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>Lung Cancer: Non-Covered Services (L35008).</td>
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<tr>
<td></td>
<td>And for facility-based services billed using a UB form, see Non-Covered Services (L34886)</td>
</tr>
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</table>

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

For Non-Medicare Members

<table>
<thead>
<tr>
<th>Service</th>
<th>Criteria Used</th>
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</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, Primary HCC and Metastatic Liver Cancer</td>
<td>Medical necessity review is no longer required for this service.</td>
</tr>
<tr>
<td>Vertebral Augmentation for Painful Spinal Metastases</td>
<td>See criteria for Vertebroplasty</td>
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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 for the Treatment of Barrett’s Esophagus
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 for the Treatment of Barrett’s Esophagus
BACKGROUND
Barrett’s esophagus is a disease wherein the stratified squamous epithelium lining the esophagus gets replaced by metaplastic columnar epithelium. The disease affects more Caucasians than Blacks and is diagnosed around 55 years (Spechler & Goyal, 1996) and its prevalence varied widely from 0.4% to 20% (Gerson, Shetler, & Triadafilopoulos, 2002; Ormsby et al., 2000; Ward et al., 2006). Barrett’s esophagus is caused by chronic gastro esophageal reflux disease (GERD). While Body mass index (BMI), is believed to be associated with increased risk of barrett’s esophagus(Kamat, Wen, Morris, & Anandasabapathy, 2009), studies have found that abdominal obesity is a risk factor for barrett’s esophagus (Corley et al., 2007; Edelstein, Farrow, Bronner, Rosen, & Vaughan, 2007; Kramer et al., 2013). It is not well known if germline mutations are associated with the disease.

Initially, Barrett’s esophagus manifests with no symptoms or patients show signs of GERD. The most common symptoms of GERD are pyrosis (heart burn), regurgitation and dysphagia. Other manifestations of GERD are chronic cough, bronchospasm and laryngitis, chest pain resembling angina pectoris. GERD is complicated by erosive esophagitis, esophageal ulceration, stricture and hemorrhage(Spechler & Goyal, 1996), and barrett’s esophagus. The annual cancer incidence varied from 0.1 to 0.4% (Desai et al., 2012; Hvid-Jensen, Pedersen, Drewes, Sørensen, & Funch-Jensen, 2011; Rugge, Fassan, Cavallin, & Zaninotto, 2012; Shakhatreh et al., 2014). Studies have shown that the risk of developing cancer is proportional to dysplasia status and length of Barrett’s esophagus (Pohl et al., 2016; Sikkema et al., 2011; Thota et al., 2015; Van der Veen, Dees, Blankensteijn, & Van Blankensteijn, 1989). Patients with high-grade dysplasia have higher risk (4-8%) of progression to adenocarcinoma while patients with Barrett’s esophagus, low-grade dysplasia and indefinite for dysplasia have a risk ranging from 0.2 to 1.2% (Singh et al., 2014; Verbeek et al., 2012). However, mortality due to esophageal adenocarcinoma is lower than that of other causes (Sikkema, De Jonge, Steyerberg, & Kuipers, 2010). Diagnostic is based on endoscopy and biopsy showing columnar epithelium and intestinal metaplasia respectively. Histology classification has described four types of Barrett’s esophagus (BE); these include non-dysplastic (ND), low-grade for dysplasia (LGD), indefinite for dysplasia (ID), high-grade dysplastic (HGD).

General management includes proton pump inhibitor (PPI). Fundoplication may be an alternative for PPI resistance. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase (COX) have been described; however, these drugs have potential side effects. Surveillance has been promoted by many guidelines (Association, 2011; Fitzgerald et al., 2014; Shaheen, Falk, Iyer, & Gerson, 2016) but its benefit is not well documented. In addition, surveillance modality depends on the type of dysplasia. Treatment of dysplasia is of greatest importance. Several approaches have been described and include endoscopic ablative therapies, endoscopic resection or the combination of both, and esophagectomy. Endoscopic resection encompasses removal of both mucosa and submucosa (Pech, May, Gossner, Rabenstein, & Ell, 2004) and can lead to stricture. Endoscopic ablative therapies consist of radiofrequency ablation (RFA), photodynamic therapy, and endoscopic spray cryotherapy.

