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Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors

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Place of Service: Outpatient; Inpatient	**Precertification:** Not required; Refer to Section IV

I. Description

In radiofrequency ablation (RFA), a probe is inserted into the center of a tumor; then, prong-shaped, non-insulated electrodes are projected into the tumor. Next, heat is generated locally by an alternating, high-frequency current that travels through the electrodes. The localized heat treats the tissue adjacent to the probe, resulting in a 3- to 5.5-cm sphere of dead tissue. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is a local recurrence, it occurs at the edge and can sometimes be retreated. RFA may be performed percutaneously, laparoscopically, or as an open procedure.

For individuals who have painful osteolytic bone metastases who have failed or are poor candidates for standard treatments who receive RFA, the evidence includes a prospective cohort study and case series. Relevant outcomes are symptoms, change in disease status, quality of life (QOL), medication use, and treatment-related morbidity. A prospective cohort study and case series have shown clinically significant pain relief (defined as a decrease of 2 units from baseline on the Brief Pain Inventory scale) or reduction in opioid use following treatment of painful osteolytic metastases. A multicenter, prospective study reported significant reductions in pain through the 6-month follow-up period, with 59% of patients achieving immediate improvement in pain within 3 days of RFA. The population is comprised of patients with few or no treatment options, for whom short-term pain relief is an appropriate clinical outcome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have painful osteoid osteomas who receive RFA, the evidence includes numerous observational studies and systematic reviews of these studies. The relevant outcomes are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. In a systematic review of thermal ablation techniques, clinical success (pain-free) was achieved in 94% to 98% of patients. Most patients (89% to 96%) remained pain-free when assessed during longer-term follow-up. Another systematic review reported similar success rates noting an average 8.3% failure rate among patients receiving computed tomography guided RFA. Although no randomized trials of RFA for osteoid osteomas have been performed, the uncontrolled studies have demonstrated RFA can provide adequate symptom relief with minimal complications, for a population for whom short-term symptom relief and avoidance of invasive procedures are appropriate clinical outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized renal cell carcinoma (RCC) that is no more than 4 cm in size who receive RFA, the evidence includes a randomized controlled trial (RCT), numerous observational

studies, and systematic reviews of these studies. The relevant outcomes are overall survival (OS), change in disease status, QOL, and treatment-related morbidity. A recent meta-analysis that included only an RCT and cohort studies found that RFA was as effective as nephrectomy for small renal tumors, with a reduction in complications. Another recent meta-analysis found that partial nephrectomy (PN) was superior to ablative techniques (the study included RFA but also cryoablation and microwave ablation) in overall mortality and local recurrence but not in cancer-specific mortality. It also found fewer complications and improved renal function with ablation. A meta-analysis from 2022 found that PN was superior to ablation (RFA, cryoablation, and microwave ablation) in local recurrence. Overall complications, decline in renal function, and cancer-specific mortality rates did not differ between ablation and nephrectomy. Although inconsistent, the evidence does suggest that, for small renal tumors, RFA may result in a similar rate of disease progression with a lower complication rate than nephrectomy. However, comparative trials are needed to determine with greater certainty the effects of these treatments in the same patient population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inoperable primary pulmonary tumors or non-pulmonary tumors metastatic to the lung who receive RFA, the evidence includes prospective observational studies and systematic reviews of these studies. The relevant outcomes are OS, change in disease status, QOL, and treatment-related morbidity. A multicenter study found that for tumors less than 3.5 cm in size, RFA can lead to a complete response in as many as 88% of patients for at least 1 year. Two-year survival rates have been reported to range from 41% to 75% in case series, with 5-year survival rates of 20% to 27%. In general, the evidence suggests that RFA results in adequate survival and tumor control in patients who are not surgical candidates, with low morbidity rates. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have breast tumors who receive RFA, the evidence includes observational studies and systematic reviews of these studies. The relevant outcomes are OS, change in disease status, QOL, and treatment-related morbidity. Evidence has reported varied and incomplete ablation rates with concerns about post-ablation tumor cell viability. Long-term improvements in health outcomes have not been demonstrated. Additionally, available studies do not permit comparisons with conventional breast-conserving procedures. Further prospective studies, with long-term follow-up, should focus on whether RFA of the breast for small tumors can provide local control and survival rates compared with conventional breast-conserving treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have benign thyroid tumors who receive RFA, the evidence includes RCTs, prospective studies, case series, and systematic reviews of these studies. Relevant outcomes are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. Systematic reviews have demonstrated that RFA results in a significant reduction in thyroid nodule size with a 2020 review showing that these changes remain durable through at least 36 months. Complication rates are generally low but include voice changes. The data are limited by significant heterogeneity in meta-analyses, a lack of generalizability to populations outside Republic of Korea and Italy, and a lack of comparators more relevant to practice in the United States. Further studies comparing RFA to percutaneous ethanol injection or surgery would be more informative in determining the potential utility of RFA in patients with symptomatic or large benign thyroid tumors as these are the recommended treatment options per the American Thyroid Association. The evidence is insufficient to determine that the technology results in an improvement in the net

health outcome.

For individuals who have miscellaneous tumors (e.g. head and neck, thyroid cancer, pancreas) who receive RFA, the evidence includes a few case series, prospective observational studies, and retrospective comparative studies. The relevant outcomes are OS, change in disease status, QOL, and treatment-related morbidity. There is a limited evidence base for these tumor types. Reporting on outcomes or comparisons with other treatments is limited. These studies do not permit conclusions on the health benefits of RFA. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Clinical input obtained in 2010 supported use of RFA for localized RCC that is no more than 4 cm in size when preservation of kidney function is necessary, and a standard surgical approach is likely to worsen kidney function substantially or when the patient is not considered a surgical candidate. Thus, absent other treatment options, RFA for small renal cell tumors was judged to be medically necessary.

II. Policy Criteria

A. Radiofrequency ablation is covered (subject to Limitations and Administrative Guidelines) in the following situations:
   1. To palliate pain in patients with osteolytic bone metastases who have failed or are poor candidates for standard treatments such as radiation or opioids;
   2. To treat osteoid osteomas that cannot be managed successfully with medical treatment;
   3. To treat localized RCC that is no more than 4 cm in size when either of the following criteria is met:
      a. In order to preserve kidney function in patients with significantly impaired renal function (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate [GFR] of less than 60 mL/min per m^2); and
      b. when the standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen existing kidney function; or
      c. the patient is not considered a surgical candidate.

B. Radiofrequency ablation is covered (subject to Limitations and Administrative Guidelines) to treat an isolated peripheral non-small cell lung cancer lesion that is no more than 3 cm in size when all of the following criteria are met:
   1. Surgical resection or radiotherapy with curative intent is considered appropriate based on stage of disease; however, medical co-morbidity renders the individual unfit for those interventions; and
   2. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery, and the heart.

C. Radiofrequency ablation is covered (subject to Limitations and Administrative Guidelines) to treat malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when all of the following criteria are met:
   1. In order to preserve lung function when surgical resection or radiotherapy is likely to substantially worsen pulmonary status; or
   2. The patient is not considered a surgical candidate; and
   3. There is no evidence of extrapulmonary metastases; and
   4. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

D. For cancers not addressed in this policy, radiofrequency ablation is covered when all the following criteria are met:
   1. Criteria II.A.1-3 are met
   2. Radiofrequency ablation is a level 1 or 2A recommendation of the National Comprehensive Cancer Network (NCCN) Testing is in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST patients the Hawaii Administrative Rules (HAR 1700.1-42).

III. Limitations

A. Radiofrequency ablation is not covered to treat the following:
   1. Breast tumors;
   2. Lung cancer not meeting the criteria above;
   3. Renal cell cancer not meeting the criteria above;
   4. Osteoid osteomas that can be managed with medical treatment;
   5. Painful bony metastases as initial treatment;
   6. All other tumors outside the liver, including but not limited to: the head and neck, thyroid, adrenal gland, ovary, and pelvic/abdominal metastases of unspecified origin.

B. The following are additional criteria that have been developed by clinical judgment/consensus and existing guidelines for use of radiofrequency ablation metastatic tumor(s) to the lung:
   1. No more than 3 tumors per lung should be ablated;
   2. Tumors should be amenable to complete ablation; and
   3. Twelve months should elapse before a repeat ablation is considered.

IV. Administrative Guidelines

Precertification is not required. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

*There are no specific CPT codes for the other indications mentioned in this policy.

CPT Codes	Description
20982	Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; radiofrequency
32998	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, radiofrequency, unilateral
50542	Laparoscopy, surgical; ablation of renal mass lesion(s)
50592	Ablation, 1 or more renal tumor(s), percutaneous, unilateral, radiofrequency
76940	Ultrasound guidance for, and monitoring of, parenchymal tissue ablation

V. Scientific Background

Health Disparities in Certain Solid Tumor Types

Based on data from 2014 through 2018, age-adjusted breast cancer mortality is approximately 40% higher among Black women compared to non-Hispanic White women in the United States (27.7 vs 20.0 deaths per 100,000 women), despite a lower overall incidence of breast cancer among Black women (125.8 vs 139.2 cases per 100,000 women). Experts postulate that this divergence in mortality may be related to access issues– Black women are more likely than White women to lack health insurance, limiting access to screening and appropriate therapies. Socioeconomic status is also a driver in health and health outcome disparities related to breast cancer. Women with low incomes have significantly lower rates of breast cancer screening, a higher probability of late-stage diagnosis, and are less likely to receive high-quality care, resulting in higher mortality from breast cancer.

Based on data from 2015 through 2019, kidney cancer is more common in men than women and occurs more often in American Indian and Alaskan Native individuals, followed by Black individuals. American Indians and Alaska Natives have higher death rates from kidney cancer than any other racial or ethnic group. A cohort study by Howard et al (2021) included 158,445 patients with localized kidney cancer from the National Cancer Database between 2010 and 2017. Investigators found that female patients were treated more aggressively compared with male patients, with lower adjusted odds of undertreatment and higher adjusted odds of overtreatment. They also found that Black and Hispanic patients had higher adjusted odds of undertreatment and overtreatment compared to White patients, and uninsured status was associated with lower adjusted odds of overtreatment and higher adjusted odds of undertreatment. These results suggest that sex, race and ethnicity, and socioeconomic status are associated with disparities in guideline-based treatment for localized kidney cancer, specifically, with increased rates of non-guideline-based treatment for women and Black and Hispanic patients.

