Medical Policy

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

Related Policies:	▪ *Cryosurgical Ablation of Primary or Metastatic Liver Tumors* ▪ *Radiofrequency Ablation of Primary or Metastatic Liver Tumors* ▪ *Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With early stage renal cancer who are surgical candidates	Interventions of interest are: • Cryoablation	Comparators of interest are: • Surgical resection • Active surveillance	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity

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Individuals: • With non-small cell lung cancer who are not surgical candidates	Interventions of interest are: Cryoablation	Comparators of interest are: • Radiation therapy • Palliative care	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With non-small cell lung cancer who require palliation for a central airway obstructing lesion	Interventions of interest are: • Cryoablation	Comparators of interest are: • Surgical resection • Radiation therapy • Palliative care	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With solid tumors located in the breast, lung, pancreas, kidney, or bone	Interventions of interest are: • Cryosurgical ablation	Comparators of interest are: • Surgical resection • Other ablative techniques • No intervention	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity

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.

OBJECTIVE

The objective of this evidence review is to determine whether cryoablation of tumors located in the kidney, lung, breast, pancreas, or bone will improve the net health outcome. This evidence review is limited to treatment in adults (age 18 years and older) and does not address pediatric populations.

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.

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.

POLICY

A. Cryosurgical ablation may be considered **medically necessary** to treat localized renal cell carcinoma that is no more than 4 cm in size when either of the following criteria is met:

1. Preservation of kidney function is necessary (i.e., the individual has 1 kidney or renal insufficiency defined by a glomerular filtration rate of <60 mL/min/m2), and standard surgical approach (i.e., resection of renal tissue) is likely to worsen kidney function substantially; **OR**
2. The individual is not considered a surgical candidate.

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

1. The individual has early-stage non-small-cell lung cancer and is a poor surgical candidate; **OR**
2. The individual requires palliation for a central airway obstructing lesion.

C. Cryosurgical ablation is considered **experimental / investigational** as a treatment for benign or malignant tumors of the breast, lung (other than defined above), pancreas, or bone and other solid tumors or metastases outside the liver and prostate and to treat renal cell carcinomas in individuals who are surgical candidates.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 6. 2023.

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

CRYOABLATION FOR EARLY STAGE KIDNEY CANCER

Clinical Context and Therapy Purpose

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

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 (eg, 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 that were identified.

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 most recent, relevant, and comprehensive reviews and meta-analyses, reported by Yanagisawa et al (2022),[1,]Uhlig et al (2019),[2,] Klatte et al (2014),[3,] and Tang et al (2014).[4,]Included studies and characteristics of the systematic reviews are described in Tables 1 and 2. The Yanagisawa et al (2022) review includes multiple types of ablation therapies (radiofrequency ablation [RFA], cryoablation, and microwave ablation) - only studies that focus on cryoablation are listed in Table 1.

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

Study	Yanagisawa et al (2022)[1,]	Uhlig et al (2018)[2,])	Klatte et al (2014)[3,]	Tang et al (2014)[4,]
Andrews et al (2019)	●			
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)		●	●	●
Fosatti et al (2015)	●			
Foyil et al (2008)		●		
Garcia et al (2021)	●			
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)	●	●		
Ko et al (2008)	●			
Lian et al (2010)			●	
Lin et al (2008)			●	●
Liu et al (2021)	●			
Lughezzani et al (2009)		●	●	
Mason et al (2017)		●		
Nisbett et al (2009)			●	
O'Malley et al (2007)		●	●	●

Study	Yanagisawa et al (2022)[1]	Uhlig et al (2018)[2]	Klatte et al (2014)[3]	Tang et al (2014)[4]
Panumatrassamee et al (2013)		●		
Rembeyo et al (2019)	●			
Tanagho et al (2013)		●		
Thompson et al (2015)		●		
Turna et al (2009)		●	●	
Weinberg et al (2015)		●		
Yanagisawa et al (2018)	●			
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)
Yanagisawa et al (2022)[1]	August 2021	Compared AT (RFA, MWA, or cryoablation) with PN in the treatment of cT1a and cT1b renal tumors. Reported on clinical outcomes, which included complication rate, hospitalization period, % decline in eGFR, recurrence, secondary efficacy, metastasis, and mortality from disease. Retrospective and prospective studies were included.	Total = 27 (13,996 patients) 12 studies focused on cryoablation compared with PN	18 studies comprise cT1a patients, 6 studies comprise cT1b patients, and 3 studies include both.	cT1a: 13,062 cT1b: 934	Not described
Uhlig et al (2018)[2]	December 2017	Evaluated PN, RFA, cryoablation, or MWA for treatment of renal masses; Comparative study design contrasting	Total = 47 (24,077 patients) 13 prospective, 34	Cryoablation: 2.53 cm PN: 2.84 cm MWA: 2.74 cm	Cryoablation: 6,618 PN: 15,238 MWA: 344 RFA: 1,877	Range 3 to 82

