APPENDIX to Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

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

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

In radiofrequency ablation (RFA), a probe is inserted into the center of a tumor and the non-insulated electrodes, which are shaped like prongs, are projected into the tumor. Heat is then generated locally by a high frequency, alternating current that flows from the electrodes. The local heat treats the tissue adjacent to the probe resulting in a 3 centimeter (cm) 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 local recurrence, it occurs at the edge, and in some cases may be retreated.

Goal(s) of RFA may include:

- Controlling local tumor growth and preventing recurrence
- Palliating symptoms
- 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 (e.g., single versus multiple tips). Potential complications associated with RFA include those caused by heat damage to normal tissue adjacent to the tumor (e.g., intestinal damage during RFA of kidney), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), or secondary tumors if cells seed during probe removal.

Radiofrequency ablation was developed initially to treat inoperable tumors of the liver, referenced in the Blue Shield of California Medical Policy: Locoregional Treatment of Primary and Metastatic Hepatic Tumors. Recently, reports have been published on use of RFA to treat renal cell carcinomas (RCCs), breast tumors, pulmonary cancers (including primary and metastatic lung tumors), bone, and 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 (e.g., preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

On September 24, 2008 the U.S. Food and Drug Administration (FDA) cleared RFA devices for the general indication of soft tissue cutting, coagulation, and ablation by thermal coagulation necrosis. The FDA also noted that some RFA devices have been cleared for additional specific treatment indications, including partial or complete ablation of non-resectable liver lesions and palliation of pain associated with metastatic lesions involving bone. However, 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.

Bone Metastases

After lung and liver, bone is the third most common metastatic site and is relatively frequent among patients with primary malignancies of the breast, prostate, and lung. Bone metastases often cause osteolysis (bone breakdown), resulting in pain, fractures, decreased mobility, and reduced quality of life. External-beam irradiation is frequently the initial palliative therapy for osteolytic bone metastases. However, pain from bone metastases is refractory to radiation therapy in 20% to 30% of patients, while recurrent pain at previously irradiated sites may be ineligible for additional radiation due to risks of normal tissue damage. Other treatment alternatives include hormonal therapy, radiopharmaceuticals such as strontium-89, and bisphosphonates. Less often, surgery or chemotherapy may be used for palliation, and intractable pain may require opioid medications. Radiofrequency ablation has been investigated as another alternative for palliating pain from bone metastases.

An earlier case series showed that palliative RFA provided significant pain relief in 9 of 10 (90%) patients with unresectable, osteolytic spine metastases who had no other treatment options (Gronemeyer et al., 2002). Pain was reduced by an average of 74%; back-pain-related disability was reduced by an average of 27%. Neurologic function was preserved in 9 patients and improved in 1 patient.

Goetz et al. (2004) reported on an international study (n=43) conducted at 9 centers in which patients with painful osteolytic bone metastases were treated palliatively with RFA. The study's primary outcome measure was the Brief Pain Inventory-Short Form, a validated scale from 0 for no pain to 10 for the worst pain imaginable. Patient eligibility required baseline values of 4 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 radiation therapy to the same lesion. 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. Forty-one (95%) of the patients achieved a clinically significant improvement in pain scores. Investigators also reported statistically significant (p=0.01) decreases in opioid use at weeks 8 (by 59%) and 12 (by 54%). Kojima et al. (2006) also reported similar pain-alleviating effects of RFA on a case series of 24 patients with metastatic bone tumors.

While these uncontrolled studies included only a limited number of cases, the patient populations comprised individuals with limited or no treatment options for whom short-term pain relief was an appropriate outcome. Therefore, the use of RFA as palliative therapy in patients with painful metastatic bone lesions may be considered medically necessary. Because data are unavailable on use of RFA as initial therapy for pain from bone metastases, this indication remains investigational.

Neither setting is addressed in the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of bone cancers (Version 1.2014).

A search of the National Cancer Institute (NCI) Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, returned no current trials on the use of RFA for bone metastases.

Osteoid Osteomas

Osteomas are the most common benign bone tumor, comprising 10% to 20% of benign and 2% to 3% of all bone tumors (Ghanem et al., 2006). They are typically seen in children and young adults, with most diagnosed in patients between 5-20 years of age. Osteomas are most common in the lower extremity (usually the long bones, mainly the femur), and less common in the spine. These tumors typically have a characteristic clinical presentation and radiologic appearance; with pain, usually continuous and worse at night, and usually relieved by aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). The natural history of the osteoid osteoma varies upon its location, and although they rarely exceed 1.5 cm, they may produce bone widening and deformation, limb length inequality, or angular deviations when near a growth plate (Ghanem et al., 2006). When located in the spine, these lesions may lead to painful scoliosis or torticollis (Rosenthal, 2006). Sometimes, they heal spontaneously after 3-7 years.