RFA uses radiofrequency energy and produces thermal injury to destroy the mucosa. Energy used comes from a balloon equipped with a series of electrodes to ablate the mucosa (Sharma et al., 2007). The radiofrequency energy can either be delivered circumferentially or focally. There are two different devices and accessories, both manufactured by BARRX. The balloon based HALO360 device is used to treat circumferential areas of BE. The system includes a high-power energy generator, a sizing balloon catheter and several balloon based ablation catheters. There are 60 tightly spaced, bipolar independent electrodes encircling the balloon through which the energy is delivered. A preselected amount of energy is delivered in less than a second at 350 W. This allows for full thickness ablation of the epithelium without damage to the submucosa. The HALO [90] ablation system is used to treat more focal areas and uses a radiofrequency generator and an endoscope mounted electrode. Both procedures can be done on an outpatient basis. Barrx90 ULTRA, Barrx60, and Channel RFA device are alternative options for focal ablations.

02/01/2010: MTAC REVIEW
Radiofrequency ablation for the treatment of Barrett’s Esophagus

Evidence Conclusion: The literature search revealed only one published randomized controlled trials (Shaheen et al, 2009) that compared radiofrequency ablation of Barrett’s esophagus to a sham endoscopic procedure. The trial had valid design and analysis; it was multicenter, appropriately randomized, controlled, blinded, had sufficient statistical power, and with low dropout rate. However, radiofrequency ablation was compared to a sham procedure and not to another established alternative procedure with a curative intent for BE with dysplasia e.g. endoscopic resection, esophagectomy, or photodynamic therapy. Moreover, the trial had only one year of follow-up which is insufficient to determine the long-term efficacy, and safety of the procedure. Due to the short follow-up duration, the authors used neoplastic progression and eradication of dysplasia and metaplasia as surrogates for death from
The trial randomized 127 patients (in a 2:1 ratio) with low or high grade dysplasia to undergo either radiofrequency ablation or sham endoscopic therapy. Randomization was stratified according to grade of dysplasia (LGD or HGD) and length of BE lesion (<4 or 4-8cm). Those in the ablation group underwent step-wise circumferential and focal ablation using HALO 360 and HALO 90 systems (BARRX Medical Inc, Sunnyvale, CA). Patients in the two groups underwent endoscopic surveillance for the study period; biopsies were obtained throughout the BE length every 3 months in patients with HGD or 6 months among those with LGD. After 12 months of follow-up, the results of the trial showed that more than three fourths of patients treated with radiofrequency ablation had complete eradication of intestinal metaplasia and dysplasia (77 % of all BE was completely reversed into normal epithelium among those who received RFA, vs. 2% in the control; 90% of patients with LGD, and 81.5% with HGD had complete eradication of the dysplasia vs. 23% and 19% of the controls respectively). The ablation therapy was also associated with a significant decrease in the risk of cancer but, as acknowledged by the authors this should be interpreted with caution due to the small number of cases. RFA therapy was not without risk as 5 (6%) cases developed esophageal stricture that required endoscopic dilatation, and 3 (3.5%) had other serious events as bleeding and chest pain.

Conclusion:
- There is fair evidence from one RCT with short-term follow-up that radiofrequency ablation using the HALO systems is superior to sham therapy (no therapy) in the treatment of BE with dysplasia.
- There is insufficient evidence to determine that RFA has better outcomes and less harms than alternative therapies with curative intent for BE with dysplasia.
- There is insufficient evidence to determine the long-term efficacy, and safety of radiofrequency ablation therapy in the management of patients with Barrett’s esophagus with dysplasia, and whether the risk of ablation is less than the risk of progression of BE.
- There is insufficient evidence to determine that radiofrequency ablation therapy eliminates the necessity for further endoscopic surveillance of patients with Barrett’s esophagus with dysplasia.
- There is insufficient evidence to determine that radiofrequency ablation therapy reduces or eliminates cancer risk in patients with Barrett’s esophagus with dysplasia.