Study	Search End Date	Study Inclusion Criteria	Studies Included	Mean Tumor size	Sample size	Follow-up Duration (months)
		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.	retrospective Cryoablation: 24 studies (668 patients)	RFA: 2.63 cm		
Klatte et al (2014)[3,]	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)[4,]	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,	Total = 92 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 glomerular filtration rate decrease, catheterization time, local recurrence, distant metastasis, and overall complications, including both intraoperative and postoperative minor and major complications; Clearly documented indications for resection of the renal tumor.				

AT: ablation therapy; eGFR: estimated glomerular filtration rate; MWA: microwave ablation; PN: partial nephrectomy; RFA: radiofrequency ablation

Yanagisawa et al (2022) published a systematic review and meta-analysis comparing ablative therapies (cryoablation, RFA, and microwave ablation) to partial nephrectomy.[1,] Twenty-seven trials published between 2005 and 2021 (N=13,996) were included; 12 of those studies directly compared cryoablation with partial nephrectomy, althouogh results were not stratified by type of ablative therapy (see Table 3). No significant differences in cancer-specific mortality for cT1a tumors (p=.50) and cT1b tumors (p=.63) were found comparing partial nephrectomy and ablation therapies. Local recurrence was higher for ablative therapies compared with partial nephrectomy in both cT1a tumors (risk ratio, 0.43; 95% confidence interval [CI], 0.28 to 03.66; p=.0001) and cT1b tumors (risk ratio, 0.41; 95% CI, 0.23 to 0.75; p=.004). There were no significant differences between partial nephrectomy and ablation therapy in terms of rate of metastases, overall complications, and decline in renal function.

Uhlig et al (2019) published a systematic review and meta-analysis comparing partial nephrectomy, RFA, cryoablation, and microwave ablation for small renal masses.[2,] 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.[4,] 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.[3,] 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
Yanagisawa et al (2022)[1,]						
cT1a tumors: Risk ratio (95% CI); p-value	Not assessed	0.87 (0.57 to 1.31);.50	0.43 (0.28 to 0.66);.0001 Favors PN	0.79 (0.47 to 1.34);.39	1.34 (0.90 to 2.0);.15	MD, 2.42 (-0.06 to 4.89);.06
I^2 (P-value)		0% (.62)	20% (.23)	20% (.28)	63% (.0003)	83% (.0004)
cT1b tumors: Risk ratio (95% CI); p-value	Not assessed	0.80 (0.32 to 1.98);.63	0.41 (0.23 to 0.75);.004 Favors PN	1.16 (0.51 to 2.64);.72	1.08 (0.76 to 1.53);.68	MD, 0.73 (-3.76 to 5.23);.75
I^2 (P-value)		0% (.76)	30% (.20)	28% (.23)	22% (.26)	0% (.71)
Uhlig et al (2019)[2,]						
Network meta-analysis Cryoablation vs PN IRR (95% CI) P-value	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

Study	All-Cause Mortality	Cancer-Specific Mortality	Local Recurrence	Metastases	Complications	Decline in Renal Function
I^2 (P-value)	0% (.968)	0% (.8283)	29.4% (.6784)		59.9% (.003)	91.8% (.9001)
Klatte et al (2014)[3,]						
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)[4,]						
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; MD: mean difference; 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.[5] 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).[6] 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).[7] 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).[8] 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 that were identified.

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 Tables 2 and 3).

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.[9] 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 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.[10] 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.[11]

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)[10,]	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)[11,]	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; SD: standard deviation.

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 individuals with non-small cell lung cancer (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 (eg, preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- 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.[12,] 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.[13,] 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.[14,] 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).[15,] 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 to 2011).[16,] 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 to 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.[17,] 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.[18,] 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)[18,]	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)[18,]	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		1. No description of patient flow or the amount of available data for any of the outcome measures.		

