7.01.92	Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone		
Original Policy Date:	March 1, 2006	**Effective Date:**	September 1, 2023
Section:	7.0 Surgery	**Page:**	Page 1 of 40

Policy Statement

I. Cryosurgical ablation may be considered **medically necessary** to treat localized renal cell carcinoma that is no more than 4 centimeters (cm) in size when **either** of the following criteria is met:
   A. Preservation of kidney function is necessary (i.e., the individual has 1 kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of less than 60 $mL/min/m^2$), and standard surgical approach (i.e., resection of renal tissue) is likely to worsen kidney function substantially
   B. The individual is not considered a surgical candidate

II. Cryosurgical ablation may be considered **medically necessary** to treat lung cancer when **either** of the following criteria is met:
   A. The individual has early-stage non-small-cell lung cancer and is a poor surgical candidate
   B. The individual requires palliation for a central airway obstructing lesion

III. Cryosurgical ablation is considered **investigational** when used to treat **any** of the following:
   A. Benign or malignant tumors of the kidney or lung (other than as defined above)
   B. Other benign or malignant solid tumors or metastases except for whole gland cryoablation for prostate cancer (see Blue Shield of California Medical Policy: Whole Gland Cryoablation of Prostate Cancer), including but not limited to breast, pancreas or bone

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

There is a Category III code to report cryoablation of a cancerous tumor in the breast:

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

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

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

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

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

There is a CPT code for cryosurgical ablation of fibroadenoma:

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

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

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

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

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

Description

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

Related Policies

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

Benefit Application

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

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

Regulatory Status

Several cryoablation devices have been cleared for marketing by the U.S. Food and Drug Administration (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).

FDA product code: GEH.

Rationale

Background

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

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

Pancreatic Cancer

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

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.

Literature Review

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

Populations

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 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 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). For patients who are not surgical candidates due to renal insufficiency or who have 1 kidney, preservation of renal function is important.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that captured longer periods of follow-up and/or larger populations were sought.
- 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 in patients 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)		●	

Study	Uhlig et al (2018)[1])	Klatte et al (2014)[2]	Tang et al (2014)[3]
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 data on histology and oncologic outcomes were provided.	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
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	Total = 9 2 prospective, 7 retrospective	Not reported	Cryoablation: 555 PN: 642	Range Cryoablation: 11.9 to 44.5 PN: 4.8 to 42.7

Study	Search End Date	Study Inclusion Criteria	Studies Included	Mean Tumor size	Sample size	Follow-up Duration (months)
		postoperative minor and major complications; Clearly documented indications for resection of the renal tumor.				

MWA: microwave ablation; PN: partial nephrectomy; RFA: radiofrequency ablation

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, 7 retrospective) 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]						

Study	All-Cause Mortality	Cancer-Specific Mortality	Local Recurrence	Metastases	Complications	Decline in Renal Function
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 (1.42 to 3.84) Favors cryoablation	Not assessed
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%, and 100% 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 to 6.662); 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, 2.006 to 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 with T1b 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 since 2010 describing 2,320 lesions treated with cryoablation.[8] Mean tumor size was 2.6 cm. The overall recurrence rate was 8.1% in studies with overall median follow-up of 41.4 months, and the technical success rate was 94.3%. Five-year OS and cancer-specific survival rates were 77.1% to 97.8% and 88% to 100%, respectively. Of the 568 lesions treated since 2016, 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:

1. Patients with NSCLC who are not surgical candidates;
2. 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 (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:

- Comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that captured longer periods of follow-up and/or larger populations were sought.
- 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 (10 studies) and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients.

Niu et al (2012) reviewed the literature on lung 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 12 months and 84.4% at 24 months. Overall survival at 12 and 24 months was 97.6% and 86.6%, respectively.

The Evaluating Cryoablation of Metastatic Lung/Pleura Tumors in Patients-Safety and Efficacy trial 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 of 1.9 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 (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:

- Comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that captured longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Breast Tumors

Systematic Reviews
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 pilot and feasibility studies. 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.

Randomized Controlled Trials

A prospective, single-arm, phase 2 trial was published by Simmons et al (2016) for the American College of Surgeons Oncology Group Z1072.[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 endpoint was complete ablation, defined as no residual evidence of tumor on magnetic resonance imaging. The investigators assigned a priori the success rates indicating that 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% CI, 67.1% to 83.2%). Most cases without complete ablation were the result of multifocal disease outside the targeted lesion.

Nonrandomized Studies

Niu et al (2013) reported on a retrospective study of 120 patients with metastatic breast cancer, including 30 metastases to the contralateral breast and other metastases to the lung, bone, liver, and skin treated with chemotherapy (n=29) or cryoablation (n=91; 35 of whom also received immunotherapy).[20] At 10-year follow-up, the median OS of all study participants was 55 months in the cryoablation group versus 27 months in the chemotherapy group (p<.001). Moreover, the median OS was greater in patients receiving multiple cryoablation and in those receiving immunotherapy. Complications with cryotherapy to the breast included ecchymosis and hematoma, pain, tenderness, and edema; all of these complications resolved within 1 week to 1 month.