Articles: The search yielded around forty articles. Many were reviews, letters, and editorials. There was one randomized controlled trial and number of case series and reports. The RCT and the majority of the case series were conducted by the same group of investigators. The RCT with the following citation was critically appraised. Shaheen NJ, Sharma P, Overholt B, et al. Radiofrequency ablation in Barrett’s esophagus with dysplasia. N Engl J Med 2009;360:2277-2288. See Evidence Table

The use of Radiofrequency ablation for the treatment of Barrett’s esophagus with dysplasia does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

09/19/2016: MTAC REVIEW
Radiofrequency ablation for the treatment of Barrett’s Esophagus
Evidence Conclusion:
RFA vs alternative treatment

Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett’s esophagus: a critical assessment of histologic outcomes and adverse events (Chadwick et al, 2014) (evidence table 1)

The first study is a systematic review aiming to compare the efficacy and safety of complete endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA) in the treatment of dysplastic BE. It was reported that dysplasia was eradicated in 95% and 92% of patients treated with EMR and RFA respectively. Intestinal metaplasia (IM) eradication was similar between both groups. After (23 and 21 months for EMR and RFA respectively) months of follow-up for patients, who were treated with EMR, dysplasia eradication was achieved in 85% of patients versus 79% among RFA group. In EMR group, additional treatments were reported in 7 studies. In EMR group, overall short term adverse events were 12.5% and most frequently acute bleeding. In RFA group, overall short term adverse events were 2.5% and most frequently acute bleeding (1%). In EMR group, overall long term adverse events were 38% and most frequently stricture compared to 4% in RFA group. Buried BE was 3.8% in EMR group vs. 0% in RFA group (not reported in table). Progression to cancer appeared to be low in both groups.

This indicates that both treatments are effective in the management of HGD BE but more events that are adverse are observed with EMR. However, the review is mostly based on observational studies. Ten studies were directly or indirectly industry funded; only 3 RCTs were represented in the review. Individual studies were small. Follow-ups periods were short (<1 year) and varied greatly limiting accurate assessment of cancer progression and incidence of recurrence. Fair evidence shows that both treatments are effective in managing HGD BE but RFA has less adverse events.
Radiofrequency ablation vs endoscopic surveillance for patients with Barrett's esophagus and low-grade dysplasia a randomized clinical trial (Phoa et al 2014) (evidence table 2)

This RCT investigated whether endoscopic radiofrequency ablation could decrease the rate of neoplastic progression. Compared to control group, patients who were treated with RFA, were less likely to progress to high grade dysplasia or cancer. At the end of endoscopic treatment, (After RFA), 92.6% and 88.2% of complete eradication of dysplasia and IM were observed respectively. During follow-up, patients who were treated with RFA were more likely to obtain complete eradication of dysplasia; the risk of complete eradication of dysplasia was increased by 70.5%. Complete eradication of intestinal metaplasia was maintained in 54of60patients (90.0%) receiving ablation compared with 0 of 68 patients receiving control (risk difference, 90% [95% CI, 82.4%-97.6%]; P < .001). Adverse events are represented by abdominal pain, bleeding, stricture, laceration, retrosternal pain while no adverse events were reported for endoscopic surveillance. The results indicate that in patients with low-grade dysplasia, RFA reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25% corresponding to an NNT of 4.0. Study had a valid methodology in general. However, it had some limitations: external validity is compromised (referral centers), study was underpowered for cancer-related death outcome which is the primary end point. Endoscopic rescue therapy was performed to decrease residual Barrett tissue. Based on the Cochrane collaboration’s tool for risk of bias assessment, the overall risk of bias is low with unclear information on blinding. Fair evidence supports efficacy of RFA over endoscopic surveillance for low grade dysplasia.

Endotherapy versus surgery for early neoplasia in Barrett’s esophagus: a meta-analysis (Wu et al., 2014) (evidence table 5)

This meta-analysis aimed to compare the efficacy and safety of endotherapy and surgery for early neoplasia in BE. A systematic literature search was performed up to December 2012 and included 870 patients. No significant difference between endotherapy and esophagectomy in the outcomes presented in the table below. However, endotherapy was associated with a higher neoplasia recurrence rate and fewer major adverse events. Limitations include: a small number of studies including retrospective studies; patients were not comparable in some studies leading to bias of the results. Different endotherapies including EMR, PDT, RFA and argon plasma coagulation were used. The type of surgery and the experiences of surgeons were different. Publication bias might also exist. Low evidence support similar efficacy between endotherapy and surgery in the treatment of early Barrett’s neoplasia with fewer adverse events.

