Clinical Review Criteria

Radiofrequency Ablation

- Barrett's Esophagus
- Lung Cancer
- Renal Tumors
- Primary HCC and Metastatic Liver Cancer
- Vertebral Augmentation for Painful Spinal Metastases

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Criteria
For Medicare Members

<table>
<thead>
<tr>
<th>Source</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS Coverage Manuals</td>
<td>None</td>
</tr>
<tr>
<td>National Coverage Determinations (NCD)</td>
<td>None</td>
</tr>
<tr>
<td>Local Coverage Determinations (LCD)</td>
<td>Non-Covered Services (L35008). And for facility-based services billed using a UB form, see Non-Covered Services (L34886)</td>
</tr>
<tr>
<td>Local Coverage Article</td>
<td>None</td>
</tr>
</tbody>
</table>

Covered without review: Esophagus, liver tumors, and renal tumors

For Non-Medicare Members

<table>
<thead>
<tr>
<th>Service</th>
<th>Criteria Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett's Esophagus</td>
<td>Radiofrequency ablation is considered medically necessary for the treatment of members with Barrett's esophagus (BE) who have histological confirmation of low-grade dysplasia by two or more endoscopies three or more months apart.</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.</td>
</tr>
<tr>
<td>Renal Tumors</td>
<td>Medical necessity review is no longer required for this service.</td>
</tr>
<tr>
<td>Primary HCC and Metastatic Liver Cancer</td>
<td></td>
</tr>
<tr>
<td>Vertebral Augmentation for Painful Spinal Metastases</td>
<td>See criteria for Vertebroplasty</td>
</tr>
</tbody>
</table>

Covered without review: Esophagus, liver tumors, and renal tumors

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Evidence and Source Documents

Radiofrequency Ablation in the Treatment of Lung Cancer
Radiofrequency Ablation of Renal Tumors
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer

Medical Technology Assessment Committee (MTAC)

Radiofrequency Ablation in the Treatment of Lung Cancer

BACKGROUND
Lung cancer is the leading cause of cancer related mortality in the United States. It has two main types; the non-small cell lung cancer (NSCLC) which accounts for approximately 80-85% of cases, and the small cell lung cancer...
Radiofrequency Ablation in the Treatment of Lung Cancer

Evidence Conclusion: There is limited evidence on the efficacy and safety of radiofrequency ablation for the treatment of lung cancer in patients who are not candidates for surgical resection. The body of evidence consists of small observational case series with no control or comparison groups that compare the RF ablation with conventional or other noninvasive techniques used for the treatments of patients with non-operable lung cancer, or those who cannot tolerate surgery. The published studies were heterogeneous; there were differences in the eligibility criteria of the studies, patient characteristics, stage of the disease, cancer type, number and sizes of the lesions, as well as other tumor characteristics. There were also variations in the ablation approaches, types of devices used to deliver the therapy, follow-up, endpoints, and outcome measures. Moreover, the follow-up duration in the majority of the studies was too short to determine the long-term safety and effectiveness of the therapy. Overall, the results of the published studies indicate that the median survival of patients receiving the therapy ranged from 8.6 months to 33 months. The one year survival rate ranged from 63-85%, the two year survival was 55-65% and the three year survival rate was 15-46%. Complete tumor necrosis ranged from 36% to 95%, and local disease recurrence varied from 3% to 38.1%. The studies indicate the RF ablation has better survival was 55-65% and the three year survival rate was 15-46%. Complete tumor necrosis ranged from 38% to 95%, and local disease recurrence varied from 3% to 38.1%. The studies indicate the RF ablation has better outcomes with tumors smaller than 3 cm in diameter vs. those >3cm in diameter, as this would allow oversizing of the ablation areas. The adverse effects associated with FR ablation included pneumothorax that often needed aspiration, pleural effusion, hemoptysis, pain, as well as other complications some of which required hospitalization of the patients. The authors of the published studies presented the results for all patients combined, with no adjustments for confounding factors as age of the patients, presence of other co-morbidities and/or malignancies, or the use of other adjuvant therapy. Moreover, in the absence of comparison groups, it is hard to determine whether radiofrequency ablation leads to better local control or improved survival outcomes than external beam radiation therapy or any other noninvasive treatment. In conclusion there is insufficient published evidence to determine the efficacy and safety of radiofrequency ablation for the treatment of lung cancer.

