Cosmetic and Reconstructive Surgery
- Cryoablation of Peripheral Nerves
- Cryosurgical Ablation of Liver Tumors

References

1. Uhlig J, Strauss A, Rücker G, et al. Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. Eur Radiol. 2019 Mar;29(3):1293-1307. PMID: 30255245.
2. Klatte T, Shariat SF, Remzi M. Systematic review and meta-analysis of perioperative and oncologic outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors. J Urol 2014; 191(5):1209-17.
3. Tang K, Yao W, Li H, et al. Laparoscopic renal cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal masses: a systematic review and meta-analysis of comparative studies. J Laparoendosc Adv Surg Tech A. Jun 2014; 24(6): 403-10. PMID 24914926
4. Andrews JR, Atwell T, Schmit G, et al. Oncologic Outcomes Following Partial Nephrectomy and Percutaneous Ablation for cT1 Renal Masses. Eur Urol. Aug 2019; 76(2): 244-251. PMID 31060824
5. Rembeyo G, Correas JM, Jantzen R, et al. Percutaneous Ablation Versus Robotic Partial Nephrectomy in the Treatment of cT1b Renal Tumors: Oncologic and Functional Outcomes of a Propensity Score-weighted Analysis. Clin Genitourin Cancer. Apr 2020; 18(2): 138-147. PMID 31982346
6. Yan S, Yang W, Zhu CM, et al. Comparison among cryoablation, radiofrequency ablation, and partial nephrectomy for renal cell carcinomas sized smaller than 2 cm or sized 2-4 cm: A population-based study. Medicine (Baltimore).May 2019; 98(21): e15610. PMID 31124938
7. Pecoraro A, Palumbo C, Knipper S, et al. Cryoablation Predisposes to Higher Cancer Specific Mortality Relative to Partial Nephrectomy in Patients with Nonmetastatic pT1b Kidney Cancer. J Urol. Dec 2019; 202(6): 1120-1126.PMID 31347950
8. Cronan J, Dariushnia S, Bercu Z, et al. Systematic Review of Contemporary Evidence for the Management of T1Renal Cell Carcinoma: What IRs Need to Know for Kidney Cancer Tumor Boards. Semin Intervent Radiol. Aug2019; 36(3): 194-202. PMID 31435127
9. Morkos J, Porosnicu Rodriguez KA, Zhou A, et al. Percutaneous Cryoablation for Stage 1 Renal Cell Carcinoma: Outcomes from a 10-year Prospective Study and Comparison with Matched Cohorts from the National Cancer Database. Radiology. Aug 2020; 296(2): 452-459. PMID 32515677
10. Stacul F, Sachs C, Giudici F, et al. Cryoablation of renal tumors: long-term follow-up from a multicenter experience. Abdom Radiol (NY). Apr 29 2021. PMID 33912986
11. Lee SH, Choi WJ, Sung SW, et al. Endoscopic cryotherapy of lung and bronchial tumors: a systematic review. Korean J Intern Med. Jun 2011; 26(2): 137-44. PMID 21716589
12. Niu L, Xu K, Mu F. Cryosurgery for lung cancer. J Thorac Dis. Aug 2012; 4(4): 408-19. PMID 22934144
13. Callstrom MR, Woodrum DA, Nichols FC, et al. Multicenter Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE). J Thorac Oncol. Jul 2020; 15(7): 1200-1209. PMID 32151777