Treatment options include medical management with NSAIDs, surgical excision (wide/en bloc excision or curetting), or the use of computed tomography (CT) or magnetic resonance imaging (MRI)-guided minimally invasive procedures including core drill excision, laser photocoagulation, or RFA. For many years, complete surgical excision was the classic treatment of osteomas, usually performed in patients with pain despite medical management. Complete surgical excision has several disadvantages. A substantial incision may be necessary and removal of a considerable amount of bone (especially in the neck of the femur), increases the need for

bone grafting and/or internal fixation (which often necessitates a second procedure to remove the metal work). Other possible risks include avascular necrosis of the femoral head and postoperative pathologic fracture. In addition, surgical excision leads to a lengthier period of convalescence and postoperative immobilization. Anatomically inaccessible tumors may not be completely resectable and may recur. Radiofrequency ablation of osteoid osteoma is done with a needle puncture, so no incision or sutures are needed, and patients may immediately walk on the treated extremity and return to daily activities as soon as the anesthetic effect wears off. The risk of recurrence with RFA of an osteoma is 5% to 10%, and recurrent tumors can be retreated with RFA (Rosenthal, 2006). In general, RFA is not performed in many spinal osteomas because of possible thermal-related nerve damage.

In 2012, Rimondi et al. 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 (0.5-9 years). Pain relief occurred in all 557 patients within the first week after RFA and continued in 533 patients (96%) who remained asymptomatic through their last follow-up. Pain recurrence occurred in 24 patients (4%). Complications occurred in 5 patients and included thrombophlebitis, a skin burn, a broken electrode and 2 procedures in which the RFA generator didn't reach maximum temperature.

In 2003, Rosenthal et al. reported their experience over an 11-year period with 271 RFA procedures for osteoid osteomas in 263 patients. 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 the necessity of additional procedures) were available in 126 patients, with a complete clinical success observed in 89%. For procedures performed as the initial treatment, the success rate was 91%.

In 2004, Cioni et al. reported on a case series of 38 patients with osteoid osteoma diagnosed clinically, as well as by radiography, scintigraphy, contrast-enhanced MRI, and CT. A total of 30 of the 38 patients reported prompt pain relief. Six of the remaining 8 patients underwent successful retreatment, and 2 underwent surgical excision.

Another case series reported primary success in 37 of 38 (97%) patients (age range: 5-43 years) who underwent CT-guided percutaneous RFA to treat clinically and radiologically suspected osteoid osteoma (Martel et al., 2005). Lesions were located in the proximal femur (n=13), tibia (n=5), foot (n=5), spine and fibula (n=3 each), acetabulum and humerus (n=2 each), and in other sites (n=5). All patients experienced sufficient pain relief to permit resumption of normal activities within 24 hours of the procedure. During follow-up, ranging from 3-24 months, no major complications were reported.

In summary, there are no randomized trials for this indication, however, uncontrolled studies have demonstrated RFA can provide adequate pain relief with minimal complications. Therefore, the use of RFA for the treatment of osteoid osteomas that cannot be successfully treated with medical treatment may be considered medically necessary.

Guidance issued in 2004 by the National Institute for Clinical Excellence (NICE) indicates that “current evidence on the safety and efficacy of computed tomography (CT)-guided thermocoagulation of osteoid osteoma appears adequate to support its use, provided that the normal arrangements are in place for consent, audit and clinical governance.”

A search of the NCI Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, returned no current trials on the use of RFA in osteoid tumors.

Renal Cell Carcinoma

The principal treatment of localized RCC is radical nephrectomy or in some select cases, nephron-sparing surgery (Abdellaoui & Watkinson, 2008; Stern et al., 2007). Other considerations include patients at high risk of developing additional renal cancers, as in von Hippel-Lindau disease. Renal tumors may require multiple cycles of RFA application at different sites within the mass.

The outcomes of RFA procedures in many patients have been described in numerous uncontrolled studies. The characteristics of the patients and RFA procedures varied widely within and across the studies in terms of tumor type (e.g., exophytic, parenchymal, central, with or without history of von Hippel-Lindau disease), tumor size (from smaller than 1 cm to larger than 8 cm), length of follow-up (from less than 1 month to 48 months), imaging modality used for guidance, and reason for using RFA.

In 2012, El Dib et al. conducted a meta-analysis evaluating RFA and cryoablation for small renal masses. Included in the review were 11 RFA case series (totaling 426 patients) and 20 cryoablation case series (totaling 457 patients) published through January 2011. Mean tumor size was 2.7 cm (range: 2-4.3 cm) in the RFA group and 2.5 cm (range: 2-4.2 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, was not significantly different between groups. The pooled proportion of clinical efficacy for RFA was 90% (95% confidence interval [CI]: 0.86-0.93) and 89% (95% CI: 0.83-0.94) for cryoablation.

Kunkle and Uzzo (2008) conducted a comparative meta-analysis evaluating cryoablation and RFA as primary treatment for small renal masses. Forty-seven case series representing 1,375 renal tumors were analyzed. Of 600 lesions treated with cryoablation, 494 were biopsied before treatment versus 482 of 775 treated with RFA. The incidence of RCC with known pathology was 71.7% in the cryoablation group and 90% in the RFA group. The mean duration of follow-up after RFA was 15.8 months. Local tumor progression was reported in 31 of 600 lesions after cryoablation and in 100 of 775 lesions after RFA, a difference that was significant ($p<0.0001$). Progression to metastatic disease was described in 6 of 600 lesions after cryoablation versus 19 of 775 after RFA ($p=0.06$). The authors cautioned that minimally invasive ablation generally has been performed selectively on older patients with smaller tumors possibly resulting in selection bias. In addition, series of ablated lesions tend to have shorter post-treatment follow-up compared with tumors managed by surgical excision or active surveillance and treatment efficacy may be overestimated in series that include tumors with unknown pathology.