Radiofrequency Ablation

Radiofrequency ablation (RFA) was initially developed to treat inoperable tumors of the liver (see evidence review 7.01.91). Recently, studies have reported on the use of RFA to treat other tumors. For some of these, RFA is being investigated as an alternative to surgery for operable tumors. Well-established local or systemic treatment alternatives are available for each of these malignancies. The hypothesized advantages of RFA for these cancers include improved local control and those common to any minimally invasive procedure (eg, preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

Goals of RFA may include (1) controlling local tumor growth and preventing recurrence; (2) palliating symptoms; and (3) extending survival duration for patients with certain tumors. The effective volume of RFA depends on the frequency and duration of applied current, local tissue characteristics, and probe configuration (eg, single vs multiple tips). RFA can be performed as an open surgical procedure, laparoscopically or percutaneously, with ultrasound or computed tomography guidance. Potential complications associated with RFA include those caused by heat damage to normal tissue adjacent to the tumor (eg, intestinal damage during RFA of kidney), structural damage along the probe track (eg, pneumothorax as a consequence of procedures on the lung), and secondary tumors (if cells seed during probe removal).

Regulatory Status

The U.S. Food and Drug Administration (FDA) issued a statement in September 2008, concerning the regulatory status of RFA. The FDA has cleared RFA devices for the general indication of soft tissue cutting, coagulation, and ablation by thermal coagulation necrosis. Under this general indication, RFA can be used to ablate tumors, including lung tumors. Some RFA devices have been cleared for additional specific treatment indications, including partial or complete ablation of nonresectable liver lesions and palliation of pain associated with metastatic lesions involving bone. The FDA has not cleared any RFA devices for the specific treatment indication of partial or complete ablation of lung tumors, citing lack of sufficient clinical data to establish safety and effectiveness for this purpose. The FDA has received reports of death and serious injuries associated with the use of RFA devices in the treatment of lung tumors.

Rationale

This evidence review was created in October 2003 and has been regularly updated with searches of the PubMed database. The most recent literature update was performed through August 10, 2022.

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 (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

Osteolytic Bone Metastases

Clinical Context and Therapy Purpose

The purpose of RFA in patients who have painful osteolytic bone metastases who have failed or are poor candidates for standard treatments is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients

The relevant populations of interest are individuals with painful osteolytic bone metastases who have failed or are poor candidates for standard treatments.

Interventions

The therapy being considered is RFA.

Comparators

The following therapies and practices are options to manage painful osteolytic bone metastases: medical management (e.g. chemotherapy) and radiotherapy.

Outcomes

The general outcomes of interest are overall survival (OS), reduction in pain and medication use, fractures, functional outcomes, and QOL.

Patients would be followed for several years given the impact of bone metastases on bone remodeling.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Cohort Studies

Levy et al (2020) conducted a global, multicenter, nonrandomized, prospective postmarketing study to evaluate the effectiveness of RFA in patients with painful osteolytic bone metastases. Between October 2017 and March 2019, 134 ablations were performed in 100 patients (68% vs. 32% of the cohort had a single vs. multiple sites treated, respectively). The most common tumor location was thoracic (44%) followed by lumbar (33%). Patient outcomes including pain, pain interference, and quality of life were collected. Forty percent of the cohort did not participate through the 6-month follow-up, with 2 additional discontinuations after 6 months. The most common reason for discontinuation was death (30 patients), which were all classified as related to the underlying malignancy. The primary endpoint evaluated was pain improvement, from baseline to 3 months. At baseline, the mean score for worst pain (measured by Brief Pain Inventory) for the entire cohort was 8.2. After RFA, worst pain significantly improved, with mean scores decreasing to 5.6, 4.7, 3.9, 3.7, and 3.5 at 3 days, 1 week, 1 month, 3 months, and 6 months, respectively ($p<.0001$ for all visits). Immediate improvement in pain (≥ 2-point change in worst pain at the treatment site(s) 3 days after RFA) was achieved by 59% of patients. Four adverse events were reported, of which 2 resulted in hospitalization for pneumonia and respiratory failure, respectively.

Case Series

Goetz et al (2004) reported on an international study conducted at 9 centers in which 43 patients with painful osteolytic bone metastases were treated palliatively with RFA.1, The study's primary outcome measure was the Brief Pain Inventory-Short Form, a validated scale from 0 (no pain) to 10 (worst pain imaginable). Patient eligibility required baseline values of four or more from two or fewer painful sites. Thirty-nine (91%) of the patients had previously received opioids to control pain

from the lesion(s) treated with RFA, and 32 (74%) had prior radiotherapy to the same lesion. The mean pain score at baseline was 7.9 (range, 4 to 10). At 4, 12, and 24 weeks after RFA, average pain scores decreased to 4.5, 3.0, and 1.4, respectively (all p<0.001). Forty-one (95%) patients achieved clinically significant reductions in pain scores, prospectively defined as a decrease of 2 units from baseline. Investigators also reported statistically significant (p=0.01) decreases in opioid use at weeks 8 (by 59%) and 12 (by 54%).

An earlier case series by Gronemeyer et al (2002) showed that palliative RFA provided significant pain relief in 9 (90%) of 10 patients with unresectable, osteolytic spine metastases who had no other treatment options.2, Pain was reduced by an average of 74%; back pain-related disability was reduced by an average of 27%. Neurologic function was preserved in nine patients and improved in the other. In another small case series, Kojima et al (2006) assessed 24 patients with painful metastatic bone tumors who experienced pain-alleviating effects with RFA is consistent with other evidence.

Section Summary: Osteolytic Bone Metastases
A prospective cohort study and case series have shown clinically significant reductions in pain relief (defined as a decrease of 2 units from baseline on the Brief Pain Inventory scale) or reductions in opioid use following treatment with RFA of osteolytic pain metastases in patients with no or limited treatment options. A multicenter, prospective study reported significant reductions in pain through the 6-month follow-up period, with 59% of patients achieving immediate improvement in pain within 3 days of RFA.

Osteoid Osteomas

Clinical Context and Therapy Purpose
The purpose of RFA in patients who have painful osteoid osteomas is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with painful osteoid osteomas.

Interventions
The therapy being considered is RFA.

Comparators
The following therapies and practices are options to treat osteoid osteomas: medical management, surgical excision, core drill excision, and laser photocoagulation.

Outcomes
The general outcomes of interest are reductions in pain and medication use, normal bone development, and postsurgical adverse events.

Patients would be followed through adolescents to ensure normal skeletal development.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Tordjman et al (2020) conducted a systematic review on CT-guided RFA for osteoid osteomas. The review included 69 studies (43 retrospective and 12 prospective studies; rest of study designs were not identifiable) comprising 3023 patients. The weighted overall failure rate was 8.3% for the entire cohort. When studies were analyzed by time period conducted the failure rate was significantly lower in studies conducted between 2011 and 2019 compared to those conducted between 2002 and 2010 (7% vs 14%, p=0.004). The complication rate for the entire cohort was 3%, with skin burns (0.7%) and infections (0.5%) as the most commonly reported.

Lanza et al (2014) reported on a systematic review of various ablative techniques for osteoid osteomas.4, Included in the review were 23 articles on RFA, 3 on interstitial laser ablation, and 1 with a combination of ablation techniques, totaling 27 articles (n=1772). The mean technical success was 100% and clinical success, defined as being pain-free, ranged from 94% to 98%, depending on the length of follow-up. Complications occurred in 2% of patients and included skin or muscle burn in nine patients, four infections, nerve lesions or tool breakage in three patients each, delayed skin healing, hematoma, and failure to reach target temperature in two patients each, and fracture, pulmonary aspiration, thrombophlebitis, and cardiac arrest in one patient each. Eighty-six patients had tumor recurrence.

Retrospective Studies

In their retrospective study of the efficacy and complications of (CT)-guided RFA of spinal osteoid osteoma, Albisinni et al (2017) concluded that CT-guided RFA is as effective as first-line therapy for the disease.5, After RFA, clinical symptoms were evaluated at 3, 6, and 12 months, with a final evaluation at the end of the study. Results showed that the complete regression of osteoid osteoma symptoms in 57 (93.4%) of 61 (p=0.001) for patients observed between 2002 and 2012. Study limitations included the retrospective design and focus on a single treatment.

Lassalle et al (2017) conducted a single-center retrospective analysis of long-term outcomes for CT-guided RFA in 126 patients with suspected osteoid osteoma.6, The study was conducted from 2008 to 2015. Phone evaluations were performed. The overall success rate was 94.3% among the 88 patients who participated in the follow-up calls. The study was limited by its retrospective design, imprecision of patients' memory over follow-up, the lack of clinical and imaging follow-up, and an inability to perform multivariate statistical analysis of factors associated with treatment failure.

Rimondi et al (2012) reported on a retrospective study of 557 patients treated with CT-guided RFA as primary treatment for nonspinal osteoid osteomas. All patients were followed for a mean of 3.5 years (range, 0.5-9 years). Pain relief occurred in all 557 patients within the first week after RFA and continued in 533 (96%) patients who remained asymptomatic through their last follow-up. Pain

recurrence occurred in 24 (4%) patients. Complications occurred in five patients and included thrombophlebitis, skin burn, broken electrode, and two procedures in which the RFA generator failed to reach maximum temperature.

Sahin et al (2019) conducted a single-center retrospective study that evaluated clinical pain symptoms to demonstrate the rapid relief of pain symptoms after CT-guided RFA for osteoid osteomas. A total of 116 patients were included and the efficacy success rate in the study was 98%. All patients reported immediate pain relief following the procedure, with scores of 0 or 1 on a 10-point visual analog pain scale within 24 hours. The mean duration of follow-up was 23 months and pain relapse was reported in 2 of 108 patients available for follow up. Seven minor complications were reported after the procedure with superficial skin burns as the most common complication (n=4).

Case Series

An observational study by Knudsen et al (2015) evaluated long-term clinical outcomes after CT-guided RFA in patients diagnosed with osteoid osteoma located in the upper and lower extremities. The study population included 52 patients with a typical clinical history and radiologically confirmed osteoid osteoma who received CT-guided RFA treatment from 1998 to 2014 at a Danish university hospital. The clinical outcome was evaluated based on patient-reported outcome measures and medical record review. The response rate was 52 (87%) of 60. After 1 RFA treatment, 46 (88%) of 52 patients experienced pain relief, and 51 (98%) of 52 patients had pain relief after repeat RFA. One patient underwent open resection after RFA. No major complications were reported; four patients reported minor complications including small skin burn, minor skin infection, and hypoesthesia at the needle entry point. In all, 50 (96%) of 52 patients were reported to be "very satisfied" with the RFA treatment.

Rosenthal et al (2003) reported their experience over an 11-year period with 271 RFA procedures for osteoid osteomas in 263 patients. The short-term outcome was evaluated to detect procedure-related problems; by this definition, all procedures were considered technically successful. Long-term clinical success data (defined as being free of pain without additional procedures) were available in 126 patients, with complete clinical success observed in 89%. For procedures performed as the initial treatment, the success rate was 91%.

Section Summary: Osteoid Osteomas

Numerous retrospective studies case series, and systematic reviews of observational data have evaluated RFA for the treatment of painful osteoid osteomas. In a systematic review of thermal ablation techniques, clinical success (pain-free) was achieved in 94% to 98% of patients. Results have indicated that most patients (89%-96%) remained pain-free at longer-term follow-up. Another systematic review reported similar success rates noting an average 8.3% failure rate among patients receiving CT-guided RFA.