14. 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): 1468-74. PMID26230972
15. 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): 312-9. PMID 25735518
16. Ratko TA, Vats V, Brock J, et al. Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non- Small-Cell Lung Cancer (AHRQ Comparative Effectiveness Review No. 112). Rockville, MD: Agency for Healthcare Research and Quality; 2013.
17. Maiwand MO, Asimakopoulos G. Cryosurgery for lung cancer: clinical results and technical aspects. Techno Cancer Res Treat. Apr 2004; 3(2): 143-50. PMID 15059020
18. Zhao Z, Wu F. Minimally-invasive thermal ablation of early-stage breast cancer: a systemic review. Eur J Surg Oncol. Dec 2010; 36(12): 1149-55. PMID 20889281
19. 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): 2438-45. PMID 27221361
20. Niu L, Mu F, Zhang C, et al. Cryotherapy protocols for metastatic breast cancer after failure of radical surgery. Cryobiology. Aug 2013; 67(1): 17-22. PMID 23619024
21. Manenti G, Perretta T, Gaspari E, et al. Percutaneous local ablation of unifocal subclinical breast cancer: clinical experience and preliminary results of cryotherapy. Eur Radiol. Nov 2011; 21(11): 2344-53. PMID 21681574
22. Pusztaszeri M, Vlastos G, Kinkel K, et al. Histopathological study of breast cancer and normal breast tissue after magnetic resonance-guided cryotherapy ablation. Cryobiology. Aug 2007; 55(1): 44-51. PMID 17604016
23. Sabel MS, Kaufman CS, Whitworth P, et al. Cryoablation of early-stage breast cancer: work-in-progress report of a multi-institutional trial. Ann Surg Oncol. May 2004; 11(5): 542-9. PMID 15123465
24. Tanaka S. Cryosurgical treatment of advanced breast cancer. Skin Cancer. Jan 1995;10:9-18.
25. Pfleiderer SO, Freesmeyer MG, Marx C, et al. Cryotherapy of breast cancer under ultrasound guidance: initial results and limitations. Eur Radiol. Dec 2002; 12(12): 3009-14. PMID 12439583
26. Suzuki Y. Cryosurgical treatment of advanced breast cancer and cryoimmunological responses. Skin Cancer.1995;10:19-26.
27. Morin J, Traore A, Dionne G, et al. Magnetic resonance-guided percutaneous cryosurgery of breast carcinoma: technique and early clinical results. Can J Surg. Oct 2004; 47(5): 347-51. PMID 15540687
28. Kaufman CS, Bachman B, Littrup PJ, et al. Office-based ultrasound-guided cryoablation of breast fibroadenomas. Am J Surg. Nov 2002; 184(5): 394-400. PMID 12433600
29. Kaufman CS, Littrup PJ, Freman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas: 12-monthfollowup. J Am Coll Surg. Jun 2004; 198(6): 914-23. PMID 15194073
30. 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): 340-8. PMID 15474424
31. Littrup PJ, Freeman-Gibb L, Andea A, et al. Cryotherapy for breast fibroadenomas. Radiology. Jan 2005; 234(1):63-72. PMID 15550369