In 2010, Salas et al. reviewed 17 studies identified from literature published between 2003 and 2009. The authors found RFA has proven to demonstrate oncologic outcomes that are almost equivalent to surgical resection when treating renal tumors with a mean size less than 4.0 cm. Renal function also declines minimally and is significantly lower than surgical resection. Van Poppel et al. (2011) also conducted a review of the literature published between 2004 and May 2011. In this review, the authors concluded RFA is a reasonable treatment option for most low-

grade renal tumors less than 4 cm in patients who are not candidates for surgical resection or active surveillance. The authors noted the need for long-term prospective studies to compare ablative techniques for renal ablation, such as RFA versus cryoablation.

A review article by Abdellaoui and Watkinson (2008) summarizes the literature from the last 5 years, which includes 713 patients who underwent RFA of 866 renal tumors with an average follow-up of 12.6 months. The average tumor-free survival rate was 85.4%. The authors noted that across different study reports there are significant variations in the practice of RFA for kidney tumors, including the types of devices used, imaging modality and performance experience, making it difficult to compare results across studies. Additionally, the article pointed out that the longest average follow-up of published studies of RFA and kidney tumors was 28 months, and that long-term follow-up data are necessary to validate the use of this technique.

Stern et al. (2007) retrospectively compared patients with stage T1a renal tumors, confirmed by pathology to be RCC, treated with either partial nephrectomy (n=34) or RFA (n=34). The mean follow-up for the partial nephrectomy group was 47 months (range: 24-93) and for the RFA group 30 months (range: 18-42). Three-year recurrence-free survival rate was 95.2% for partial nephrectomy and 91.4% for RFA (p=0.58). There were no disease-specific deaths in either group. In this small study, intermediate outcomes for patients with T1a RCCs were similar whether treated with partial nephrectomy or RFA.

The NCCN guidelines for the treatment of kidney cancer (Version 2.2014) indicate RFA is a thermal ablation option in select patients with clinical stage T1 lesions who are not candidates for surgery and in select patients such as elderly patients and others with competing health risks.

Guidance updated in 2010 by NICE indicates that:

> evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) for renal cancer in the short and medium term appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit, and provided that patients are followed up in the long term.

In summary, based on scientific data (large numbers of patients treated with follow-up), and national and societal clinical input, RFA of small (i.e., 4 cm or less) renal cancers may be considered medically necessary in those patients who are not surgical candidates due to comorbid conditions or who have baseline renal insufficiency such that standard surgical procedures would impair their kidney function.

A search of the NCI Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, identified one ongoing randomized controlled trial. In NCT01838720, 90 patients will be randomized to compare laparoscopic RFA to laparoscopic partial nephrectomy for stage T1a renal cell carcinoma tumor removal.

Pulmonary Tumors

Surgery is the current treatment of choice in patients with stage 1 primary non-small cell lung carcinoma (NSCLC); tumor/node/metastasis (TNM) stages 1a: T1N0M0 and 1b: T2N0M0. Only around 20% of patients present with stage 1 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 (Haasbeek et al., 2008). Postsurgical recurrence rates of stage 1 NSCLC have been reported between 20% and 30%, with most occurring at distant sites; locoregional recurrence rates occur in approximately 12%. Large differences in survival outcome are observed after surgery in stage 1 patients, with five-year overall survival rates ranging from 77% for small T1 tumors to 35% for large T2 tumors. Untreated, stage 1 NSCLC has a five-year overall survival rate of 6% to 14% (Haasbeek et al., 2008).

In the two largest retrospective radiation therapy series, patients with inoperable disease treated with definitive radiation therapy achieved five-year survival rates of 10% and 27% (Physician Data Query (PDQ), 2008). In both studies, patients with T1N0 tumors had better five-year survival rates of 60% and 32% (PDQ, 2008). One study reported on nearly 100 patients who refused surgery for stage 1 NSCLC, and had a five-year survival rate of 71% with stereotactic radiation therapy, a rate that is at least equivalent to surgical outcomes (Haasbeek et al., 2008; Onishi et al., 2007).

Radiofrequency ablation is being investigated in patients who are medically inoperable, with small primary lung cancers or lung metastases.