Localized RCC

Clinical Context and Therapy Purpose

Radical nephrectomy remains the principal treatment of RCC; however, partial nephrectomy (PN) or nephron-sparing surgery has been shown to be as effective as radical nephrectomy, with

comparable long-term recurrence-free survival rates, in a select group of patients. Alternative therapy such as RFA is of interest in patients with small renal tumors when preservation of renal function is necessary (e.g. in patients with marginal renal function, a solitary kidney, bilateral tumors) and in patients with comorbidities that would render them unfit for surgery. Another consideration would be in patients at high-risk of developing additional renal cancers (eg, von Hippel-Lindau disease).

The purpose of RFA in patients who have localized RCC no more than 4 cm in size is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with localized RCC no more than 4 cm in size. Small renal masses (SRM), defined as 4cm or less, are common findings on diagnostic imaging of the abdomen pelvis. Some of these masses are assessed to be suspicious for malignancy or have been identified by biopsy as a localized RCC. Tumors can be further categorized according to international tumor, nodes, metastasis (TNM) staging where cT1a is a clinically diagnosed tumor ≤ 4cm that is confined to the kidney without any nodal involvement.

Interventions
The therapy being considered is RFA.

Comparators
The following practice is currently being used to treat localized RCC: surgical excision, either total nephrectomy or PN.

Outcomes
The general outcomes of interest are recurrence rates and reduction in rates of renal failure.

Patients should be followed for at least ten years to monitor for tumor recurrence.

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

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

Review of Evidence

Systematic Reviews
In a systematic review and meta-analysis, Yanagisawa et al (2022) compared differential clinical outcomes of patients treated with PN versus those treated with ablation techniques, including RFA, cryoablation, and microwave ablation, for cT1b and cT1a renal tumors. They identified 27 studies

with 13,996 total patients who received either PN or ablation for treatment of their tumors. Investigators found that in both cT1a and cT1b renal tumors, there were no differences in the percent decline of eGFR or in the overall complication rates between PN and ablation therapy. There was also no difference in cancer mortality rates between PN and ablation in patients with either cT1a or cT1b tumors. However, compared to ablation, PN was associated with a lower risk of local recurrence in patients with either tumor type. There was significant heterogeneity across studies, which limits conclusions.

In their systematic review and meta-analysis, Uhlig et al (2019) compared oncologic, perioperative, and functional outcomes for PN) with outcomes for various ablative techniques, including RFA and others, for small renal masses (mean diameter=2.53-2.84 cm). They identified 47 moderate-quality studies, mostly retrospective, published from 2005 to 2017, with a total of 24077 patients. Of these patients, 15238 received PN and 1877 received RFA. The network meta-analysis used PN as the reference point. The overall results indicated that PN had better OS and local control over ablative techniques but it was not significantly better for cancer-related mortality. In addition, ablation had fewer complications and better renal function outcomes. Across the studies included, patients treated by PN tended to be younger with less comorbidities compared with patients receiving thermal ablation—a consideration when assessing the outcomes for survival and local control.

The network meta-analysis used PN as the reference point. The overall results indicated that PN had better OS and local control over ablative techniques, but it was not significantly better for cancer-related mortality. In addition, ablation had fewer complications and better renal function outcomes. Across the studies included, patients treated by PN tended to be younger with less comorbidity compared with patients receiving thermal ablation—a consideration when assessing the outcomes for survival and local control.

In a systematic review and meta-analysis, Katsanos et al (2014) reviewed 1 RCT and 5 cohort studies (n=587) assessing thermal ablation (RFA or microwave) or nephrectomy for small renal tumors (size, 2.5 cm). The local recurrence rate was 3.6% in both groups (relative risk, 0.92; 95% confidence interval [CI], 0.4 to 2.14; p=0.79). Disease-free survival was also similar in both groups up to 5 years (hazard ratio, 1.04; 95% CI, 0.48 to 2.24; p=0.92). However, the overall complication rate was significantly lower in the patients undergoing ablation (7.4%) vs nephrectomy (11.1%; pooled relative risk, 0.55; 95% CI, 0.31 to 0.97; p=0.04).

El Dib et al (2012) conducted a meta-analysis evaluating RFA and cryoablation for small renal masses. Selected were 11 RFA case series (426 patients) and 20 cryoablation case series (457 patients) published through January 2011. The mean tumor size was 2.7 cm (range, 2-4.3 cm) in the RFA group and 2.5 cm (range, 2 to 4.2 cm) in the cryoablation group. Mean follow-up times for the RFA and cryoablation groups were 18.1 and 17.9 months, respectively. Clinical efficacy, defined as cancer-specific survival rate, radiographic success, no evidence of local tumor progression, or distant metastases, did not differ significantly between groups. The pooled proportion of clinical efficacy for RFA was 90% (95% CI, 86% to 93%) and 89% (95% CI, 83% to 94%) for cryoablation.

Table 1: Characteristics of Meta-Analyses Assessing Radiofrequency Ablation for Renal Masses

Study	Dates	Trials	Participants	N (Range	Design Duration	Duration
Uhlig (2018)	2006-2017	47	Patients who had received PN, RFA, CRA, or MWA for small renal masses	24,077 (18-1803)	Prospective, retrospective, 1 RCT	3-82 months

Katsanos 2014	2007-2012	6	6 Patients with small renal tumors receiving RFA or nephrectomy	587 (69-150)	1 RCT, cohort	Up to 6 years
El Dib (2012)	2000-2008	31	Patients who had received RFA or CRA for renal tumors, regardless of size	957	Case series	7 – 45.7 months

CRA: cryoablation; RCT: randomized controlled trial; RFA: radiofrequency ablation; n/a: data not available; MWA: microwave ablation; PN: partial nephrectomy.

Table 2: Results of Select Meta-Analyses Assessing Radiofrequency Ablation for Renal Masses

Study	**Cancer Specific mortality**		**Local Recurrence**		**Complications**		**Renal Function Decline, MD**	
	RFA (IRR)	PN (IRR)	RFA (IRR)	PN (IRR)	RFA (OR)	PN (OR)	RFA	PN
Uhlig, 2018	2.03	1.00	1.79	1.00	0.89	1.00	6.49	0.00
95% CI	0.81 to 5.08		1.16 to 2.76		0.59 to 1.33		2.87 to 10.10	
	RFA (events)	PN (events)	RFA (events)	PN (events)	RFA (events)	PN (events)	RFA (total decline)	PN (total decline)
Yanagisawa (2022)	cT1a: 27 cT1b: 8	cT1a: 113 cT1b: 18	cT1a: 64 cT1b: 32	cT1a: 59 cT1b: 34	cT1a: 126 cT1b: 50	cT1a: 204 cT1b: 62	cT1a: 176 cT1b: 154	cT1a: 217 cT1b: 184
Pooled RR (95% CI)	cT1a: 0.87 (0.57 to 1.31) cT1b: 0.80 (0.32 to 1.98)		cT1a: 0.43 (0.28 to 0.66) cT1b: 0.41 (0.23 to 0.75)		cT1a: 1.34 (0.90 to 2.00) cT1b: 1.08 (0.76 to 1.53)		cT1a: MD, 2.42 (-0.06 to 4.89) cT1b: MD, 0.73 (-3.76 to 5.23)	
I^2 (p-value)	cT1a: 0% (.62) cT1b: 0% (.76)		cT1a: 20% (.23) cT1b: 30% (.20)		cT1a: 63% (.003) cT1b: 22% (.26)		cT1a: 83% (.0004) cT1b: 0% (.71)	

CI: confidence interval; IRR: incidence rate ratio; MD: mean difference in glomerular filtration rate; OR: odds ratio; RFA: radiofrequency ablation; PN: partial nephrectomy.

Randomized Controlled Trials

In an RCT, Liu et al (2016) analyzed the safety and efficacy of the operative effects of percutaneous RFA in early-state RCC vs retroperitoneoscopic radical operation of RCC. There were 35 women and 28 men included; race and ethnicity of participants were not described. The observation group was treated with percutaneous RFA and the control group with a radical retro-peritoneoscopy. A total of 76 clinically confirmed diagnosed cases, from January 2011 to January 2013, with RCC, were randomized to the observation (n=41) or the control (n=35) groups. Operation time, blood loss during operation, length of stay, and incidence complications were lower in the control group ($p<0.05$). Total efficacy, tumor-free survival times, and survival rates did not differ statistically between groups ($p>0.05$), however, percutaneous RFA reduced postoperative recovery time and was associated with fewer complications. Trial limitations included small sample size and the brief duration of follow-up.

Retrospective Studies

Marshall et al (2020) conducted a single-center retrospective evaluation in 100 patients with 125 RCCs who received percutaneous RFA between 2004 and 2015. Median follow-up in the study was 62.8 months. Five-year overall, cancer-specific, and local progression-free survival were 75%, 92%, and 92%, respectively. Ten-year overall, cancer-specific, and local progression-free survival were 32%, 86%,and 92%, respectively. The rate of local tumor progression was higher in patients with tumors >4 cm compared to those with tumors ≤4 cm, but the difference was not statistically

significant (6% vs 13%, p=0.466). The study also noted no significant changes in eGFR from baseline to 2 to 3 years post-procedure (65.2 vs 62.1 mL/min/1.73 m2; p=0.443. The overall complication rate in the study was 9%. Limitations of the study include its retrospective design, lack of a control group, and selection bias where patients selected for RFA over surgical resection likely had worse baseline comorbidity status, which may have negatively impacted OS rates.
Andrews et al (2019) retrospectively evaluated 1798 patients with primary cT1 renal masses who underwent PN, percutaneous RFA, or percutaneous cryoablation between 2000 and 2011 at a single center. For cT1a tumors, 1422 patients were treated, receiving PN (n=1055), RFA (n=180), or cryoablation (n=187). Five-year local recurrence-free survival rates for PN, RFA, and cryoablation were 97.7%, 95.9%, and 95.9%, respectively. Five-year cancer-specific survival rates for PN, RFA, and cryoablation were 99.3%, 95.6%, and 100%, respectively. Propensity score-adjusted OS risk was significantly higher for RFA (hazard ratio [HR], 1.81; 95% confidence interval [CI], 1.35 to 2.44) and cryoablation (HR, 2.03; 95% CI, 1.51 to 2.74) compared to PN. For cT1b tumors, 376 patients were treated, but none received RFA. Limitations of the study include its retrospective design and selection bias arising from whom was treated with PN versus ablation.