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		biased which is complicated by the fact that there is no comparator.				

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 individuals with solid tumors in the breast, pancreas, or bone.

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

Population

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

Interventions

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

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

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

Regarding tumors located in the breast, the selection of lumpectomy, modified radical mastectomy, or another approach is balanced against the patient's desire for breast conservation, the need for tumor-free margins in resected tissue, and the patient's age, hormone receptor status, and other factors.

Palliative treatments for bone metastases include analgesics, opioids, osteoclast inhibitors, and radiation therapy.

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

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- 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.[19] 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% to 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.[20] 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 cancers (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).[21] 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.[22] 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.[23] 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.[24] This phase 1 study included 29 patients who underwent cryoablation of primary breast cancers measuring less than 2 cm in diameter, followed 1 to 4 weeks later by standard surgical excision. Cryoablation was successful in patients with invasive ductal carcinoma less than 1.5 cm in diameter, and with less than 25% ductal carcinoma in situ identified in a prior biopsy specimen.

Other studies have described outcomes from cryosurgery for advanced primary or recurrent breast cancer.[25,26,27,28] 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 to 2005) have published several case series on office-based ultrasound-guided cryoablation as a treatment of breast fibroadenomas.[29,30,31,32,33] 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.[33,] 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.[34,] 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.[35,] 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% to 40.9% in 3 studies), pancreatic leak (0% to 6.8% in 4 studies), biliary leak (0% to 6.8% in 3 studies), and 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.[36,] 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.[37,] 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).[38] 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.[39] 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 to 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 (eg, 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.[40] At a median follow-up of 7 years (range, 3 to 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 to 11 cm) metastatic to the bone.[41] 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.[42,] 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.

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 2021) 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 effective and safe alternatives [to surgical resection] for the treatment of small, localized RCCs."[43,44,] These recommendations are based on a review of the data and expert consensus.

American Urological Association
The American Urological Association (2021) updated its guidelines on the evaluation and management of clinically localized sporadic renal masses suspicious for renal cell carcinoma.[45,] 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 25		
Clinicians 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.	Moderate	C
Guideline statement 26		
Both radiofrequency ablation (RFA) and cryoablation may be offered as options for patients who elect thermal ablation.	Conditional	C
Guideline statement 28		
Counseling about thermal ablation should include information regarding an increased likelihood of tumor persistence or local recurrence after primary thermal ablation relative to surgical excision, 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 National Comprehensive Network (NCCN) (v.4.2023) 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 may require multiple treatments to achieve the same local oncologic outcomes as conventional surgery."

The NCCN guidelines also note that "ablative techniques such as cryotherapy 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 of ablative techniques with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been performed." [46,]

Non-Small Cell Lung Cancer

The NCCN (v.3.2023) guidelines for NSCLC made the following relevant recommendations:[47,]

- 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.1.2023) 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."[48,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

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 No.	Trial Name	Planned Enrollment	Completion Date
NCT04506671	A Prospective, Non-randomized, in Parallel Groups Study Evaluating the Efficacy and Safety of Percutaneous Cryoablation and Partial Nephrectomy in Localized T1b Renal Tumor	142	Jun 2025
Breast cancer			
NCT05505643	COOL-IT: Cryoablation vs Lumpectomy in T1 Breast Cancers: A Randomized Controlled Trial With Safety Lead-in	256	Dec 2030
NCT04334785	Evaluation for the Effectiveness and Safety of Cryo-ablation in the Treatment of Early Invasive Breast Cancer	186	May 2025
Bone cancer			
NCT05615545	Safety and Efficacy of Cryoablation in the Treatment of Advanced Bone and Soft Tissue Tumors: a Single-center Retrospective Study	30	Oct 2023

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral

REVISIONS	
03-04-2019	Policy added to the bcbsks.com web site on 02-01-2019 with an effective date of 03-04-2019.
01-01-2020	In Coding section: ▪ Added CPT Code: 0581T
04-19-2021	Updated Description section
	Updated Rationale
	Updated References
09-17-2021	Changed Title from "Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors" to "Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone"
	Updated Rationale
	Updated References
08-23-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes: C64.1, C64.2, C64.9, C65.1, C65.2

REVISIONS	
	▪ Added: "An appropriate ICD-10 diagnosis should be used when reporting Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone.:" statement to the ICD-10 section
	Updated References Section
09-12-2023	Updated Description Section
	Updated Ratianole Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box
	Updated References Section

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