Radiofrequency ablation has been used to treat pulmonary tumors in many studies. Numerous systematic reviews have been published and have found the available evidence on RFA for pulmonary tumors is lacking and consists primarily of uncontrolled studies. In a 2013 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review of local nonsurgical therapies for stage I NSCLC, no comparative RFA studies were identified (Ratko et al., 2013). The AHRQ report found available evidence is insufficient to draw conclusions on the comparative effectiveness of local nonsurgical therapies for NSCLC including RFA. In a 2013 systematic review by Schlijper et al. of RFA, surgery, and stereotactic ablative radiotherapy (SABR) for colorectal cancer lung metastases, no randomized trials were identified and evidence was also insufficient to draw conclusions on the comparative effectiveness of these therapies. In a 2011 evidence-based review by Chan et al., 46 studies on RFA for lung tumors were evaluated, which included 2,905 ablations in 1,584 patients with a mean tumor size of 2.8 ± 1.0 cm. Twenty-four studies (51.2%) reported rates of local recurrence, which ranged from 0% to 64% and occurred in 282 cases (12.2%) with a mean follow-up time of 13 months (range: 3-45 months of 19 studies reporting). Primary lung cancer rates of local recurrence were not significantly different at 22.2% than for metastases at 18.1%. Twenty-one studies reported rates of overall survival, which ranged from 25% to 100% with a mean of 59.4% and a mean follow-up time of 17.7 ± 12.4 months. The mean cancer-specific survival rate was 82.6%, as reported in 24 studies with a range of 55% to 100% with a mean of 17.4 ± 14.1 months' follow-up. 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. The authors observed that RFA for the treatment of lung tumors is promising, noting better outcomes with RFA than traditional external-beam radiotherapy and RFA outcomes comparable to surgery but with lower rates of procedural mortality (0.21% versus 1%, respectively). Additionally, repeated RFA procedures can be performed without reducing lung function. The authors acknowledged the current evidence is limited to case series and indicated further prospective studies are needed to compare RFA to other local treatment options

A systematic review of RFA for primary and secondary lung tumors included studies that reported procedure-related morbidity and mortality, rates of complete tumor ablation, local recurrence, and/or overall survival (Zhu et al., 2008). Seventeen studies were included for a total of 707 patients (range: 12-142), and all were observational case series with no control groups. All studies were classified as poor quality by the authors of the systematic review. No randomized controlled trials (RCTs) or comparative studies were found. The definition of non-surgical candidates differed from study to study, and there were differences in the criteria used for tumor resectability. An additional confounding factor was that in some studies, additional therapies were used with RFA, such as systemic chemotherapy. The mean size of lesions treated ranged from 1.7 cm to 5.2 cm (median: 2.2 cm). Seven of the studies reported survival; 3 reported on three-year survival rates. One-, two-, and three-year survival rates ranged from 63% to 85%, 55% to 65%, and 15% to 45%, respectively. The authors of the systematic review concluded there was limited evidence reporting clinical outcomes of RFA treatment of lung tumors, and the quality of the evidence was relatively low, with no RCTs or case-control trials comparing the use of RFA with conventional treatment for non-surgical patients. Of the studies included in their review, there were a wide range in results of local recurrence rates, heterogeneity of the patients selected, and tumor characteristics, with relatively short follow-up in most.

In a 2012 review of evidence from 16 studies, Bilal et al. compared RFA to SABR in patients with inoperable early stage NSCLC. The authors found overall survival rates for RFA and SABR were similar in patients at 1 year (68.2% to 95% versus 81% to 85.7%) and 3 years (36% to 87.5% versus 42.7% to 56%, all respectively). However, survival rates at 5 years were lower with RFA (20.1% to 27%) than with SABR (47%). Caution must be used in interpreting these findings drawn from comparisons of results from uncontrolled case series and retrospective reviews.

In 2010, Zemlyak et al. prospectively compared 3 treatments for medically inoperable patients with stage I NSCLC; radiofrequency ablation in 12 patients, sublobar resection in 25 patients, and percutaneous cryoablation in 27 patients. At 3 years' follow-up, survival rates were not significantly different between groups. Overall three-year survival rates were 87.5%, 87.1%, and 77%; respectively. Cancer-specific three-year survival rates were 87.5%, 90.6%, and 90.2%; respectively. The authors concluded any of the 3 procedures were reasonable options for treatment of lung tumors in patients unfit for major surgery. The authors noted since surgeons chose the treatment option with patient input for this study, selection bias limits interpretation of his study, and further studies are warranted. In 2011, Huang et al. prospectively followed 329 consecutive patients treated with RFA for lung tumors (237 primary and 92 metastatic). Complications were experienced by 113 (34.3%) patients and were most commonly pneumothorax (19.1%). Overall survival at 2 and 5 years was 35.3% and 20.1%, respectively. The risk of local progression was not significantly different in tumors less than 4 cm but became significant in tumors greater than 4 cm.