A retrospective study by Park et al (2018) compared the mid-term oncologic and functional outcomes of robotic PN with RFA for treating T1a RCC. Using propensity score matching, the study analyzed 63 similar patient cases from each treatment group for changes in tumor location, eGFR preservation, and 2-year recurrence-free survival rate. Preservation of estimated glomerular filtration rate in the robotic PN group was 91.7% and 86.8% of the RFA group (p=0.088), and exophytic and endophytic RCC occurred in 73% (46/63) and 27% (17/63) of the robotic PN group and 52.4% (33/63) and 47.6% (30/63) of the RFA group, respectively. The 2-year recurrence-free survival rate was 100% in the robotic PN group and 95.2% in the RFA group (p=0.029). The mismatching of RCC locations between the robotic PN and RFA groups is a study limitation. Other limitations included the retrospective design, the relatively small sample and the lack of long-term outcomes assessing and kidney function measures.

Dai et al (2017) conducted a retrospective evaluation of 30 patients with 31 central renal tumors who underwent percutaneous RFA between 2005 and 2010 to assess the clinical efficacy and safety of image-guided percutaneous RFA of central RCC with adjunctive pyeloperfusion.15, OS was 96.0% (95% CI, 88.4% to 100.0%) and progression-free survival at 5 years was 80.9% (95% CI, 65.8% to 95.9%). The investigators found that complications were significantly higher for tumors located within 5 mm of the renal pelvis or 0 mm of a major calyx (28.6% vs 4.0%; p<0.05) and major complications occurred in 5 (12.8%) of 39 RFA sessions. They concluded that image-guided percutaneous RFA combined with pyeloper fusion had satisfactory clinical efficacy in the treatment of renal tumor but may be associated with significant major complications. The retrospective design and the small sample base are limitations to this analysis.

Over 10 years, Dvorak et al (2017) retrospectively evaluated the technical success as well as mid-term and long-term efficacy and safety of RFA and microwave ablation with guided CT in 64 patients with small, non-central renal tumors. Ninety-one ablation procedures were performed on 68 tumors, 12 to 60 mm in size. Treatment was successful in 50 (73.5%) tumors; a second procedure was successful in 13 (19.1%) cases; and for the 5 largest tumors (range, 45-60 mm; 7.4%), a third treatment was required. Investigators concluded that percutaneous ablation is safe and effective in treating small, non-central renal tumors of the T1a group. The retrospective study design is the major limitation of this study.

Pantelidou et al (2016) retrospectively compared the oncologic outcomes of RFA with robotic-assisted PN for the treatment of T1 stage RCC.17, Sixty-three cases were included in each treatment group. Baseline renal function for those who received RFA was poorer; and there was an imbalance between groups in the number of patients with tumors in a single kidney (16/63 RFA patients vs 1/63 PN patients; p<0.001). Post procedure renal function decline at 30 days was significantly smaller in the RFA group (-0.8 mL/min/1.73 m2 vs -16.1 mL/min/1.73 m2; p<0.001). The robotic-assisted PN group experienced more minor complications (10/63 vs 4/63, p=0.15) and the RFA group had a higher local recurrence (6/63 vs 1/63, p=0.11). The authors concluded that both RFA and robotic-assisted PN offered good oncologic outcomes for T1 RCC with low morbidity. The retrospective study design, the tertiary center location's specific referral procedures, a loss of follow-up case data, and the heterogeneous patient demographics are study limitations.

A publication by Iannuccilli et al (2016) reported a mean 34.1-months follow-up (range, 1 to 131 months) of RFA with intent to cure in 203 patients with renal tumors. Patients referred for RFA were at high-risk or had refused surgery. Smaller tumors were treated with a single electrode with a 2 or 3 cm active tip. Larger tumors were treated with a cluster electrode with three active tips. Patients were assessed annually for the appearance of residual tumor at the treatment site, and 26 (13%) had residual disease. Treatment effectiveness was 87% during follow-up. The likelihood of recurrence was increased for tumors 3.5 cm or larger, clear cell subtype, and treatment temperature of 70° or less. All-cause mortality increased with increasing tumor size. The median survival was 7 years for patients with tumors less than 4 cm, with 80% survival at 5 years. Major complications, including urinary stricture or urine leak, occurred in eight (3.9%) treatments.

Section Summary: Localized RCC
The evidence on RFA for small renal tumors (≤ 4 cm) includes an RCT, meta-analyses, retrospective and cohort studies, and case series, that have compared RFA with nephrectomy or cryoablation. A 2014 meta-analysis that included 1 RCT and 5 cohort studies found that RFA was as effective as nephrectomy for small renal tumors, with a reduction in complications. Another, more recent, meta-analysis (2019) found that PN was superior to ablative techniques (the study included RFA but also cryoablation and microwave ablation) in overall mortality and local recurrence but not in cancer-specific mortality. It also found fewer complications and improved renal function with ablation. A meta-analysis from 2022 found that PN was superior to ablation (RFA, cryoablation, and microwave ablation) in local recurrence. Overall complications, decline in renal function, and cancer-specific mortality rates did not differ between ablation and PN. The correlation between tumor size and RFA efficacy has been demonstrated by a large case series with a mean 34-month follow-up; it found that residual disease and mortality increased with tumors over 4 cm. Long-term follow up in one single center study found that RFA resulted in similar cancer-specific survival outcomes as PN in patients with cT1a renal tumors.

Primary Pulmonary and Non-pulmonary Tumors

Clinical Context and Therapy Purpose
Surgery is the current treatment of choice in patients with stage I primary non-small-cell lung cancer (NSCLC; stage I includes 1a [T1N0M0] and 1b [T2N0M0]). Approximately 20% of patients present with stage I disease, although this number is expected to increase as a result of screening programs, advances in imaging modalities and widespread use of CT scans for other indications. Postsurgical recurrence rates of stage I NSCLC have been reported as between 20% and 30%, with most occurring at distant sites; locoregional recurrences occur in approximately 12%. Large differences in

survival outcome are observed after surgery in stage I patients, with 5-year OS rates ranging from 77% for small T1 tumors to 35% for large T2 tumors. Untreated, stage I NSCLC has a 5-year OS rate range from 6% to 14%.

Patients with early-stage NSCLC who are not surgical candidates may be candidates for radiotherapy with curative intent. In 2 large retrospective radiotherapy series, patients with the inoperable disease treated with definitive radiotherapy achieved 5-year survival rates of 10% and 27%. In both studies, patients with T1 N0 tumors had better 5-year survival rates of 60% and 32%, respectively.

Stereotactic body radiotherapy has gained more widespread use as a treatment option because it is a high-precision mode of therapy that delivers very high doses of radiation. Two- to 3-year local control rates of stage I NSCLC with stereotactic body radiotherapy have ranged from 80% to 95%. Stereotactic body radiotherapy has been investigated in patients unfit to undergo surgery, with survival rates similar to surgical outcomes.

RFA also is being investigated in patients with small primary lung cancers or lung metastases who are deemed medically inoperable.

The purpose of RFA in patients who have inoperable primary pulmonary tumors or no pulmonary tumors metastatic to the lung is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with inoperable primary pulmonary tumors or non-pulmonary tumors metastatic to the lung.

Interventions
The therapy being considered is RFA.

Comparators
The following practice is currently being used to treat primary pulmonary tumors or non-pulmonary tumors metastatic to the lung: radiotherapy.

Outcomes
The general outcomes of interest are OS, tumor recurrence, and treatment-related adverse events (e.g. pneumothorax). Patients would be followed for at least five years.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Systematic Reviews
In a systematic review of RFA, surgery, and stereotactic body radiotherapy for colorectal cancer (CRC) lung metastases, Schlijper et al (2014) did not identify any randomized trials, and evidence was insufficient to draw conclusions on the comparative effectiveness of these therapies.

In comparative effectiveness review conducted for the Agency for Healthcare Research and Quality, Ratko et al (2013) assessed local nonsurgical therapies for stage INSCLC. In this review, no

comparative RFA studies were identified. Reviewers found that available evidence was insufficient to draw conclusions on the comparative effectiveness of local nonsurgical therapies for NSCLC, including RFA.

In a review of 16 studies, Bilal et al (2012) compared RFA with stereotactic ablative radiotherapy in patients with inoperable early-stage NSCLC. Reviewers found that OS rates for RFA and stereotactic ablative radiotherapy were similar in patients at 1 year (68.2% to 95% vs 81% to 85.7%) and 3 years (36%-87.5% vs 42.7%-56%), all respectively. However, survival rates at 5 years were lower with RFA (20.1%-27%) than with stereotactic body radiotherapy (47%). These findings were drawn from comparisons of results from uncontrolled case series and retrospective reviews.

In an evidence-based review by Chan et al (2011), 46 studies on RFA for lung tumors were evaluated, which included 2905 ablations in 1584 patients with a mean tumor size of 2.8 cm.22, Twenty-four studies reported rates of local recurrence, which occurred in 282 (12.2%) cases at a mean follow-up of 13 months (range, 3-45 months). Primary lung cancer rates of local recurrence did not differ significantly (22.2%) from metastases (18.1%). Twenty-one studies reported mean OS rates of 59.4% at a mean follow-up of 17.7 months. The mean cancer-specific survival rate was 82.6%, at a mean follow-up of 17.4 months. The mean overall morbidity was 24.6% and most commonly included pneumothorax (28.3%), pleural effusion (14.8%), and pain (14.1%). Mortality related to the RFA procedure was 0.21%, overall.

Prospective Studies
Huang et al (2011) prospectively followed 329 consecutive patients treated with RFA for lung tumors (237 primary, 92 metastatic). Complications were experienced by 34.3% (113) of patients, most commonly pneumothorax (19.1%). OS rates at 2 and 5 years were 35.3% and 20.1%, respectively. The risk of local progression did not differ significantly for tumors less than 4 cm but was statistically significant for tumors greater than 4 cm.

Zemlyak et al (2010) prospectively compared 3 treatments for medically inoperable patients with stage I NSCLC: RFA in 12 patients, sublobar resection in 25 patients, and percutaneous cryoablation in 27 patients.24, At 3-year follow-up, survival rates did not differ significantly between groups. OS and cancer-specific 3-year survival rates were 87.5%, 87.1%, and 77% and 87.5%, 90.6%, and 90.2%, respectively, in the 3 groups. The authors concluded that all three procedures were reasonable options for treating lung tumors in patients unfit for major surgery. The authors also noted that because surgeons chose the treatment option with patient input for this study, selection bias limited study interpretation.