32. 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): 344-50. PMID 16174156
33. Nurko J, Mabry CD, Whitworth P, et al. Interim results from the FibroAdenoma Cryoablation Treatment Registry. Am J Surg. Oct 2005; 190(4): 647-51; discussion 651-2. PMID 16164941
34. Tao Z, Tang Y, Li B, et al. Safety and effectiveness of cryosurgery on advanced pancreatic cancer: a systematic review. Pancreas. Jul 2012; 41(5): 809-11. PMID 22695092
35. Keane MG, Bramis K, Pereira SP, et al. Systematic review of novel ablative methods in locally advanced pancreatic cancer. World J Gastroenterol. Mar 07 2014; 20(9): 2267-78. PMID 24605026
36. Li J, Chen X, Yang H, et al. Tumour cryoablation combined with palliative bypass surgery in the treatment of unresectable pancreatic cancer: a retrospective study of 142 patients. Postgrad Med J. Feb 2011; 87(1024): 89-95.PMID 21131612
37. Xu KC, Niu LZ, Hu YZ, et al. A pilot study on combination of cryosurgery and (125)iodine seed implantation for treatment of locally advanced pancreatic cancer. World J Gastroenterol. Mar 14 2008; 14(10): 1603-11. PMID18330956
38. Kovach SJ, Hendrickson RJ, Cappadona CR, et al. Cryoablation of unresectable pancreatic cancer. Surgery. Apr2002; 131(4): 463-4. PMID 11935137
39. Meller I, Weinbroum A, Bickels J, et al. Fifteen years of bone tumor cryosurgery: a single-center experience of 440procedures and long-term follow-up. Eur J Surg Oncol. Aug 2008; 34(8): 921-7. PMID 18158228
40. 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): 1033-41. PMID 23065947
41. Jennings JW, Prologo JD, Garnon J, et al. Cryoablation for Palliation of Painful Bone Metastases: The MOTION Multicenter Study. Radiol Imaging Cancer. Mar 2021; 3(2): e200101. PMID 33817650
42. Purysko AS, Nikolaidis P, Dogra VS, et al. ACR Appropriateness Criteria(R) Post-Treatment Follow-up and Active Surveillance of Clinically Localized Renal Cell Cancer. J Am Coll Radiol. Nov 2019; 16(11S): S399-S416. PMID 31685108
43. Campbell S, Uzzo RG, Allaf ME, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol. Sep 2017;198(3): 520-529. PMID 28479239
44. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. Version 4.2021. http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed Jan 20, 2022.
45. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 4.2021. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed Jan 20, 2022.
46. National Comprehensive Cancer Network. Adult Cancer Pain. Version 2. 2021.https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed Jan 20, 2022.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/14	6/17/14	6/23/14	Joint policy established; incorporated policy "Cryosurgical Ablation of Renal Tumors" into this policy.
7/1/15	4/24/15	5/8/15	Code update: Added 20983
7/1/16	4/19/16	4/19/16	Routine maintenance Title changed from "Cryosurgical Ablation of Renal and Bone Tumors" to "Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors."
5/1/17	2/21/17	2/21/17	Routine maintenance References and rationale updated Added unlisted procedure code 48999
5/1/18	2/20/18	2/20/18	• Routine maintenance • Added inclusions for lung cancer • Added clinical input • Revised summary of evidence • References and rationale updated • Deleted 0340T • Added NOC code and 32994
5/1/19	2/19/19		• Routine maintenance
5/1/20	2/18/20		• Routine maintenance
5/1/21	2/16/21		• Routine maintenance, references added, statements unchanged.
5/1/22	2/15/22		• Routine maintenance • Rationale section substantially revised to separate out indications by tumor location. • Title changed from "Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors" to "Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone."

Next Review Date: 1st Qtr, 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CRYOABLATION OF TUMORS LOCATED IN THE KIDNEY, LUNG, BREAST, PANCREAS, OR BONE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.

APPENDIX 1: CLINICAL INPUT

Appendix Table 1. Respondent Profile

	Specialty Society				
No.	Name of Organization			Clinical Specialty	
1	American Society of Breast Surgeons			Breast Surgery	
2	Society of Interventional Radiology[a]			Interventional Radiology	
	Physician				
No.	**Name**	**Degree**	**Institutional Affiliation**	**Clinical Specialty**	**Board Certification and Fellowship Training**
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 8 No	Served on scientific advisory board that designed IceSense3 cryoablation protocol for breast cancer for IceCure in 2014. Unpaid Position.	9 No		9 No	
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.** Our full statement is publicly available on our website: https://www.sirweb.org/about-sir/governance/policies/ 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 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. • 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. • 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. 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. Indications for cryoablation of fibroadenoma are as follows: a. The lesion must be easily visualized on ultrasound. b. The diagnosis of fibroadenoma must be confirmed histologically on core biopsy prior to treatment. c. The diagnosis of fibroadenoma must be concordant with the imaging findings, patient history, and physical exam. d. Lesions should be less than 4 cm in largest diameter • 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 • 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 • 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 • 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
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. • 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 • 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 • 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. 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. The literature surrounding cryoablation vs external beam radiation also seems to suggest better outcomes with cryoablation. 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. 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.
3	Not my clinical realm.
4	NR
5	NR
6	For patients with early stage - we have not used cryoablation. For advanced lung carcinoma - we use it in selected patients: - Oligometastatic disease when most sites are under control, if 1-2 sites are progressing, will consider cryoablation for the progressive sites - 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. 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. 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. In general, recurrence rates seen with cryoablation are comparable to partial nephrectomy, but with near total preservation of renal function. 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. • 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 • 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. 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. 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 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, 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. 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					
	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					
	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	
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. • 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 • 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