Efficacy of RFA (non-comparative studies)

Efficacy and durability of radiofrequency ablation for Barrett’s esophagus: systematic review and meta-analysis (Orman et al, 2013) (evidence table 3)

This systematic review aimed to determine the efficacy and durability of RFA for patients with dysplastic and nondysplastic BE. The authors found 91% of patients achieved CE-IM while 78% achieved CE-D and that in 13% of cases, IM recurred after successful treatment. Most common adverse events were stricture (5%) and pain (3%). Although the study has valid methodology, limitations included the poor quality of included studies and external validity. Settings include referral centers with capability in RFA. Heterogeneity was high. Adverse events may have been underestimated due to the retrospective design of a number of studies. Individual studies were small in size. Follow-ups periods were short. RFA was not compared to alternative treatment limiting accurate assessment. The results indicate that CE-IM and CE-D were achieved in most of the patients undergoing RFA with low IM recurrence and low adverse events.

Several prospective studies have assessed the efficacy of RFA. Their findings can be found in the following table. However, none of these studies compare RFA to alternative treatment.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Intervention</th>
<th>Protocol</th>
<th>BE baseline</th>
<th>Median Follow-up (mos)</th>
<th>Findings</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Phoa et al., 2014)</td>
<td>132</td>
<td>ER combined with RFA</td>
<td>Visible lesions were removed with ER, followed by serial RFA every 3 months. Follow-up endoscopy was scheduled at 6 months after the first negative post-treatment endoscopic control and annually thereafter</td>
<td>BE≤12 cm with HGD and/or EC</td>
<td>27</td>
<td>CE-neo:92%</td>
<td>Mucosal lacerations (8%) and stenosis (6%).</td>
</tr>
</tbody>
</table>
RFA was used at baseline to treat all unstained lesions (USL), and then biopsy (and focal RFA if USL persisted) was performed every 3 months until all biopsies were negative for MGIN, HGIN, and ESCC.

Moderate/high grade intraepithelial neoplasia [MGIN/HGIN] and early flat-type esophageal squamous cell carcinoma [ESCC]

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73% & 84% of complete response at 3 and 12 months respectively. Progression in 2%

Stricture (21%)

RFA was used at baseline to treat all unstained lesions (USL), and then biopsy (and focal RFA if USL persisted) was performed every 3 months until all biopsies were negative for MGIN, HGIN, and ESCC.

HGD or IMC

6 years

CE-D: 77% to 92%
CE-IM: 56% to 83%
(p<0.0001) Progression to OAC at 12 months (3.6% vs. 2.1%; p=0.51)
Risk of IM recurrence at 5 years: 32%

BE, Barrett’s esophagus; ER, endoscopic resection; EMR, endoscopic mucosal resection

Low grade dysplasia

Meta-analysis of endoscopic therapy for low-grade dysplasia in Barrett’s oesophagus (Almond et al 2014) (evidence table 4)
This systematic review aimed to identify systematically all reports of endoscopic treatment of LGD, and to assess outcomes in terms of disease progression, eradication of dysplasia and intestinal metaplasia, and complication rates. The search was performed from January 1988 to January 2013. 37 studies reporting outcomes of endoscopic therapy for 521 patients with LGD. Study quality was assessed using Jadad scale for controlled trials and the Newcastle–Ottawa scale for uncontrolled trials. The results indicated that 67.8% and 88.9% achieved CE-IM and CE-D respectively. The overall incidence of progression to cancer is 3.90. The authors concluded that RFA does not eradicate the risk of progression to cancer but it appears to be safe and effective at eliminating LGD. Fair evidence supports the efficacy and safety of RFA in the treatment of low grade dysplastic BE. However, studies with longer follow-up are needed.