In a prospective, single-arm, multicenter trial from 7 centers in Europe, the U. S., and Australia, Lencioni et al (2008) reported the technical success, safety, response of tumors, and survival in 106 patients with 183 lung tumors.25, All patients were considered unsuitable for surgery and unfit for radiotherapy or chemotherapy. Tumors measured less than 3.5 cm (mean, 1.7 cm) and included patients with NSCLC (n=22), colorectal metastases (n=41), and other metastases (n=16). The technical success rate was 99%. Patients were followed for 2 years, and a confirmed complete response lasting at least 1 year was observed in 88% of assessable patients, with no differences in response rate between those with primary and metastatic tumors. OS rates in patients with NSCLC were 70% at 1 year (95% CI, 51% to 83%; cancer-specific survival, 92% [78% to 98%]), and 48% at 2 years (95% CI, 30% to 65%; cancer-specific survival, 73% [54% to 86%]). OS rates in patients with metastatic CRC were 89% at 1 year (95% CI, 76% to 95%; cancer-specific survival, 91% [78% to 96%])

and 66% at 2 years (95% CI, 53% to 79%; cancer-specific survival 68% [54% to 80%]). OS rates in patients with other metastases were 92% at 1 year (95% CI, 65% to 99%; cancer-specific survival, 93% [67% to 99%]) and 64% at 2 years (95% CI, 43% to 82%; cancer-specific survival, 67% [48% to 84%]). Patients with stage I NSCLC (n=13) had an OS rate of 75% (95% CI, 45% to 92%) at 2 years (cancer-specific, 92%; 95% CI, 66% to 99%). No differences in response rates were seen between patients with NSCLC or lung metastases.

Zhu et al (2009) assessed the incidence and risk factors of various pulmonary neoplastic complications after RFA.26, They prospectively evaluated the clinical and treatment-related data for 129 consecutive percutaneous RFA treatment sessions for 100 patients with inoperable lung tumors. There was no postprocedural mortality. The overall morbidity rate was 43% (55/129). The most common adverse event was a pneumothorax, occurring in 32% (41/129) of treatment sessions. Other significant complications included pleuritic chest pain (18%), hemoptysis (7%), pleural effusions (12%), and chest drain insertion (20%). Both univariate and multivariate analyses identified more than two lesions ablated per session as a significant risk factor for overall morbidity, pneumothorax, and chest drain insertion. The length of the ablation probe trajectory greater than 3 cm was an additional independent risk factor for overall morbidity and pneumothorax.

Pennathur et al (2009) reported on 100 patients with inoperable lung tumors. Forty-six patients had primary lung neoplasm, 25 had recurrent cancer, and 29 had pulmonary metastases. The mean follow-up was 17 months. Median OS for all patients was 23 months. The probability of 2-year OS for primary lung cancer patients, recurrent cancer patients, and metastatic cancer patients were 50% (95% CI, 33% to 65%), 55% (95% CI, 25% to 77%), and 41% (95% CI, 19% to 62%), respectively.

Section Summary: Primary Pulmonary and Non-pulmonary Tumors
The evidence on RFA for primary NSCLC and non-pulmonary tumors metastatic to the lung includes prospective and observational studies and systematic reviews of those studies. No RCTs identified compared treatment approaches. For inoperable lung tumors, a multicenter study found that RFA for tumors less than 3.5 cm can lead to a complete response in as many as 88% of patients for at least 1 year. Two-year survival has been reported to range from 41% to 75% in case series. Survival at one and two years appears to be similar, following treatment with RFA or stereotactic ablative radiotherapy in patients with inoperable lung tumors. Survival rates at 5 years were lower with RFA (20.1% to 27%) than with stereotactic ablative radiotherapy (47%), but this finding was drawn from comparisons of uncontrolled case series and retrospective reviews. Prospective comparison in an RCT would permit greater certainty for this finding but the studies are consistent with some effect of RFA on lung tumors.

Breast Tumors
Clinical Context and Therapy Purpose
The treatment of small cancers of the breast has evolved from total mastectomy to more conservative treatment options such as lumpectomy, with more acceptable cosmetic outcomes and preservation of the breast. The selection of the surgical approach balances the patient's desire for breast conservation and the need for tumor-free margins in resected tissue. Minimally invasive nonsurgical techniques such as RFA are appealing if they can produce local control and survival equivalent to breast-conserving surgical alternatives. Nonsurgical ablative techniques pose difficulties such as the inability to determine tumor size, complete tumor cell death, and local recurrence. Additionally, RFA can burn the skin and cause damage to muscle, possibly limiting use in patients with tumors near the skin or chest wall.

The purpose of RFA in patients who have breast tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with breast tumors.

Interventions
The therapy being considered is RFA.

Comparators
The following practices are currently being used to make decisions about managing breast cancer: radiotherapy and surgical excision.

Outcomes
The general outcomes of interest are tumor recurrence, reduction in medication, and treatment-related adverse events.

Patients would be followed for up to five years.

Study Selection Criteria

Methodologically credible studies were selected using the principles described in the first indication.

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

Review of Evidence
Systematic Reviews
Xia et al (2021) conducted a systematic review and meta-analysis of studies assessing RFA in patients with breast cancer and tumors that were 2 cm or smaller. The primary endpoints of interest were technical success rate, complete ablation rate, and rate of complications. A total of 17 studies were identified, which accounted for 399 patients (401 lesions). Technical success rates ranged from 86.67% to 100% in the included studies; the pooled technical success rate was 99% (95% CI, 98% to 100%). After RFA, the majority of patients underwent surgical tumor excision (65.74%, 261/397). The pooled complete ablation rate was 98% (95%CI, 97% to 100%). The complication rate in the entire cohort was 6.8%; the most common complications were skin burns (2%), breast inflammation (1.5%), and infections (1%). The pooled complications rate was 2% (95% CI, 1% to 4%). Local recurrence was reported in 10 studies (232 cases); there was no local recurrence reported after a median follow-up of 27 months in these patients. The authors noted that prospective studies evaluating the use of RFA alone are needed to validate the place in therapy.

Peek et al (2017) conducted a systematic review and meta-analysis of all studies evaluating the role of ablative techniques in the treatment of breast cancer published between 1994 and 2016. Selection criteria included at least 10 patients with breast cancer treated with RFA, high-intensity ultrasound, or cryo-, laser, or microwave ablation; 63 studies (n=1608) were identified through PubMed and MEDLINE library databases. Fifty studies reported complete ablation, and RFA had the highest rate of complete ablation (87.1% [491/564]) as well as the shortest treatment time (15.6 minutes). A major limitation of this systematic review was the authors' inability to perform a comparative meta-analysis due to the inclusion of only four RCTs and one retrospective analysis that compared two or more of techniques. There was also considerable heterogeneity across included studies.

Zhao and Wu (2010) conducted a systematic review of 38 studies on ablation techniques for breast cancer treatment published from 1994 to 2009. Nine studies focused on RFA. Reviewers included small tumors ranging in size from 0.5 to 7 cm. Tumor resection was performed immediately after ablation or up to four weeks after RFA. Complete coagulation necrosis rates of 76% to 100% were reported. The results suggested RFA for breast cancer tumors is feasible but further studies with longer follow-up on survival, tumor recurrence, and cosmetic outcomes would be needed to establish clinical efficacy.

In another review, Soukup et al (2010) examined 17 studies on RFA for the treatment of breast tumors and found RFA is feasible. Even though few adverse events and complications occurred with breast RFA, incomplete tumor ablation remains a concern.

Clinical Studies

Retrospectively, Ito et al (2018) studied the safety and efficacy of percutaneous RFA of breast carcinomas in 386 patients from 10 institutions treated with RFA between 2003 and 2009. Race and ethnicity of participants were not described. Patients were followed for a median of 50 months and ipsilateral breast tumor recurrence was more frequent in patients with initial tumor sizes of 2 cm or more (10% [3/30]) than those with initial tumors 2 cm or less (2.3% [8/355]; p=0.015). Ipsilateral breast tumor recurrence rates 5 years after RFA were 97%, 94%, and 87% in patients with initial tumor sizes of 1 cm or less, 1.1 to 2.0 cm, and greater than 2 cm, respectively. The authors concluded that RFA was safe for tumors of 2 cm or less. The retrospective design and lack of data on ipsilateral breast tumor recurrence for different types of chemotherapy and endocrine therapy and analyses to ascertain whether adjuvant chemotherapy or endocrine therapy influenced outcomes are the limitations of this study.

The efficacy and safety of using ultrasound guided RFA for multiple breast fibroadenoma as an alternative to surgical resection were retrospectively analyzed by Li et al (2016). From 2014 to 2016, 65 patients with 256 nodules were treated with ultrasound guided RFA and complete ablation was achieved for 251 nodules (98.04%) after the first month of treatment; after the first and third months, tumor volume overall was reduced by 39.06% and 75.99%, respectively. The study reported minimal to no complications such as skin burns, hematoma, or nipple discharge. The retrospective design and short follow-up time limited the conclusions drawn from this study.

Wilson et al (2012) reported on 73 patients with invasive breast cancer who had a lumpectomy followed immediately by RFA to the lumpectomy bed. The average breast tumor size was 1.0 cm (range, 0.2-2.6 cm) and follow-up averaged 51 months. Disease-free survival was 100%, 92%, and 86% at 1, 3, and 5 years, respectively. One patient had tumor recurrence within 5 cm of the

lumpectomy site, and three patients had ipsilateral breast recurrences. Race and ethnicity of participants were also not described.

In a phase 1/2 study reported by Kinoshita et al (2011), 49 patients were treated with RFA for breast tumors (mean size, 1.7 cm) followed immediately with surgical resection. Complete ablation was achieved in 30 (61%) patients. The complete ablation rate increased to 83% in 24 patients with tumor sizes of 2 cm or less in diameter. Adverse events related to the procedure included three muscle and two skin burns.

Imoto et al (2009) reported on a series of 30 patients with T1N0 breast cancer who had sentinel node biopsy followed by RFA and breast-conserving surgery. Twenty-six patients showed pathologic degenerative changes in tumor specimens, and, in 24 of 26 cases, tumor cell viability was diagnosed. Two patients had skin burns, and seven had muscle burns related to RFA.

In a 2-stage, phase 2 clinical trial reported by Garbay et al (2008), patients with histologically confirmed noninflammatory and 3 cm or less ipsilateral breast tumor recurrence were treated with RFA followed by mastectomy. The study was ended early due to lack of efficacy of the technique tested.

Section Summary: Breast Tumors
Systematic reviews, retrospective studies, and observational studies have reported varied and incomplete ablation rates as well as concerns about post ablation tumor cell viability. Long-term improvements in health outcomes have not been demonstrated. Additionally, available studies have not compared RFA with conventional breast-conserving procedures. For small breast tumors, further prospective study, with long-term follow-up, is needed to determine whether RFA can provide local control and survival rates compared with conventional breast-conserving treatment.

Benign Thyroid Nodules

Clinical Context and Therapy Purpose
Surgical resection is the primary treatment choice for medically unresponsive, symptomatic benign thyroid tumors and thyroid carcinomas. However, techniques for ablation of thyroid tumors (eg, RFA, microwave ablation) are being investigated.

The purpose of RFA in patients who have benign thyroid tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with large or symptomatic benign thyroid tumors. Patients with a benign cytology diagnosis or those very unlikely to be malignant (eg, purely cystic nodule) should undergo surveillance with the frequency determined by the level of suspicion for a missed malignancy. Medical or surgical intervention is considered if the nodules are large (> 4 cm), causing compressive or structural symptoms, or if there is clinical concern.

Interventions

The therapy being considered is RFA, which is administered in an outpatient setting by oncologists and radiologists.