A prospective, single-arm, multicenter trial from 7 centers in Europe, the United States, and Australia reported the technical success, safety, response of tumors, and survival in 106 patients with 183 lung tumors (Lencioni et al., 2008). All patients were considered to be unsuitable for surgery and unfit for radiotherapy or chemotherapy. Tumors measured less than 3.5 cm, and

included patients with NSCLC (n=22), colorectal metastases (n=41) and other metastases (n=16). Technical success rate was 99%. Patients were followed for 2 years, and a confirmed complete response lasting at least a year was observed in 88% of assessable patients, with no differences in response rate between patients with primary and metastatic tumors. Overall survival in patients with NSCLC was 70% at 1 year (95% CI: 51%-83%; cancer-specific survival 92% [78%-98%]), and 48% at 2 years (95% CI: 30%-65%; cancer-specific survival 73% [54%-86%]). Overall survival in patients with metastatic colorectal cancer was 89% at 1 year (95% CI: 76%-95%; cancer-specific survival 91% [78% to 96%]) and 66% at 2 years (95% CI: 53%-79%; cancer-specific survival 68% [54%-80%]). Overall survival in patients with other metastases was 92% at 1 year (95% CI: 65%-99%; cancer-specific survival 93% [67%-99%]) and 64% at 2 years (95% CI: 43%-82%; cancer-specific survival 67% [48%-84%]). Patients with stage 1 NSCLC (n=13) had overall survival rates of 75% (45% to 92%) at 2 years (cancer-specific 92% [66% to 99%]). No differences in response were seen between patients with NSCLC or lung metastases. The authors concluded RFA yields high proportions of sustained complete response in selected patients and RCTs comparing RFA with standard non-surgical treatment options are warranted. Comparison of patient survival rates with those from other studies in which different modalities were used are unreliable due to the heterogeneity of the study population, the severe pulmonary impairment, and significant comorbidities of the patients in this study.

Zhu et al. (2009) reported on a study to assess the incidence and risk factors of various complications after RFA of pulmonary neoplasms. The authors prospectively evaluated the clinical and treatment-related data regarding 129 consecutive percutaneous RFA treatment sessions for 100 patients with inoperable lung tumors. In this study, there was no post-procedural mortality. The overall morbidity rate was 43% (n=55 of 129). The most common adverse event was pneumothorax, occurring in 32% (n=41 of 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 2 lesions ablated per session as a significant risk factor for overall morbidity, pneumothorax, and chest drain insertion. Length of the ablation probe trajectory greater than 3 cm was an additional independent risk factor for overall morbidity and pneumothorax. The authors concluded that RFA for lung tumors could be considered safe and technically feasible, with an acceptable incidence of complications.

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. Mean follow-up was 17 months. Median overall survival for all patients was 23 months. The probability of two-year overall survival for primary lung cancer patients, recurrent cancer patients, and metastatic cancer patients were 50% (95% CI: 33%-65%), 55% (95% CI: 25%-77%), and 41% (95% CI: 19%-62%), respectively. In a retrospective review, Beland et al. (2010) reviewed recurrence patterns in patients with primary NSCLC treated with RFA between 1998 and 2008. Ninety-one patients were identified. Mean tumor size was 2.5 cm (range: 1-5.5 cm). Nineteen patients had adjuvant external beam radiation, and 9 had brachytherapy. At follow-up imaging at a mean of 17 months (range: 1-72 months), 45 patients demonstrated no evidence of recurrence. Recurrence after RFA was local in 13 cases, intrapulmonary in 6, nodal in 6, mixed in 2, and distant metastases in 7 cases. Median disease-free survival was 23 months. Increasing tumor size and stage were related to risk of recurrence. The most common pattern of recurrence

was local suggesting more aggressive initial RFA and adjuvant radiation may offer better outcomes.

In another series with 31 consecutive patients with NSCLC deemed ineligible for resection, RFA was performed 38 times (Lanuti et al., 2009). Mean tumor size was 2.0 cm (range: 0.8-4.4 cm). Recurrence was confirmed radiographically after 32% of treatments. Two of these patients were successfully retreated for technical failures related to pneumothorax and 3 underwent radiotherapy with stable disease. After mean follow-up of 17 months, 23 of the 31 patients were alive. Three patients died of metastatic disease, and 5 died of pneumonia remote from treatment. Two-and four-year survivals were 78% and 47%, respectively. Local tumor progression appeared to be related to tumors larger than 3 cm. The authors concluded RFA of inoperable early-stage lung cancer in carefully selected patients yields encouraging results. Positron emission tomography (PET) and CT need further validation for the early identification of local tumor progression following RFA.

Authors of 2 case series from Japan reported outcomes at median follow-up periods of 2 years. Yamakado et al. (2009) reported on a series of 78 patients with 198 pulmonary metastases of colorectal cancer with median follow-up of 24.6 months. The respective one-, three-, and five-year local tumor progression rates were 10.1%, 20.6% and 20.6%. The one-, three-, and five-year survival rates were 83.9%, 56.1% and 34.9%, respectively, with median survival time of 38.0 months. Lack of extrapulmonary metastasis and normal carcinoembryonic antigen (CEA) level were significant independent prognostic factors. In a smaller series, 39 patients with unresectable pulmonary metastases of RCC were treated with RFA (Soga et al., 2009). Patients with 6 or fewer lung metastases measuring 6 cm or smaller that were confined in the lung, had all lung tumors ablated (curative ablation). Patients with extrapulmonary lesions, 7 or more lung tumors, or large tumors of greater than 6 cm, had mass reduction (palliative ablation). Overall survival rates in the curative and palliative groups were 100% versus 90% at 1 year, 100% versus 52% at 3 years, and 100% versus 52% at 5 years ($p<0.05$), respectively. Maximum lung tumor diameter was a significant prognostic factor. In the curative ablation group, the recurrence-free survival rates were 92% at 1 year, 23% at 3 years, and 23% at 5 years.