Articles: The search yielded over 300 articles. Many were review articles or publications not related to the current review. No meta-analyses of empirical studies, randomized or non-randomized controlled studies were identified. The majority were observational prospective case series with population sizes ranging from <10 to 60 patients. There was a larger (N=153) retrospective observational study that evaluated the long-term efficacy and safety of the therapy. Prospective series with at least 50 patients, and/or with longer-term follow-up, as well as the larger retrospective series were selected for critical appraisal. The following studies were critically appraised:

Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer

BACKGROUND
The liver is a common site for primary and secondary malignancies. Hepatocellular carcinoma (HCC), the most common primary tumor, is the fifth most common cancer in the world, and the third most common cause of cancer-related mortality. It is responsible for more than half a million deaths across the globe each year. Treatment options for patients diagnosed with primary and secondary malignancies are limited. Less than 15% are candidates for surgical resection at presentation because of inadequate liver functional reserve, extrahepatic disease, anatomic constraints of the tumor, or medical comorbidities. The use of external beam radiation is limited due to the intolerance of normal liver parenchyma to tumoricidal radiation doses (the dose required to destroy solid tumors (>70 Gy) is much higher than the liver tolerance dose of 35 Gy). In addition, systematic chemotherapy was found to have little impact on survival, and negative impact on the health-related quality of life due to the toxicity to other organs and systems. These limitations have led to the emergence of other therapies, such as radiofrequency ablation (RFA), cryosurgical ablation (CSA), percutaneous ethanol injections (PEI), hepatic arterial infusion chemotherapy, transarterial chemo-embolization (TACE), and selective intrarterial radioembolization therapy (Steel 2003, Salem 2005, Ibrahim 2008, Bult 2009, Riaz 2009, Bhardwaj 2010). Ablative techniques improve the ability to treat patients with unresectable hepatic tumors. Thermal ablative techniques, such as RFA, destroy tumors via a source that changes temperature to levels that are associated with cell death while causing minimal damage to adjacent, normal tissue. Chemical ablative techniques, such as PEI, involve the injection of cancer killing chemicals such as pure alcohol (ethanol) or acetic acid directly into the tumor. The choice of technique depends on equipment availability and physician preference. PEI is a chemical ablative technique where absolute or 95% ethanol is injected into tumor tissue resulting in coagulative necrosis through cytoplasmic dehydration, denaturation of cellular proteins, and small vessel thrombosis. When the consistency of the tumor is ‘soft’ within a ‘hard’ cirrhotic liver (most HCCs), the distribution of ethanol is relatively uniform; however, when the tumor is ‘hard’ within a ‘soft’ normal liver (most metastases), the distribution is not as uniform.
For this reason, PEI works better for HCC than for metastases. Complications of PEI include: hyperthermia, pain, elevated serum liver function tests, needle-tract seeding, pleural effusion, biliary stricture, portal vein thrombosis, and bleeding in the biliary tract (Clark 2007, Yamane 2009). The most commonly used ablative technique in the United States is RFA. RFA causes tumor destruction through the use of alternating high-frequency electric current in the radiofrequency range (460-500 kHz). This current is delivered through an electrode placed in the center of a lesion. Ions within the cell follow the alternating current creating frictional heat producing local tissue temperatures that can exceed 100°C. This ionic agitation leads to tissue destruction via tissue boiling and creation of water vapors. Once temperatures greater than 60°C are reached, protein denaturation, tissue coagulation, and vascular thrombosis result in a zone of complete ablation. Partial tissue destruction can occur up to 8 mm in diameter from the zone of complete ablation. RFA can be delivered either percutaneously, laparoscopically, or through open approaches (laparotomy). Complications from RFA include: pleural effusion, hepatic abscess, biliary injury, liver failure, intra-abdominal hemorrhage, pneumothorax, and hypoxemia. The most troubling complications arise when a probe is placed too close to the diaphragm or intra-abdominal organ, resulting in ablation of the surrounding viscera with the accompanying complications of perforation, diaphragmatic injury, or pulmonary damage. Limitations of RFA include: treating lesions in perihilar areas or near large vascular structures, and real time monitoring of the ablative zone is difficult due to air released during heating (Yamane 2009, Arciero 2006). RFA has received FDA approval for generic tissue ablation and the ablation of unresectable colorectal cancer metastases.

08/11/1999: MTAC REVIEW
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer

**Evidence Conclusion:** The best published scientific evidence evaluating percutaneous radiofrequency (RF) ablation of liver cancer consists of one case series of 39 patients with primary hepatocellular carcinoma and 11 patients with other primary tumors who had liver metastases. The majority of patients had 3-4 treatments with one or more nodules being ablated at each session. Five patients experienced mild pain during the procedure; no other complications were reported. The 5-year survival rate among those with primary hepatocellular carcinoma was 40%; the period of follow-up for persons with liver metastases was too short for the calculation of a 5-year survival rate. Because the survival rate of patients treated with RF ablation was not directly compared to that of a control group, it is not possible to determine whether this treatment improves survival among patients with liver cancer.