Comparators
The following practices are currently being used to treat large or symptomatic benign thyroid tumors in the United States: percutaneous ethanol injection **(PEI):** ~~radiotherapy~~ and surgical excision, which are administered in an outpatient or hospital setting by oncologists, radiologists, and surgeons.

Outcomes
The general outcomes of interest are a reduction in nodule volume, hyper- and hypothyroidism, and treatment-related adverse events (e.g. voice changes).

Patients would be followed for at least five years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Cho et al (2020) evaluated the efficacy of thermal ablation (RFA and laser ablation) for the treatment of benign thyroid nodules. The analysis demonstrated long-term maintenance (up to 36 months) of volume reduction. Further, RFA was found to be superior to laser ablation. The volume reduction rate for RFA at last follow up was 92.2%, whereas in the laser ablation group, the volume reduction rate peaked at 12 months (52.3%) and was at 43.3% at last follow up.

To evaluate the efficacy of RFA for the treatment of benign thyroid nodules, Chen et al (2016) conducted a systematic review and meta-analysis and found that RFA was associated with a significant decrease in nodule volume at months 1, 3, 6, 12, and last follow-up.

Fuller et al (2014) reported on a systematic review of studies on RFA for benign thyroid tumors. After RFA, statistically significant improvements were reported in combined symptom improvement and cosmetic scores on the 0 to 6 scale (mean, -2.96; 95% CI, -2.66 to -3.25), and withdrawal from methimazole (odds ratio, 40.34; 95% CI, 7.78 to 209.09). Twelve adverse events were reported, two of which were considered significant but did not require hospitalization.

Table 3 includes a comparison of studies included in the systematic reviews; the analysis by Cho et al (2020) contains the fewest number of included studies as a minimum follow up duration of 3 years was required for inclusion. Table 4 summarizes the characteristics of the systematic reviews and Table 5 contains the available results for nodule size reduction and complication rates. All of the systematic reviews are limited by high heterogeneity, inclusion of mostly single-center retrospective

and/or noncontrolled studies, and generalizability concerns as included studies were mainly conducted in the Republic of Korea and Italy. They are further limited by a lack of comparison to surgical excision or PEI.

Table 3: Comparison of Meta-Analyses Assessing Radiofrequency Ablation for Benign Thyroid Nodules

Study	Cho (2020)	Chen (2016)	Fuller (2014)
Aldea Martinez 2019	•		
Deandrea 2019	•		
Jung 2018	•		
Sim 2017	•		
Cesareo 2015		•	
Sung 2015		•	
Che 2015		•	
Ugurlu 2015		•	
Ji Hong 2015		•	
Valcavi 2015		•	
Bernardi 2014		•	
Turtulici 2014		•	
Yoon 2014		•	
Lim 2013	•	•	
Ha 2013		•	
Sung 2013		•	•
Huh 2012			•
Faggiano 2012		•	•
Jang 2012			•
Kim 2012			•
Baek 2010		•	•
Lee 2010		•	
Spiezia 2009		•	•
Jeong 2008		•	
Deandrea 2008		•	•
Kim 2006		•	•

Table 4: Characteristics of Meta-Analyses Assessing Radiofrequency Ablation for Benign Thyroid Nodules

Study	Date	Trials	Participants	N (range)	Design	Duration
Cho	2010-2019	12	Patients with a benign thyroid nodule treated with thermal ablation (RFA [5 studies] or laser [7 studies])	1208 (24-276)	2 prospective and 10 retrospective cohorts	At least 3 years
Chen 2016	2006-2016	20	Patients with a benign thyroid nodule treated with RFA	1090 (11-236)	Prospective and retrospective cohorts	Varied, 6-49.4 months
Fuller 2014	2006-2013	9	Patients with benign thyroid nodule treated with RFA	284 (15-94)	Prospective studies – 5 observational, 4 randomized trials	Varied 3-12 months

Table 5: Key Results of Meta-Analyses Assessing Radiofrequency Ablation for Benign Thyroid Nodules

Study	Reduction in nodule size from baseline	Complication rate

Cho – 2020	Relative volume reduction, VRR	
Total N, nodules patients	695 (680)	695 (680)
Pooled effect (95% Ci)	6 mo: 64.5% (56.1% to 72.1%) 12 mo: 76.9% (65% to 85.7%) 24 mo: 80.1% (66.4% to 89.2%) 36 mo: 80.3% (66% to 89.5%)	4.6%
I^2 (p)	73.7% to 95.9%	
Chen 2016	Absolute volume reduction, SMD	
Total N, nodule (patients)	1406 (1090)	
	1 mo: 0.83 (0.47 to 1.19) 3 mo: 1.31 (0.76 to 1.85) 6 mo: 1.25 (0.90 to 1.59) 12 mo: 4.16 (2.25 to 6.07)	
I^2 (p)	90.3% to 98.7%	
Fuller 2014	Absolute volume reduction, SMD (follow up time frame not specified)	
Total N, nodule (patients)	284 (276)	
Pooled effect (95% CI)	-9.77 mL (-13.83 to -5.72)	
I^2 (p)	98% (<0.00001)	

CI: confidence interval; SMD: standard mean difference; VRR: volume reduction rate.

Section Summary: Benign Thyroid Tumors

Evidence on the treatment of benign thyroid nodules includes randomized and nonrandomized trials, case series, and systematic reviews of these studies. Systematic reviews have demonstrated that RFA results in a significant reduction in thyroid nodule size with a 2020 review showing that these changes remain durable through at least 36 months. Complication rates are generally low but include voice changes. The data are limited by significant heterogeneity in meta-analyses, a lack of generalizability to populations outside Republic of Korea and Italy, and a lack of comparators more relevant to practice in the United States.

Miscellaneous Solid Tumors

Clinical Context and Therapy Purpose

RFA has been investigated for use in individuals with different lesions in different anatomic sites. These anatomic sites include but are not limited to, thyroid, pancreas, and head and neck.

In patients with head and neck cancer with recurrent disease, surgical salvage attempts are poor in terms of local control, survival, and QOL; further, these recurrent tumors are often untreatable with standard salvage therapies. Palliative chemotherapy or comfort measures may be offered. The safety and efficacy of RFA have been investigated as an option for palliative treatment in these situations.

The purpose of RFA in patients who have miscellaneous solid tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with miscellaneous solid tumors (e.g. head and neck, thyroid cancer, pancreas).

Interventions

The therapy being considered is RFA.

Comparators

The following practices are currently being used to treat miscellaneous solid tumors: surgical excision or other local treatments specific to the tumor type.

Outcomes

The general outcomes of interest vary by disease state but include OS, tumor recurrence, and reductions in pain.

Patient follow-up will vary by disease state.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Thyroid Cancer

Kim et al (2015) reported on a comparative review of 73 patients with recurrent thyroid cancer smaller than 2 cm who had been treated with RFA (n=27) or repeat surgery (n=46).43, RFA was performed in cases of patient refusal to undergo surgery or poor medical condition. Data were weighted to minimize potential confounders. The 3-year recurrence-free survival rates were similar for RFA (92.6%) and surgery (92.2%, p=0.681). Posttreatment hoarseness rate did not differ between the RFA (7.3%) and surgery (9.0%) groups. Posttreatment hypocalcemia occurred only in the surgery group (11.6%).

Head and Neck Cancer

Owen et al (2011) reported on RFA for 13 patients with recurrent and/or unresectable head and neck cancer who failed curative treatment. Median patient survival was 127 days. While the stable disease was reported in eight patients after RFA, and QOL scores improved, three deaths occurred (one carotid hemorrhage, two strokes).

A case series of RFA for 14 patients with recurrent advanced head and neck malignancies was reported by Brook et al (2008). Tumor targeting and electrode deployment were successful in all cases, and four of six patients who completed QOL assessments showed improvement. Three major complications (in 27 [11%] applications) occurred 7 days to 2 weeks post procedure. They included stroke, carotid artery rupture leading to death, and threatened carotid artery rupture with subsequent stroke. Retrospective analysis of intraprocedural CT scans revealed that the retractable electrodes were within 1 cm of the carotid artery during ablation in these cases.

A case series by Owen et al (2004) showed that palliative CT-guided RFA provided subjective

improvement with regard to pain, appearance, and function in 12 patients who had recurrent and advanced head and neck malignancies and were not candidates for radiotherapy or surgery. The procedure appeared reasonably safe and feasible for this indication.

Uterine Myomas

A prospective observational study by Rey et al (2019) assessed the effectiveness of transvaginal ultrasound guided RFA of myomas in reducing tumor volume and eliminating metrorrhagia associated with myomas. The study included 205 women with symptomatic type II/III uterine submucosal or intramural cavity-distorting myomas undergoing RFA. The preoperative mean standard deviation volume of the myomas was 122.4 (182.5) cm3 (95% CI, 82.1 to 162.8). Mean myoma volume decreased significantly at 1 (85.2 [147.9] cm3; p=0.001), 3 (67.3 [138.0] cm3; p=0.001), 6 (59.3 [135.3] cm3; p=0.001, and 12 months (49.6 [121.4] cm3; p=0.001). At 12 months, the mean volume reduction was 60% compared with preoperative volume. All patients returned to normal menstruation at a mean follow-up of 3 months and 12 months. Of the 205 patients, 201 (98.04%) were satisfied with the procedure. The investigators conceded that a larger population with a longer follow-up is needed but their study suggests that transvaginal ultrasound guided RFA of myomas is effective and safe for treating select patients with metrorrhagia secondary to myomas.

In a large series, Yin et al (2015) evaluated the effectiveness and safety of RFA for uterine myomas in a 10-year retrospective cohort study. From 2001 to 2011, a total of 1216 patients treated for uterine myomas were divided into 2 groups. Group A consisted of 476 premenopausal patients (average age, 36 years) who had an average of 1.7 myomas with an average diameter of 4.5 cm. Group B consisted of 740 menopausal patients (average age, 48 years) with an average of 2.6 myomas with an average diameter of 5.0 cm. Patients were followed for a mean of 36 months. At 1, 3, 6, 12, and 24 months after RFA, the average diameters of myomas in group A were 3.8, 3.0, 2.7, 2.4, and 2.2 cm, respectively; 48% (227/476) of patients had a residual tumor at 12 months. In group B, myoma diameters were 4.7, 3.7, 3.3, 2.3, and 2.3 cm, respectively; 59% (435/740) of patients had trace disease at 12 months. Three months after RFA treatment, myoma volumes were significantly reduced in both groups ($p<0.01$), although group B had a higher rate of residual tumor 12 months after RFA than group A ($p<0.05$). Clinical symptoms and health related QOL were significantly improved after RFA in both groups. The postoperative recurrence rate of uterine myomas was significantly higher in group A at 10.7% (51/476) than in group B at 2.4% (18/740; $p<0.05$).