However, these results are compromised by the retrospective nature of the data; the potential for confounding effects of undefined prior and adjuvant chemo- or radiotherapy; lack of histopathologic proof of treatment completeness; substantial patient and disease heterogeneity; and failure to separate overall survival rates according to disease.

In summary, while available studies are limited by study design, accumulating evidence from case series suggests that RFA may be a treatment option in selected patients with primary, non-small-cell lung cancer and metastatic pulmonary tumors. Although complications have been reported with the use of RFA in the lung, evidence suggests RFA may have survival rates and rates of procedure-related complications and mortality similar to surgery. Surgical resection remains the treatment of choice, but in patients unable to tolerate surgery due to medical comorbidities, RFA may be considered a treatment option.

The American College of Chest Physicians (ACCP) guidelines on the treatment of stage I and II non-small-cell lung cancer indicate RFA has been used effectively in clinical stage 1 NSCLC. Therefore, in medically inoperable patients, peripheral NSCLC tumors less than 3 cm may be

treated with RFA (Howington et al., 2013). The ACCP also joined with the Society of Thoracic Surgeons to develop consensus guidelines on the treatment of high-risk patients with stage I NSCLC (Donington et al., 2012). These consensus guidelines indicate RFA is an alternative treatment option in patients who are not surgical candidates due to severe medical comorbidity.

The NCCN practice guidelines for the treatment of non-small-cell lung cancer (Version 3.2014) state “studies suggest that RFA may be an option for node-negative patients who either refuse surgery or cannot tolerate surgery” and that “optimal candidates for RFA include patients with an isolated peripheral lesion less than 3 cm.” Additionally, the NCCN guidelines note “RFA can be used for previously irradiated tissue and for palliation.” The NCCN guidelines for colon cancer (Version 3.2014) indicate that ablative techniques can be considered in those whose primary colon tumor was resected for cure when metastatic lung tumors are unresectable but amenable to complete ablation [category 2A].

Guidance on RFA for primary and secondary lung cancers issued in 2010 by NICE states, “[C]urrent evidence on the efficacy of percutaneous radiofrequency ablation (RFA) for primary or secondary lung cancers is adequate in terms of tumor control.” The NICE Guidance also indicates RFA may “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.”

A search of the NCI Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, identified 3 ongoing, nonrandomized studies of RFA and lung tumors. Radiofrequency ablation will be evaluated for resectable colorectal lung metastasis (NCT00776399). Radiofrequency ablation combined with stereotactic body radiotherapy will be evaluated for lung tumors near the central airway (NCT01051037). An additional study assessing short- and long-term outcomes after RFA of pulmonary malignancies in patients who are not candidates for surgical resection is ongoing (NCT00280189).

Breast Tumors

There has been a trend in the treatment of small breast cancers from total mastectomy towards increasingly more conservative treatment options like lumpectomy, with more acceptable cosmetic outcomes and preservation of the breast. The selection of surgical approach balances the patient's desire for breast conservation and the need for tumor-free margins in resected tissue. Minimally invasive non-surgical techniques like RFA are appealing if they can produce local control and survival equivalent to breast-conserving surgical alternatives. Non-surgical ablative techniques pose difficulties such as the inability to determine tumor size, complete tumor cell killing, and local recurrence. Additionally, RFA can cause burning of the skin or damage to muscle, possibly limiting the use in patients with tumors near the skin or chest wall (Noguchi, 2007).

In 2010, Zhao and Wu conducted a systematic review of 38 studies on ablation techniques for breast cancer treatment published from 1994 to 2009. Nine of the studies reviewed focused on RFA. The RFA studies included small breast tumors ranging in size from 0.5-7 cm. Tumor resection was performed immediately after ablation or up to 4 weeks after RFA. Complete coagulation necrosis rates of 76% to 100% were reported. The authors concluded RFA for breast cancer tumors is feasible, but further studies with longer follow-up on survival, tumor

recurrence, and cosmetic outcomes are needed. In another 2010 review, Soukup et al. examined 17 studies on RFA for the treatment of breast tumors and found RFA is feasible and promising. However, while minimal adverse effects and complications occurred with breast RFA, the authors noted incomplete tumor ablation remains a concern.

In 2007, van der Ploeg et al. conducted a broad search of the literature regarding the use of RFA for the treatment of breast cancer. The analyzed studies were all feasibility or pilot studies of small numbers of patients using different patient and tumor characteristics, and ablation settings. The authors concluded while RFA is a "promising new tool for minimally invasive ablation" of small cancers of the breast, "a large randomized control study is required to assess the long-term advantages of RFA compared to the current breast conserving therapies."