The use of radiofrequency ablation in the treatment of primary HCC does not meet the Group Health Medical Technology Assessment Criteria.

08/08/2001: MTAC REVIEW
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer

**Evidence Conclusion:** Only one study on radiofrequency ablation was a controlled trial. The remainder were case series. The trial reported on a clinically intermediate outcome, liver necrosis, not survival. The case series reports had survival information but this was not presented in a standardized format (e.g. 1-year survival, 3-year survival). Instead, they reported on survival after a certain mean or median follow-up time (patients had different amounts of follow-up time) which is more difficult to interpret. For primary HCC, in the one trial comparing RF ablation to an alternative technique, PEI, both techniques resulted in high rates of complete necrosis and the difference in rates was not statistically significant (Livraghi). PEI required more sessions and RF ablation had more adverse effects (there was 1 major and 4 minor complications with RF ablation, none with PEI). In the case series reviewed (Curley), there was a 72% survival rate after a median of 19 months of follow-up (all patients had at least 12 months follow-up). Livraghi (2001)(not critically appraised for this review) reported on a case series of patients with HCC treated with PEI. The 1-year survival rate for patients with a single HCC 5 cm or smaller was 98, 93 and 64%, respectively for Child’s A, B and C cirrhosis. For metastatic hepatic cancer, de Barre found that 81% patients survived after a mean follow-up of 14 months; 62% of these who survived had hepatic disease or distant metastases. 2-year or longer follow-up data were not available. This does not appear to be a dramatic increase in survival compared to untreated metastatic liver cancer (mean survival 6 to 21 months), but there is not strong evidence to support this claim. No studies compared RF ablation treatment to another treatment for metastatic liver cancer such as cryosurgery. In a case series on cryosurgery for hepatic colorectal metastases (Ruers, 2001) (not critically appraised for this review), the 1-year survival was 76% and the 2-year survival was 61%. The effectiveness of RF ablation may differ depending on the type of metastatic tumor.

**Articles:** The search yielded 85 articles, many of which were review articles, opinion pieces, dealt with technical aspects of the procedures or addressed other, similar treatments. There were no randomized controlled trials or meta-analysis. There was one non-randomized controlled trial and the rest of the empirical articles were case...
The use of radiofrequency ablation in the treatment of primary HCC does not meet the Group Health Medical Technology Assessment Criteria.

06/21/2010: MTAC REVIEW
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer

Evidence Conclusion: While there are many studies comparing RFA with resection and other ablative techniques, such as PEI, for the treatment of liver cancer, the data are difficult to compare since the studies are heterogeneous in study design, patient selection, data collection, tumor characteristics, primary cause of liver disease, route of access, electrode types used, and perinterventional systemic treatment.