For osteoid osteoma, see:
- 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
- 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
- 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

Bone cryoablation bibliography
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- Callstrom MR, Kurup AN. Percutaneous ablation for bone and soft tissue metastases--why cryoablation? *Skeletal Radiol.* Sep 2009;38(9):835-839. PMID 19590871

		• Ullrick SR, Hebert JJ, Davis KW. Cryoablation in the musculoskeletal system. *Curr Probl Diagn Radiol.* Jan-Feb 2008;37(1):39-48. PMID 18054665 • van der Geest IC, van Noort MP, Schreuder HW, et al. The cryosurgical treatment of chondroblastoma of bone: long-term oncologic and functional results. *J Surg Oncol.* Sep 01 2007;96(3):230-234. PMID 1744372 • Tuncali K, Morrison PR, Winalski CS, et al. MRI-guided percutaneous cryotherapy for soft-tissue and bone metastases: initial experience. *AJR Am J Roentgenol.* Jul 2007;189(1):232-239. PMID 17579176 • Callstrom MR, Atwell TD, Charboneau JW, et al. Painful metastases involving bone: percutaneous image-guided cryoablation--prospective trial interim analysis. *Radiology.* Nov 2006;241(2):572-580. PMID 17057075 • Ahlmann ER, Menendez LR, Fedenko AN, et al. Influence of cryosurgery on treatment outcome of low-grade chondrosarcoma. *Clin Orthop Relat Res.* Oct 2006;451:201-207. PMID 16788412 • Veth R, Schreuder B, van Beem H, et al. Cryosurgery in aggressive, benign, and low-grade malignant bone tumours. *Lancet Oncol.* Jan 2005;6(1):25-34. PMID 15629273 • Bickels J, Kollender Y, Merimsky O, et al. Closed argon-based cryoablation of bone tumours. *J Bone Joint Surg Br.* Jul 2004;86(5):714-718. PMID 15274269 • Robinson D, Yassin M, Nevo Z. Cryotherapy of musculoskeletal tumors--from basic science to clinical results. *Technol Cancer Res Treat.* Aug 2004;3(4):371-375. PMID 15270588 • Wakitani S, Imoto K, Saito M, et al. A case report: reconstruction of a damaged knee following treatment of giant cell tumor of the proximal tibia with cryosurgery and cementation. *Osteoarthritis Cartilage.* May 2002;10(5):402-407. PMID 12027541 • Littrup PJ, Bang HJ, Currier BP, et al. Soft-tissue cryoablation in diffuse locations: feasibility and intermediate-term outcomes. *J Vasc Interv Radiol.* Dec 2013;24(12):1817-1825. PMID 24060437
3	Yes	• Li J, Sheng S, Zhang K, et al. Pain Analysis in Patients with Pancreatic Carcinoma: Irreversible Electroporation versus Cryoablation. *Biomed Res Int.* 2016;2016:2543026. PMID 28074177 • He L, Niu L, Korpan NN, et al. Clinical Practice Guidelines for Cryosurgery of Pancreatic Cancer: A Consensus Statement From the China Cooperative Group of Cryosurgery on Pancreatic Cancer, International Society of Cryosurgery, and Asian Society of Cryosurgery. *Pancreas.* Sep 2017;46(8):967-972. PMID 28742542
4	No	Not as it pertains to cryoablation and pancreatic adenocarcinoma. 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.