The following are examples of published studies on RFA for breast tumors. In 2012, Wilson et al. 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 ± 0.54 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 3 patients had ipsilateral breast recurrences. In 2009, Imoto et al. 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 with hematoxylin-eosin (H&E) staining, and in 24 of 26 cases, tumor cell viability was diagnosed as negative by nicotinamide adenine dinucleotide (NADH) diaphorase staining. Two patients had skin burns and 7 had muscle burn related to RFA. In a 2008 2-stage Phase II clinical trial by Garbay et al., 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 because of insufficient efficacy of the technique tested. Athanassiou et al. (2009) conducted a small (n=10) series in which tumor size and fat content were analyzed. The authors concluded that "the fat content of small primary breast cancer could serve as a heat sink' and should be considered as a preventing factor of complete local tumor destruction by RF thermal ablation." In a 2011 Phase I/II study by Kinoshita et al., 49 patients were treated with RFA for breast tumors (mean size: 1.70 cm) followed immediately with surgical resection. Complete ablation was achieved in 30 patients (61%) by H&E staining and/or NADH diaphorase staining. Complete ablation increased to 83% in 24 patients with tumor size equal to or less than 2 cm in diameter. Adverse events related to the procedure included 3 muscle burns and 2 skin burns.

In summary, studies on RFA for breast tumors have reported varied and incomplete ablation rates with concerns about postablation tumor cell viability. Long-term improvements in health outcomes have not been demonstrated. Additionally, available studies do not allow comparisons to conventional breast-conserving procedures. Further studies, with long-term follow-up, are needed to determine whether RFA for small breast cancers can provide local control and survival rates comparable to conventional breast-conserving treatment. Therefore, RFA in the treatment of breast cancer is considered investigational.

The 2014 NCCN Guidelines (Version 1.2014) do not address RFA in the management of breast cancer.

A search of the NCI Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, identified no randomized studies on RFA for breast cancer. One nonrandomized study will evaluate outcomes of RFA after breast cancer lumpectomy in 250 patients (NCT01153035). One other ongoing (but no longer recruiting) Phase I/II NCI clinical trial was identified, including a pilot study of RFA to breast cancer lumpectomy sites to achieve negative margins without removing large volumes of tissue (NCT00571987).

Head and Neck Cancer

In patients with head and neck cancer with recurrent disease, surgical salvage attempts are poor in terms of local control, survival, and quality of life. These recurrent tumors are often untreatable with standard salvage therapies (Brook et al., 2008). Palliative chemotherapy or comfort measures may be offered. The safety and efficacy of RFA has been investigated as an option for palliative treatment in these situations.

A case series showed 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 radiation or surgery (Owen et al., 2004). The procedure was deemed reasonably safe and feasible for this indication, but further study is needed.

A case series of 14 patients with recurrent advanced head and neck malignancies was reported by Brook et al. (2008). Tumor targeting and electrode deployment was successful in all cases and 4 of 6 patients who completed quality of life assessments showed improvement. Three major complications (in 27 applications, 11%) occurred 7 days to 2 weeks after the procedure. These 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.

In 2011, Owen et al. 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 stable disease was reported in 8 patients after RFA, and quality-of-life scores improved, 3 deaths occurred (1 carotid hemorrhage and 2 strokes).

In summary, the evidence for RFA in head and neck tumors is limited to small case series. While RFA may have a role in palliation, complications are common and severe. Therefore, RFA for the treatment of head and neck tumors is considered investigational.

The NCCN guidelines (Version 2.2013) do not address the use of RFA in head and neck cancer.

A search of the NCI Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, returned no current trials on the use of RFA in head and neck cancer.

Thyroid Tumors

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

In 2013 Lim et al. reported on a case series of 111 patients treated with RFA for 126 benign nonfunctioning thyroid nodules. Patient follow-up was a mean duration of 49.4 ± 13.6 months.

Radiofrequency ablation significantly decreased the volume of the thyroid nodules from 9.8 ± 8.5 mL to 0.9 ± 3.3 mL ($p<0.001$) for a mean volume decrease of 93.4 ± 11.7%. Tumor recurrence occurred in 7 patients (5.6%). Complications occurred in 4 patients (3.6 %). Additionally, there was significant improvement in thyroid symptom scores ($p<0.001$).

A case series of 94 elderly subjects with solid or mainly solid benign thyroid nodules was reported by an Italian center (Spiezia et al., 2009). Thyroid nodule volume, compressive symptoms, and thyroid function were evaluated at baseline and 12 to 24 months after treatment. All thyroid nodules significantly decreased in size after RFA. Compressive symptoms improved in all patients and disappeared completely in 88% of patients. Hyperthyroidism resolved in most patients allowing methimazole therapy to be completely withdrawn in 79% of patients with pretoxic and toxic thyroid nodules (100% in pretoxic and 53% in toxic thyroid nodules). The authors observed that RFA is particularly attractive for elderly people for whom surgery and radioiodine therapy are often contraindicated or ineffective. A smaller series (n=33) also from Italy found similar outcomes in terms of reduction in compressive symptoms and improvement in thyroid function (Deandrea et al., 2008). Hyperfunction was fully controlled in 24% of patients and partially reduced in the others.