Conclusion:

- Fair evidence shows that Radio frequency ablation (RFA) and endoscopic mucosal resection are both effective in managing HGD BE but RFA has less adverse events.
- Fair evidence supports efficacy of RFA over endoscopic surveillance for low grade dysplasia.
- Low evidence support similar efficacy between endotherapy and surgery in the treatment of early Barrett’s neoplasia
- There is fair evidence that RFA is effective and safe for the treatment of low grade dysplasia; however, studies with long follow-up are needed.
- There is sufficient evidence to determine whether RFA is effective and safe for the treatment of high grade dysplastic Barrett’s esophagus.

Articles:
The literature revealed a number of articles, but the following articles were selected for critical appraisal:

The use of Radiofrequency ablation for the treatment of Barrett’s esophagus with dysplasia does meet the Kaiser Permanente Medical Technology Assessment Criteria.
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 (SCLC). After the initial diagnosis of the disease is made, it is essential to have an accurate TNM staging in order to determine the appropriate therapy. The standard treatment of patients with stage I or II NSCLC is surgical resection, and in order to achieve a potential cure from the disease, the cancer must be completely resectable through pneumonectomy or lobectomy, and the patient should be able to tolerate the surgery, and have adequate pulmonary function. Patients with more advanced or metastatic lung disease, or who cannot tolerate surgery, due to age or the presence of other co-morbidities, are poor surgical candidates. They are traditionally offered treatment with conventional external beam radiotherapy which is considered the most reasonable alternative. However, its results have not been satisfactory, and it has lower overall long-term survival than complete surgical resection. This radiation therapy may also be associated with regional complications as radiation pneumonitis, fibrosis, and esophagitis, and is not indicated for pulmonary metastases. Chemotherapy was found to have only a modest therapeutic effect, and is usually used as palliative therapy. This has led the researchers to develop minimally invasive techniques as stereotactic radiotherapy, brachytherapy, photodynamic therapy, bronchial artery infusion of chemotherapy, cryotherapy and radiofrequency ablation (RFA) (D’Amico 2003, Qiao 2003, Pennathur 2007). Radiofrequency ablation is a relatively new minimally invasive therapy that potentially leads to localized tissue destruction. It works by transferring radiofrequency (RF) energy from a generator through an electrode, to the target tissues. The waves are converted into heat, resulting in thermal damage, and coagulative necrosis of the tissues. For solid organ tumor ablation, thin RF electrodes are introduced laparoscopically or percutaneously to the target lesion under ultrasound, CT, or MRI guidance. A power of 5-120W is delivered to the electrodes, and an alternating current of 450-1,200 KHz passes from the tip to the surrounding tissue. When the temperature of the tumor cells is raised above 70°C cell destruction occurs. Several radiofrequency ablation devices were cleared by the FDA as tools for general ablation of soft tissue by thermal necrosis. The devices were also cleared for ablation of liver lesions, and bone metastases. According to the FDA, they have not been cleared for lung tumor ablation as their safety and effectiveness have not been fully established. In December 2007, the FDA issued a public health notification to alert the health practitioners of the deaths associated with lung tumor ablation using the radiofrequency devices (FDA Web site).

06/04/2008: MTAC REVIEW

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 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 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 Stated 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 perihiliar 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 Kaiser Permanente 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 series. Articles on HCC and metastatic liver cancer were analyzed separately. Two studies on primary hepatocellular carcinoma were reviewed (the non-randomized trial and a recent case series with a moderate patient sample size by a different research group): Livraghi T, Goldberg SN, Lazzarini S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: Treatment with radiofrequency ablation versus ethanol injection. Radiology 1999; 210: 655-661. See Evidence Table. Curley SA, Izzo F, Ellis LM, Vaughter JN, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000; 232: 381-91. See Evidence Table.

One study on metastatic liver cancer was reviewed (the largest case series with the longest follow-up): de Barre T, Elias D, Dromain C, El Din MG, Kuoch V, Ducreux M. et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. AJR 2000; 175: 1619-25. See Evidence Table.

The use of radiofrequency ablation in the treatment of primary HCC does not meet the Kaiser Permanente 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 periinterventional 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

The use of radiofrequency ablation in the treatment of primary HCC does not meet the Kaiser Permanente Medical Technology Assessment Criteria.
Codes
CPT: 32998