In a case series by Manteni et al (2011), who assessed 15 breast cancer patients, percutaneous cryoablation 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.[22] 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.[24-27] 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 has focused on the role of cryosurgery as an alternative to surgical excision of benign fibroadenomas. Kaufman et al (2002-2005) have published several case series on office-based ultrasound-guided 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 included overlapping patients. At 1 year, patients reported 91% patient satisfaction and fibroadenomas became nonpalpable in 75% of cases. At follow-up averaging 2.6 years in 37 patients, the authors noted only 16% of 84% palpable fibroadenomas remained palpable after treatment and, of the fibroadenomas initially 2 cm or less in diameter, only 6% remained palpable.[32] In this series, the authors also noted that cryoablation did not produce artifacts that could interfere with the interpretation of mammograms. These small case series, which were done by the same group of investigators, are inadequate to permit scientific conclusions.

Nurko et al (2005) reported on outcomes at 6 and 12 months for 444 treated fibroadenomas reported to the FibroAdenoma Cryoablation Treatment registry by 55 different practice settings.[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, the treatment area was palpable in 28% of subjects for lesions 2 cm or less in diameter and 59% for lesions more than 2 cm at 12 months.

Section Summary: Breast Tumors

For the treatment of primary and recurrent breast cancer, available evidence has shown that complete ablation can be achieved in most cases for variably defined small tumors, but studies have not included control groups or compared outcomes of cryosurgery with alternative strategies for managing similar patients. Therefore, no conclusions can be made on the net health outcome of cryosurgery for breast cancer. For the treatment of fibroadenomas, there is a small body of evidence. This evidence has demonstrated that most fibroadenomas become "nonpalpable" following cryoablation. However, there is a lack of comparative trials. Comparative trials are needed to assess this technology and determine how this approach compares with surgery, as well as with vacuum-assisted excision and 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 included 5. All 5 were case series and considered of low quality. Adverse events, when mentioned, included delayed gastric emptying (0%-40.9% in 3 studies), pancreatic leak (0%-6.8% in 4 studies), biliary leak (0%-6.8% in 3 studies), and a single instance of upper gastrointestinal hemorrhage. Pain relief was reported in 3 studies and ranged from 66.7% to 100%. Median survival times reported in 3 studies ranged from 13.4 to 16 months. One-year total survival rates, as reported in 2 studies, were 57.5% and 63.6%. Keane et al (2014) reported on a systematic review of ablation therapy for locally advanced pancreatic cancer.[35] Reviewers noted that studies had demonstrated ablative therapies, including cryoablation, are feasible, but larger studies are needed. No conclusions could be made on whether ablation resulted in better outcomes than best supportive care.

Nonrandomized Trials

Li et al (2011) reported on a retrospective study of 142 patients with unresectable pancreatic cancer treated with a palliative bypass with (n=68) or without 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 versus 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 on 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 and no intraoperative morbidity or mortality. At publication, all patients had died at an average of 5 months postoperatively (range, 1-11 months).

Section Summary: Pancreatic Cancer

The available evidence on cryosurgery for pancreatic cancer consists of retrospective case series that used cryosurgery for palliation of inoperable disease and a systematic review of these studies. These studies reported that pain relief was achieved in most cases and that complications (e.g., delayed gastric emptying) are common but the true rate of complications is uncertain. Because these studies did not include control groups or compare outcomes of cryosurgery with alternative strategies for managing similar patients, no conclusions can be made on the net health outcome of cryosurgery for pancreatic cancer.

Bone Cancer and Bone Metastases

Review of Evidence

Meller et al (2008) retrospectively analyzed a single-center experience with 440 bone tumor cryosurgery procedures performed between 1988 and 2002, two-thirds of them for primary benign-aggressive and low-grade malignant lesions, and one-third for primary high-grade and metastatic bone tumors.[39] At a median follow-up of 7 years (range, 3-18 years), the overall recurrence rate was 8%. Based on their data, the authors suggested that the ideal case for cryosurgery is a young adult with involvement of long bone, a benign-aggressive or low-grade malignant bone tumor, a good cavity with greater than 75%-thick surrounding walls, no or minimal soft-tissue component, and at least ±1 cm of subchondral bone left near a joint surface after curettage and burr drilling.

Callstrom et al (2013) reported on 61 patients treated with 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 ($p<.001$) 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 Bone Metastases

There is a small amount of literature on cryoablation 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

Clinical input was sought to help determine whether the use of cryoablation for individuals with non small cell lung cancer (NSCLC)who are either poor surgical candidates or who required palliation for a lesion obstructing the central airway would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input 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.

For individuals with NSCLC who are either poor surgical candidates or who required palliation for a lesion obstructing the central airway who receive cryoablation, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

2009 Input

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

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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, 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.2.2022) guidelines on kidney cancer state that "thermal ablation (cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions. Thermal ablation is an option for masses <3 cm, but may also be an option for larger masses in select patients. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications. Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies. Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes. The 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." Additionally, the guidelines note that "randomized phase III comparison with surgical resection (i.e., radical or partial nephrectomy by open or laparoscopic techniques) has not been done" and "ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes."[44,]

Non-Small Cell Lung Cancer

The NCCN (v.3.2022) guidelines for NSCLC 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.1.2022) 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,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review 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	Feb 2026

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Appendix 1

Appendix 1: 2017 Clinical Input
CI - Objective
Clinical input is sought to help determine whether the use of cryosurgical ablation in clinical practice for the management of solid tumors of the breast, lung, pancreas, kidney, or bone results in a meaningful clinical benefit in improved net health outcome and whether this use is consistent with generally accepted medical practice.