Adrenal Tumors

Liu et al (2020) retrospectively evaluated the clinical outcomes of percutaneous ultrasound guided RFA in the treatment of adrenal metastasis as compared to adrenalectomy.55, Of the 60 patients included, 29 received RFA and 31 received adrenalectomy. The first technical success rate for RFA was 72.4%; 5 of the 8 patients had a repeat RFA and 4 of those achieved a complete response. In the adrenalectomy group, all patients achieved a R0 resection. Major complications were reported in 1 patient in the RFA group (ventricular fibrillation) and 2 patients in the adrenalectomy group (ascites, surgical site infection). The 1-, 2-, and 3-year local tumor progression rates after RFA were 17.1%, 30.9% and 44.7%, respectively, compared to 6.5%, 6.5% and 6.5% in adrenalectomy group ($p=0.028$). There was no significant difference between groups for mean OS (2.3 ± 0.3 years for RFA and 3.9 ± 0.6 years for adrenalectomy, $p=0.057$). Limitations of the study include its retrospective design, potential selection bias on which patients received each treatment, and a high prevalence of patients with adrenal metastasis secondary to hepatocellular carcinoma, which exceeded the expected number of cases based on global prevalence rates.

Liu et al (2016) retrospectively compared laparoscopic adrenalectomy with CT-guided percutaneous RFA for the treatment of aldosterone-producing adenoma, evaluating short-term and long-term outcomes of normalized aldosterone-to-renin ratio, hypokalemia, and hypertension.13, Of 63 patients, 27 were in the laparoscopic adrenalectomy group and 36 were in the RFA group. Primary aldosteronism was seen in 33 of 36 patients treated with RFA and all 27 who had laparoscopic adrenalectomy (p=0.180), within a median follow-up of 5 to 7 years. RFA was associated with faster recovery post procedure, but hypertension was less frequently resolved using RFA (13/36 patients) compared with laparoscopic adrenalectomy (19/27 patients; p=0.007). The use of posture test and CT for subtype classification of primary aldosteronism is the major limitation of the study, as well as the retrospective design.

Retrospectively, Yang et al (2016) compared the efficacy and safety of RFA with laparoscopic adrenalectomy in treating aldosterone-producing adenoma of the adrenal gland.48, From 2009 to 2013, 25 patients diagnosed with unilateral adrenal aldosterone-producing adenoma and similar tumor size (<25 mm) were allocated to a control group (n=18) that underwent laparoscopic adrenalectomy and a test group (n=7) that underwent CT-guided percutaneous RFA. Complete tumor ablation on follow-up CT scan and normalization of serum aldosterone-to-renin were the primary outcomes compared in this study. Success in the RFA group reached 100% within 3 to 6 months, compared with 94.4% in the laparoscopic adrenalectomy group, and normalization ability was statistically equivalent in both groups. The study's retrospective design and small sample are the main limitations of this study.

Operable Nonpulmonary Tumors Metastatic to the Lung

Hasegawa et al (2020) conducted a prospective, single-arm, multicenter study to evaluate the efficacy of RFA in patients with surgically resectable CRC lung metastases measuring 3 cm or smaller. A total of 70 patients with CRC and 100 lung metastases were enrolled.

All tumors were considered technically resectable, but all not all patients were clinically able to undergo surgery. A total of 85 initial RFA sessions were performed for 100 target lung metastases. The 3-year OS rate after RFA was 84%. Primary and secondary technical success rates for RFA were 96% and 100%, respectively. Over a mean follow-up of 57 ± 32 months, local tumor progression was found in 6 patients (9%) at 6 to 19 months after the initial RFA. The 3-year progression-free survival rate was 41%. Grade 2 pneumothorax occurred after 18 of the 88 RFA sessions. The study is limited by its lack of a comparator arm.

Other Tumors

A single-arm, retrospective, paired-comparison study by Locklin et al (2004) evaluated the short-term efficacy of RFA in reducing pain and improving function in patients with unresectable, painful soft tissue neoplasms recalcitrant to conventional therapies. Patients had tumors located in a variety of sites including chest wall, pelvis, breast, perirectal, renal, aortocaval, retroperitoneal, and superficial soft tissues. All had failed conventional methods of palliation or experienced dose-limiting adverse events from pain medication. Although not all Brief Pain Inventory scores were statistically significant, all mean scores trended down over time after ablation. Complications from RFA were minor or insignificant in all but one patient who had skin breakdown and infection of an ablated superficial tumor site.

Additional research has addressed the use of RFA in solid malignancies and in the pancreas. A systematic review by Rombouts et al (2015) has examined studies of ablative therapies, including RFA, in patients with locally advanced pancreatic cancer. No RCTs were identified, and conclusions limited by the sparse evidence available on RFA in this setting.

Stereotactic radiofrequency thermocoagulation for epileptogenic hypothalamic hamartomas was described in a retrospective analysis by Kameyama et al (2009) who evaluated 25 patients with gelastic seizures (a rare type of seizure). Other seizure types were exhibited in 22 (88.0%) patients, precocious puberty in 8 (32.0%), behavioral disorder in 10 (40.0%), and mental disability in 14 (56.0%). Gelastic seizures resolved in all but two patients. Complete seizure freedom was achieved in 19 (76.0%) patients. These patients experienced resolution of all seizure types and behavioral disorder and also demonstrated intellectual improvement.

Preliminary results of endoscopic RFA of rectosigmoid tumors have been described by Vavra et al (2009). Twelve patients were treated with the Endoblate RFA device, with ten patients having surgical resection after ablation. Histology of the resected specimens showed that, on average, 82% (range, 60% to 99%) of the tumor mass was destroyed in the ablation zone.

Small case series on RFA for colorectal and rectal carcinoma have demonstrated a debulking role for RFA. These case series did not permit comparison with an available alternative.

Section Summary: Miscellaneous Solid Tumor
Evidence on the use of RFA to treat other types of solid tumors consists of a small number of case series, prospective studies, or retrospective comparative studies. Reporting on outcomes is limited.

The evidence base does not support a conclusion on the effects of RFA for the tumor types included in this evidence review.

Summary of Evidence
For individuals who have painful osteolytic bone metastases who have failed or are poor candidates for standard treatments who receive RFA, the evidence includes a prospective cohort study and case series. Relevant outcomes are symptoms, change in disease status, quality of life (QOL), medication use, and treatment-related morbidity. A prospective cohort study and case series have shown clinically significant pain relief (defined as a decrease of 2 units from baseline on the Brief Pain Inventory scale) or reduction in opioid use following treatment of painful osteolytic metastases. A multicenter, prospective study reported significant reductions in pain through the 6-month follow-up period, with 59% of patients achieving immediate improvement in pain within 3 days of RFA. The population is comprised of patients with few or no treatment options, for whom short-term pain relief is an appropriate clinical outcome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have painful osteoid osteomas who receive RFA, the evidence includes numerous observational studies and systematic reviews of these studies. The relevant outcomes are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. In a systematic review of thermal ablation techniques, clinical success (pain-free) was achieved in 94% to 98% of patients. Most patients (89% to 96%) remained pain-free when assessed during longer-term follow-up. Another systematic review reported similar success rates noting an average 8.3% failure rate among patients receiving computed tomography guided RFA. Although no randomized trials of RFA for osteoid osteomas have been performed, the uncontrolled studies have demonstrated RFA can provide adequate symptom relief with minimal complications, for a population for whom short-

term symptom relief and avoidance of invasive procedures are appropriate clinical outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized RCC that is no more than 4 cm in size who receive RFA, the evidence includes a randomized controlled trial (RCT), numerous observational studies, and systematic reviews of these studies. The relevant outcomes are overall survival (OS), change in disease status, QOL, and treatment-related morbidity. A recent meta-analysis that included only an RCT and cohort studies found that RFA was as effective as nephrectomy for small renal tumors, with a reduction in complications. Another recent meta-analysis found that partial nephrectomy was superior to ablative techniques (the study included RFA but also cryoablation and microwave ablation) in overall mortality and local recurrence but not in cancer-specific mortality. It also found fewer complications and improved renal function with ablation. A meta-analysis from 2022 found that PN was superior to ablation (RFA, cryoablation, and microwave ablation) in local recurrence. Overall complications, decline in renal function, and cancer-specific mortality rates did not differ between ablation and PN. Although inconsistent, the evidence does suggest that, for small renal tumors, RFA may result in a similar rate of disease progression with a lower complication rate than nephrectomy. However, comparative trials are needed to determine with greater certainty the effects of these treatments in the same patient population.
The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inoperable primary pulmonary tumors or non-pulmonary tumors metastatic to the lung who receive RFA, the evidence includes prospective observational studies and systematic reviews of these studies. The relevant outcomes are OS, change in disease status, QOL, and treatment-related morbidity. A multicenter study found that for tumors less than 3.5 cm in size, RFA can lead to a complete response in as many as 88% of patients for at least 1 year. Two-year survival rates have been reported to range from 41% to 75% in case series, with 5-year survival rates of 20% to 27%. In general, the evidence suggests that RFA results in adequate survival and tumor control in patients who are not surgical candidates, with low morbidity rates. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have breast tumors who receive RFA, the evidence includes observational studies and systematic reviews of these studies. The relevant outcomes are OS, change in disease status, QOL, and treatment-related morbidity. Evidence has reported varied and incomplete ablation rates with concerns about post-ablation tumor cell viability. Long-term improvements in health outcomes have not been demonstrated. Additionally, available studies do not permit comparisons with conventional breast-conserving procedures. Further prospective studies, with long-term follow-up, should focus on whether RFA of the breast for small tumors can provide local control and survival rates compared with conventional breast-conserving treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have benign thyroid tumors who receive RFA, the evidence includes RCTs, prospective studies, case series, and systematic reviews of these studies. Relevant outcomes are symptoms, change in disease status, QOL, medication use, and treatment-related morbidity. Systematic reviews have demonstrated that RFA results in a significant reduction in thyroid nodule size with a 2020 review showing that these changes remain durable through at least 36 months. Complication rates are generally low but include voice changes. The data are limited by significant

heterogeneity in meta-analyses, a lack of generalizability to populations outside Republic of Korea and Italy, and a lack of comparators more relevant to practice in the United States. Further studies comparing RFA to percutaneous ethanol injection or surgery would be more informative in determining the potential utility of RFA in patients with symptomatic or large benign thyroid tumors as these are the recommended treatment options per the American Thyroid Association. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have miscellaneous tumors (e.g. head and neck, thyroid cancer, pancreas) who receive RFA, the evidence includes a few case series, prospective observational studies, and retrospective comparative studies. The relevant outcomes are OS, change in disease status, QOL, and treatment-related morbidity. There is a limited evidence base for these tumor types. Reporting on outcomes or comparisons with other treatments is limited. These studies do not permit conclusions on the health benefits of RFA. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

VI. 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

2010 Input

In response to requests, input was received from 2 physician specialty societies (4 reviewers) and 2 academic medical centers (4 reviewers) while this policy was under review in 2010. Input was similar to that received in 2009, except support for the use of radiofrequency ablation (RFA) to treat lung tumors was declined (only 1 respondent indicated this was an option in tumors metastatic to lung). One respondent also indicated a potential use for adrenal tumors. Input supported RFA for localized RCC no more than 4 cm in size when preservation of kidney function is necessary, and a standard surgical approach would likely substantially worsen kidney function or when the patient is not considered a surgical candidate.