In 2012, Huh et al. reported on 30 patients randomized to receive either 1 or 2 RFA sessions for the treatment of benign thyroid nodules. Significant volume reduction occurred in each group of 15 patients after RFA. A single session of RFA was sufficient to reduce tumor volume and improve clinical symptoms in 12 patients (80%). Only 3 patients with nodules larger than 20 mL required an additional session of RFA. Baek et al. (2012) reported on a retrospective review of RFA for 1,543 benign thyroid nodules in 1,459 patients at 13 thyroid centers. Forty-eight (3.3%) complications occurred and included 20 major complications: voice changes (n=15), brachial plexus injury (n=1), tumor rupture (n=3), and permanent hypothyroidism (n=1). Twenty-eight minor complications included: hematoma (n=15), skin burn (n=4), and vomiting (n=9). One patient experienced permanent hypothyroidism while another required surgery.

In 2012, the Korean Society of Thyroid Radiology (KSTR) developed consensus recommendations for RFA of thyroid tumors after a review of the literature found few controlled studies (Na et al., 2012). The KSTR recommendations indicate RFA may be appropriate for the treatment of benign thyroid nodules, inoperable thyroid nodules, and recurrent thyroid cancers in the operation bed and lymph nodes. The KSTR recommendations also indicate RFA should not be used for primary thyroid cancers or follicular neoplasms citing no evidence of treatment benefit.

In summary, the evidence for RFA in thyroid tumors is primarily limited to case series and uncontrolled studies. While RFA has been shown to reduce thyroid tumor volume and improve clinical symptoms, complications can be common and available evidence is insufficient to determine the impact of RFA on net health outcomes. Therefore, RFA for the treatment of thyroid tumors is considered investigational.

The NCCN guidelines for thyroid carcinoma (Version 2.2013) indicate ablation techniques such as radiofrequency may be considered for palliative resection of symptomatic distant metastases. Ablation may also be considered for asymptomatic distant metastases when there is progressive disease.

A search of the NCI Clinical Trials Database (PDQ®) at ClinicalTrials.gov in February 2014, returned one current trial on the use of RFA in thyroid tumors. In NCT01778400, 50 patients will be randomized to compare RFA to ethanol injections for thyroid tumors.

Miscellaneous Neoplasms

One case series of 13 patients with adrenal neoplasms treated with RFA was identified (Mayo-Smith & Dupuy, 2004). Eleven of the 13 lesions were treated successfully with RFA, defined by follow-up CT scans, and normalization of preprocedural biochemical abnormalities.

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

Additional articles addressed the use of RFA in solid malignancies (Liapi & Geschwind, 2007; Rosenthal, 2006) and in the pancreas (Spiliotis et al., 2007).

Preliminary results of endoscopic RFA of rectosigmoid tumors have been described in a paper by Vavra et al. (2009). Twelve patients were treated with the Endoblate RFA device with 10 patients having surgical resection after ablation. Histology of the resected specimens showed that, on average, 82% (range: 60%-99%) of the tumor mass was destroyed in the ablation zone.

Stereotactic radiofrequency thermocoagulation for epileptogenic hypothalamic hamartomas is described in a retrospective analysis of a series of 25 patients with gelastic seizures (a rare type of seizure that involves a sudden burst of energy, usually in the form of laughing or crying) (Kameyama et al., 2009). Other seizure types were exhibited in 22 patients (88.0%), precocious puberty in eight (32.0%), behavioral disorder in 10 (40.0%), and mental retardation in 14 (56.0%). Gelastic seizures resolved in all but 2 patients. Complete seizure freedom was achieved in 19 patients (76.0%). These patients had disappearance of all seizure types and behavioral disorder, and also demonstrated intellectual improvement.

Small case series on RFA for colorectal and rectal carcinoma have demonstrated a debulking role for RFA (Mylona et al., 2012; Ripley et al., 2013). These case series do not allow comparison with available alternative treatments and are investigational in the policy statement.

Benefit Application

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

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

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	20982	Ablation, bone tumor(s) (e.g., osteoid osteoma, metastasis) radiofrequency, percutaneous, including computed tomographic guidance
	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), including intraoperative ultrasound guidance and monitoring, when performed
	50592	Ablation, 1 or more renal tumor(s), percutaneous, unilateral, radiofrequency
	76940	Ultrasound guidance for, and monitoring of, parenchymal tissue ablation
	77013	Computed tomography guidance for, and monitoring of, parenchymal tissue ablation
	77022	Magnetic resonance guidance for, and monitoring of, parenchymal tissue ablation
HCPC	None	
ICD9 Procedure	None	
ICD9 Diagnosis	All Diagnoses	

Type	Number	Description
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Cryosurgical Ablation of Miscellaneous Solid Tumors
- Cryosurgical Ablation of Prostate Cancer
- Locoregional Treatment of Primary and Metastatic Hepatic Tumors
- Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Key / Related Searchable Words

N/A

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Policy History

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

Effective Date	Action	Reason
12/7/2006	BCBSA Medical Policy adoption	Medical Policy Committee
1/7/2011	Policy title change from Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors Policy revision with position change	Medical Policy Committee
4/4/2014	Policy title change from Radiofrequency Ablation of Solid Tumors Excluding Liver Tumors Policy revision with position change	Medical Policy Committee

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