Primary Liver Cancer

RFA vs. Resection The study selected for critical appraisal was a randomized controlled trial that compared the results of RFA with resection for the treatment of solitary and small HCC. Overall and disease-free survival rates were not statistically different for patients with solitary HCC < 5 cm in diameter treated with either RFA or resection. Additionally, patients treated with RFA had less major complications than patients treated with resection (0.04% vs. 56%, p<0.05). Treatment groups were comparable at baseline for all characteristic measured with the exception of serum alanine aminotransferase (ALT). Patients in the RFA group had higher serum ALT concentrations compared to patients in the resection group. Factors that limit the validity of the study include: uneven dropout rates, use of additional techniques, and lack of generalizability (Chen 2006). Another nonrandomized study comparing RFA with resection demonstrated similar survival outcomes between RFA and resection for tumors <5 cm (Montorsi 2005). One recent retrospective study suggested that overall and disease-free survival was higher for patients treated with resection compared to patients treated with RFA. However, in a subgroup analysis by tumor size, there was no significant difference in survival between RFA and resection for patients with tumors ≤3 cm. Results from this study should be interpreted with caution as this study contained significant selection bias; most patients who underwent RFA had more advanced tumors and worse liver function than those who received resection (Guglielmi 2008). RFA vs. PEI There are several published randomized controlled trials and meta-analyses comparing the efficacy of RFA versus PEI. Two of the most recent meta-analyses were selected for appraisal (Germani 2010, Bouza 2009). Results were consistent across the two analyses. Compared to patients treated with PEI, patients treated with RFA had higher three-year overall survival rates (73% RFA vs. 58% PEI, p<0.001) and lower rates of local recurrence (7% RFA vs. 22% PEI, p<0.001). Patients treated with RFA experienced more complications (19% RFA vs. 11% PEI, p<0.001) than those treated with PEI; however, there was no difference in the rate of major complications (4% RFA vs. 3% PEI, p=0.22). The most frequent complication reported in both groups was severe pain. All studies included in the analysis were classified to be trials with high-risk of bias. RFA + PEI vs. RFA alone There have been several published studies comparing PEI + RFA versus RFA alone. A randomized controlled trial was selected for review (Zhang 2007). Results from this trial suggest that overall survival is higher for patients with HCC treated with PEI + RFA versus RFA only (p=0.04). In a subgroup analysis by tumor size, survival was significantly better for those treated with PEI + RFA who had tumors between 3.1 and 5.0 cm compared to those treated with RFA only (p=0.03). There was no significant difference in survival for patients with tumors ≤3 cm or tumors 5.1-7.0 cm. The local recurrence rate was higher for those treated with RFA alone compared to those treated with PEI + RFA (p=0.01). There was no significant difference in overall, intrahepatic, or extrahepatic recurrence rates. There were no procedure related mortalities or major complications. Pain and fever were the most commonly seen minor complications. Data after 2-years should be interpreted with caution as less than 45% of patients were followed for 3-years. Results are not generalizable to women as less than 15% of the patients enrolled in the study were women. Additionally, the predominant cause of HCC in the study was hepatitis B while the predominant cause of HCC in Japan, Europe, and the United States is hepatitis C and alcohol abuse. Secondary Liver Cancer RFA vs. Resection No randomized controlled trials evaluating RFA compared to resection for unresectable liver metastases from colorectal cancer were identified. Results from a retrospective cohort study indicate that patients treated with resection had the highest overall and disease-free survival rates and the lowest rates of recurrence compared to patients treated with RFA alone or RFA + resection. Results from this study should be interpreted with caution as this study contained significant selection bias. Patients who were treated with RFA were not eligible for resection (Abdalla 2004). The majority of other studies (Park 2007, Aloia 2006, Hur 2009) comparing RFA and resection...
reached similar conclusions regarding survival and recurrence rates; however, a few studies have found that survival rates were comparable (Oshowo 2003). It is hard to compare results across studies as the primary cause of the disease differs, techniques differ, and disease characteristics differ. Additionally, none of the treatment groups were comparable at baseline. Patients treated with RFA were not eligible for resection. **Conclusion:** There is fair evidence that overall and disease-free survival rates were not statistically different for patient with solitary HCC <5 cm in diameter treated with either RFA or surgical resection. There is fair evidence that patients with HCC treated with RFA have better survival and lower recurrence rates than patients treated with PEI. There is fair evidence that for patients with HCC and tumors between 3.1 and 5.0 cm in diameter the combined treatment of PEI plus RFA versus RFA alone increases survival; however, long term follow-up is needed. There is insufficient evidence to determine the efficacy of RFA compared to surgical resection for patients with liver metastases.

**Articles:** The literature search yielded around 250 articles pertaining to the use of RFA. The majority of these articles were case series and cohort studies. Only one randomized controlled trial (Chen 2006) was identified that compared RFA with resection for small HCC. There were several RCTs and meta-analyses comparing RFA with PEI. The two most recent meta-analyses (Bouza 2009, Germani 2010) were selected for review. There were several studies comparing the combined use of PEI and RFA. Many of these studies did not have a control group or did not assess survival as an outcome. A RCT that compared PEI + RFA with RFA alone was selected for review (Zhang 2007). No randomized controlled trials or meta-analyses were found pertaining to the use of RFA for metastatic liver cancer. The literature consisted mainly of case series and cohort studies. A retrospective cohort study (Abdalla 2004) that compared resection to RFA was selected for review. The following studies were critically appraised. Chen MS, Li JQ, Zheng Y et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. **Ann Surg** 2006; 243:321-328. See Evidence Table. Bhardwaj N, Strickland AD, Ahmad F et al. Liver ablation techniques: a review. **Surg Endosc** 2010; 24:254-265. Bouza C, López-Cuadrado T, Alcázar R et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. **BMC Gastroenterol** 2009; 9:31-39. See Evidence Table. Germani G, Pleugeuzuelo M, Gurusamy K et al. Clinical outcomes of radiofrequency ablation, percutaneous alcohol ablation and acetic acid injection for hepatocellular carcinoma: A meta-analysis. **J Hepatol** 2010; 52:380-388. See Evidence Table. Zhang YJ, Liang HH, Chen MS et al. Hepatocellular carcinoma treated with radiofrequency ablation with or without ethanol injection in hepatocellular carcinoma. **Radiology** 2007; 244:599-607. See Evidence Table. Abdalla EK, Vauthey JN, Ellis LM et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. **Ann Surg** 2004; 239:818-827. See Evidence Table.

The use of radiofrequency ablation in the treatment of primary HCC does not meet the **Group Health Medical Technology Assessment Criteria**.