2009 Input

In response to requests, input was received from 1 physician specialty society (4 reviews) and from 2 academic medical centers (3 reviews) while this policy was under review in 2009. All reviewers supported the use of RFA in the treatment of painful bone metastases that have failed standard treatment and in the treatment of osteoid osteomas. Reviewers were divided over the use of RFA for lung tumors, although several agreed that, while it may be useful in a select population of patients, it should be used in the clinical trial setting. Reviewers were also split with regard to RFA in the treatment of renal tumors, with some supporting its use in a select population of patients. With the exception of one disagreement and one nonresponse, the reviewers agreed to the investigational statement on the use of RFA in all other tumors outside the liver that are addressed in this policy.

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 Chest Physicians

The American College of Chest Physicians (2013) guidelines on the treatment of stage I and II non-small-cell lung cancer (NSCLC) have indicated RFA has been used effectively in clinical stage I NSCLC. Therefore, in medically inoperable patients, peripheral NSCLC tumors less than 3 cm may be treated with RFA. The College also collaborated with the Society of Thoracic Surgeons to develop consensus guidelines on the treatment of high-risk patients with stage I NSCLC.63, These 2012 consensus guidelines indicated RFA is an alternative treatment option for patients who are not surgical candidates due to severe medical comorbidity.

American Head and Neck Society - Endocrine Surgery Section

An international, multidisciplinary consensus statement on RFA and related ultrasound-guided ablation technologies for the treatment of benign and malignant thyroid disease was released in 2022 through a collaboration of international professional societies, including the Endocrine Surgery Section of the American Head and Neck Society. Select relevant recommendations from the guideline are listed in Table 6.

Table 6. Summary of RFA Recommendations for Treatment of Benign and Malignant Thyroid Disease*

Recommendation 1	US-guided ablation procedures may be used as a first-line alternative to surgery for patients with benign thyroid nodules contributing to compressive and/or cosmetic symptoms.
Recommendation 2	Although less efficacious than surgery or RAI in normalizing thyroid function, thermal ablation procedures can be a safe therapeutic alternative in patients with an autonomously functional thyroid nodule and contraindications to first-line techniques.
Recommendation 3a	US-guided ablation procedures may be considered in patients with suitable primary papillary microcarcinoma who are unfit for surgery or decline surgery or active surveillance
Recommendation 3b	US-guided ablation procedures may be considered in patients with suitable recurrent papillary thyroid carcinoma who are unfit for surgery or decline surgery or active surveillance
Recommendation 3c	Repeat ablation of a benign nodule can be considered for remnant nodular tissue

	contributing to unresolved symptomatic or cosmetic concerns

*This is not a comprehensive list of recommendations from the guideline.
RAI: radioactive iodine; RFA: radiofrequency ablation; US: Ultrasound.

American Urological Association

The American Urological Association (AUA; 2017) guideline on renal masses and localized renal cancer affirms that partial nephrectomy should be prioritized for the management of cT1a renal masses when intervention is indicated. Thermal ablation should be considered "as an alternate approach for the management of cT1a renal masses <3 cm in size." The guidelines were updated in 2021 and recommendations are generally consistent with what was published in the 2017 guideline. The 2021 AUA guideline explicitly states that RFA and cryoablation may be offered as options to patients who elect thermal ablation.

American Thyroid Association

The American Thyroid Association (2015) guideline on management of thyroid nodules and differentiated thyroid cancer. Patients with a benign cytology diagnosis or those very unlikely to be malignant (eg, purely cystic nodule) should undergo surveillance with the frequency determined by the level of suspicion for a missed malignancy. Medical or surgical intervention is considered if the nodules are large (>4 cm), causing compressive or structural symptoms, or if there is clinical concern. Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection. For differentiated thyroid cancer, "localized treatments with thermal (radiofrequency or cryo-) ablation, ethanol ablation, or chemoembolization may be beneficial in patients with a single or a few metastases and in those with metastases at high risk of local complications."

National Comprehensive Cancer Network

The NCCN guidelines for the treatment of non-small cell lung cancer (v.3.2023) state: "For medically operable disease, resection is the preferred local treatment modality (other modalities include SABR, thermal ablation such as radiofrequency ablation and cryotherapy). "For patients who are not amenable to surgery image-guided thermal ablation therapy (IGTA; includes RFA, microwave ablation, and cryoablation) may be considered. The guidance states "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 NCCN guidelines for thyroid carcinoma (v.3.2023) indicate that local therapies such as RFA may be considered for locoregional recurrence of thyroid carcinoma-papillary carcinoma in select patients with limited burden nodal disease. Additionally, local therapies, including RFA, can be considered in those with metastatic disease.

The NCCN guidelines (v.1.2024) for renal cancer indicate that “[t]hermal ablation (e.g. 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 it 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."

The NCCN guidelines (v.1.2024)2.2023) for renal cancer indicate that “thermal ablation (eg, cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of

clinical stage T1 renal lesions. Thermal ablation is an option for clinical T1b masses in select patients not eligible for surgery. Biopsy of lesions is recommended to be done prior toor at time of ablation. Ablative techniques may require mutiple treatments to achieve the same oncologic outcomes asconventional surgery."

The NCCN guidelines for head and neck cancers (v.3.2021) and pancreatic adenocarcinoma (v.2.2021) do not mention RFA.

National Institute for Health and Care Excellence
The NICE guidance (2004) on osteoid osteoma indicated that "current evidence on the safety and efficacy of computed tomography (CT)-guided thermocoagulation of osteoid osteoma appears adequate to support its use."

Updated NICE guidance (2010) on renal cancer has indicated that "evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) … in the short and medium term appears adequate to support the use of this procedure provided that patients are followed up in the long term."

The NICE guidance (2010) on RFA for primary and secondary lung cancers has stated: "[C]urrent evidence on the efficacy of percutaneous radiofrequency ablation (RFA) … is adequate in terms of tumor control." The NICE also indicated RFA might "be used in patients with small, early-stage lung cancers or small numbers of lung metastases who are unsuitable for, or prefer not to undergo, surgery. It may also have a place in multi-modality treatment of more advanced primary lung cancers." The guidance warned of serious complications (e.g. pneumothorax) among lung cancer patients.

The NICE guidance (2016) on benign thyroid nodules stated: "Current evidence on the safety and efficacy of ultrasound-guided percutaneous radiofrequency ablation … is adequate to support the use of this procedure."

Society of Interventional Radiology
The Society of Interventional Radiology (2020) published a position statement on the role of percutaneous ablation in renal cell carcinoma. Their relevant recommendations are as follows:

- "In patients with small renal tumors (stage T1a), percutaneous thermal ablation is a safe and effective treatment with fewer complications than nephrectomy and acceptable long-term oncological and survival outcomes. (Level of Evidence: C; Strength of Recommendation: Moderate)"
- "In selected patients with suspected T1a renal cell carcinoma, percutaneous thermal ablation should be offered over active surveillance. (Level of Evidence: C; Strength of Recommendation: Moderate)"
- "In high-risk patients with T1b renal cell carcinoma who are not surgical candidates, percutaneous thermal ablation may be an appropriate treatment option; however, further research in this area is required. (Level of Evidence: D; Strength of Recommendation: Weak)"
- "Radiofrequency ablation, cryoablation, and microwave ablation are all appropriate modalities for thermal ablation, and method of ablation should be left to the discretion of the operating physician. (Level of Evidence: D; Strength of Recommendation: Weak)"

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.

Table 7. Ongoing and Unpublished Clinical Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05189821	RFA Treatment for Papillary Thyroid Microcarcinoma Cohort	50	Nov 2026
NCT05189808	Radiofrequency Ablation for Indeterminate Bethesda III Thyroid Nodules	50	Aug 2024
NCT03808779	A Multicenter, Randomized and Controlled Trial of Radiofrequency Ablation vs. Conventional Surgery as Treatment of Papillary Thyroid Microcarcinoma (PTMC)	200	Feb 2024
NCT04619472	A Multicenter, Single Group Target Value Clinical Study to Evaluate Safety and Effectiveness of Radiofrequency Ablation System in the Treatment of Peripheral Lung Tumors	126	Jan 2022
Unpublished			
NCT01051037	Phase II Study Evaluating Safety and Efficacy of Stereotactic Body Radiotherapy and Radiofrequency Ablation for Medically Inoperable and Recurrent Lung Tumors Near Central Airways	17	Dec 2017 (completed)

NCT: national clinical trial

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42)**,** generally accepted standards of medical practice and review of medical literature and government approval status. Medicare defines medical necessity as health care services or supplies needed to diagnose or treat an illness, injury, condition, disease, or its symptoms and that meet accepted standards of medicine. This definition applies only to Medicare Advantage (PPO and HMO) plans.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References

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IX. Policy History

June 11, 2012	Went to TEC Committee voted on developing a policy
June 29, 2012	Policy reviewed by Mark Mugiishi, M.D.
August 07, 2012	Policy approved by OMD
August 24, 2012	Policy approved by UMC
August 20, 2013	Policy reviewed by Mark Mugiishi, M.D.
September 3, 2013	Policy approved by OMD
September 27, 2013	Policy approved by UMC
July 20, 2014	Policy reviewed by Mark Mugiishi, M.D.
August 5, 2014	Policy approved by OMD
August 22, 2014	Policy approved by UMC
October 15, 2015	Policy reviewed by Stefanie Park, M.D.
October 20, 2015	Policy approved by OMD
October 23, 2015	Policy approved by UMC
November 30, 2016	Policy reviewed by Stefanie Park, M.D.
December 6, 2016	Policy approved by OMD
December 16, 2016	Policy approved by UMC
June 15, 2017	Policy reviewed by Joan Kendall, M.D.
June 20, 2017	Policy approved by OMD
July 28, 2017	Policy approved by UMC
October 24, 2018	Policy reviewed by Joan Kendall, M.D.
November 6, 2018	Policy approved by OMD
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October 8, 2019	Policy reviewed by Joan Kendall, M.D.
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October 20, 2020	Policy reviewed by Joan Kendall, M.D.
November 3, 2020	Policy approved by OMD
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November 6, 2021	Policy reviewed by Joan Kendall, M.D.
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November 19, 2021	Policy approved by UMC
September 27, 2022	Policy reviewed by Joan Kendall, M.D.
October 4, 2022	Policy approved by OMD
October 28, 2022	Policy approved by UMC
September 28, 2023	Policy reviewed by Joan Kendall, M.D.
October 3, 2023	Policy approved by OMD
October 27, 2023	Policy approved by UMC