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

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

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

Clinical Input Responses

Appendix Figure 1. 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.

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,	Cleveland Clinic	Hepato-Pancreato-Biliary Surgery	Fellowship of the Royal College of Surgeons (FRCS) England

	Specialty Society				
		FRCS, FACS			
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 Yes8 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	

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
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.

Detailed Responses

- 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.
  - 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.

No.	Response
	• 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 (i.e.. Cryo vs surgery).
9	NR

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

- 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 o 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 o 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 o 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 o 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

No.	Response
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.

- 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

No.	Response
	bronchoscopy. Patients should not have a coagulopathy, require uninterrupted anticoagulation or severe thrombocytopenia (less than 50K 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(T1a-b, N0, M0) are considered an option for inoperable patients or in patients who refuse surgery. It is not currently clear that cryosurgery is equivalent in outcomes or safety to other ablative therapies (i.e. SBRT). Additional studies are needed. Based on the Eclipse trial (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.

- 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

- 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.

No.	Response
	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

- 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

No.	Response
	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.

- Based on the evidence and your clinical experience for the indications described in Question 1:
  - 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.
  - 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

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
	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.

- Based on the evidence and your clinical experience for the indications described in Question 1:
  - Respond YES or NO for each indication whether this intervention is consistent with generally accepted medical practice.
  - 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					

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	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.

- 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.

- 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	
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No.	Yes/No	Citations of Missing Evidence
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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.

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Documentation for Clinical Review

Please provide the following documentation:

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

Post Service (in addition to the above, please include the following):

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

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral

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

Policy History

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

Effective Date	Action
03/01/2006	New Policy Adoption
09/25/2009	Policy title change from Cryoablation for the Treatment of Breast Fibroadenoma Policy revision with position change
01/04/2011	Documentation required revised
07/14/2014	Policy title change from Cryosurgical Ablation of Miscellaneous Solid Tumors Policy revision with position change
09/30/2014	Policy revision without position change
01/01/2015	Coding update
10/01/2016	Policy revision without position change
10/01/2017	Policy revision without position change
01/01/2018	Coding update
09/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
03/01/2020	Coding update
09/01/2020	Annual review. No change to policy statement. Literature review updated.
09/01/2021	Annual review. No change to policy statement. Policy title changed from Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors to current one. Policy Guidelines and literature review updated.
09/01/2022	Annual review. Policy statement and literature review updated.
09/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements and Feedback (as applicable to your plan)

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

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

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Appendix A

<table>
<tr><th colspan="2">POLICY STATEMENT
(No changes)</th></tr>
<tr><th>BEFORE</th><th>AFTER</th></tr>
<tr><td>Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone 7.01.92

Policy Statement:

I. Cryosurgical ablation may be considered medically necessary to treat localized renal cell carcinoma that is no more than 4 centimeters (cm) in size when either of the following criteria is met:
A. Preservation of kidney function is necessary (i.e., the individual has 1 kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of less than 60 $mL/min/m^2$), and standard surgical approach (i.e., resection of renal tissue) is likely to worsen kidney function substantially
B. The individual is not considered a surgical candidate

II. Cryosurgical ablation may be considered medically necessary to treat lung cancer when either of the following criteria is met:
A. The individual has early-stage non-small-cell lung cancer and is a poor surgical candidate
B. The individual requires palliation for a central airway obstructing lesion

III. Cryosurgical ablation is considered investigational when used to treat any of the following:
A. Benign or malignant tumors of the kidney or lung (other than as defined above)
B. Other benign or malignant solid tumors or metastases except for whole gland cryoablation for prostate cancer (see Blue Shield of California Medical Policy: Whole Gland Cryoablation of Prostate Cancer), including but not limited to breast, pancreas or bone</td><td>Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone 7.01.92

Policy Statement:

I. Cryosurgical ablation may be considered medically necessary to treat localized renal cell carcinoma that is no more than 4 centimeters (cm) in size when either of the following criteria is met:
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B. The individual is not considered a surgical candidate

II. Cryosurgical ablation may be considered medically necessary to treat lung cancer when either of the following criteria is met:
A. The individual has early-stage non-small-cell lung cancer and is a poor surgical candidate
B. The individual requires palliation for a central airway obstructing lesion

III. Cryosurgical ablation is considered investigational when used to treat any of the following:
A. Benign or malignant tumors of the kidney or lung (other than as defined above)
B. Other benign or malignant solid tumors or metastases except for whole gland cryoablation for prostate cancer (see Blue Shield of California Medical Policy: Whole Gland Cryoablation of Prostate Cancer), including but not limited to breast, pancreas or bone</td></tr>
</table>