Medical Policy Manual

Topic: Radiofrequency Ablation of Tumors (RFA)

Section: Surgery

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Radiofrequency ablation (RFA) is one of a number of locoregional thermal ablation therapies for unresectable liver tumors. RFA kills cells (cancerous and normal) by applying a heat-generating rapidly alternating radiofrequency current through probes inserted into the tumor. 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. RFA can be performed as an open surgical procedure, laparoscopically, or percutaneously with ultrasound or computed tomography (CT) guidance. The goals of RFA may include 1) controlling local tumor growth and preventing recurrence; 2) palliating symptoms; and 3) extending survival duration for patients with certain tumors.

Reports have been published on use of RFA to treat renal cell carcinomas, breast cancer, pulmonary (including primary and metastatic lung tumors), bone, and other tumors. Well-established local or systemic treatment alternatives are available for each of these malignancies.

Regulatory Issues

The U.S. Food and Drug Administration (FDA) issued the following statement September 24, 2008 concerning the regulatory status of radiofrequency ablation.[1] “The FDA has cleared RF ablation devices for the general indication of soft tissue cutting, coagulation, and ablation by thermal coagulation necrosis. Some RF ablation devices have been cleared for additional specific treatment indications, including partial or complete ablation of nonresectable liver lesions and palliation of pain associated with metastatic lesions involving bone. The FDA has not cleared any RF ablation 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 RF ablation devices in the treatment of lung tumors."

MEDICAL POLICY CRITERIA

I. Radiofrequency ablation may be considered **medically necessary** for treatment of the following:

A. Liver tumors

1. Unresectable primary liver tumors [hepatocellular carcinoma (HCC)] when **all** of the following criteria are met:

a. The tumor(s) is 5 cm or less in diameter; and

b. There are no more than 3 hepatic lesions; and

c. The tumor(s) is unresectable due to comorbidities, lesion location (i.e., adjacent to a major vein), or an estimate of inadequate liver volume following resection; and

d. The goal of treatment is curative, defined as complete ablation of <u>all</u> tumor foci; and

e. The patient is not a candidate for liver transplantation

2. Hepatic metastases from colorectal tumors when **all** of the following criteria are met:

a. The metastatic tumor(s) is 5 cm or less in diameter; and

b. There are no more than 5 hepatic lesions; and

c. The tumor(s) is unresectable due to comorbidities, lesion location (i.e., adjacent to a major vein), or an estimate of inadequate liver volume following resection; and

d. No extrahepatic metastatic disease is present; and

e. The goal of treatment is curative, defined as complete resection/ablation of <u>all</u> tumor foci.

3. Hepatic metastases from neuroendocrine tumors when **all** of the following criteria are met:

a. The disease is symptomatic; and

b. Systemic therapy has failed to control symptoms; and

c. The tumor(s) is unresectable due to comorbidities, lesion location (i.e., adjacent to a major vein), or an estimate of inadequate liver volume following resection

4. As a bridge to liver transplantation when the intent is to prevent tumor progression or decrease tumor size to achieve or maintain a patient's candidacy for liver transplant

B. Localized renal cell carcinoma that is no more than 4 cm in size when one or both of the following criteria are met:

1. Preservation of kidney function is necessary (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate (GFR) of less than 60 mL/min per m^2) and standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen kidney function; or

2. Patient is not considered a surgical candidate

C. Osteoid osteomas that are unresponsive to initial medical treatment

D. To palliate pain in patients with osteolytic bone metastases who have failed or are poor candidates for standard treatments such as radiation or opioids

E. Isolated peripheral non-small cell lung cancer lesion that is no more than 3 cm in size when the following criteria are met:

1. Surgical resection or radiation treatment with curative intent is considered appropriate based on stage of disease, however, medical co-morbidity renders the individual unfit for those interventions; AND

2. Tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

F. Malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when the following criteria are met:

1. In order to preserve lung function when surgical resection or radiation treatment is likely to substantially worsen pulmonary status OR the patient is not considered a surgical candidate; AND

2. There is no evidence of extrapulmonary metastases; AND

3. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

II. Radiofrequency ablation is considered **investigational** as a technique for ablating all other tumors, including but not limited to:

A. Adrenal cancer

B. Breast cancer

C. Breast fibroadenomas

D. Chondroblastomas

E. Chordomas

F. Hamartomas

G. Head and neck cancers

H. Initial treatment of osteoid osteomas

I. Initial treatment of painful bony metastases

J. Liver tumors that do not meet the medical necessity criteria above, including but not limited to the following:

   1. In the absence of contraindications for surgical resection

   2. More than 3 HCC tumors or 5 metastatic colorectal tumors in the liver

   3. Metastases to the liver from organ tumors other than colorectal or the following neuroendocrine tumors:

      a. Asymptomatic neuroendocrine tumors

      b. Neuroendocrine tumors with symptoms controlled by systemic therapy

   4. Metastatic or primary liver tumors larger than 5 cm in diameter

   5. Debulking procedures with a goal of less than complete resection/ablation

K. Lung (pulmonary) tumors except isolated peripheral non-small cell lung cancer that meets the above medical necessity criteria

L. Lymphoma

M. Ovarian cancer

N. Pancreatic cancer other than pancreatic neuroendocrine metastases in the liver that meet the criteria above

O. Pelvic/abdominal metastases of unspecified origin

P. Thyroid nodules, benign or malignant

POLICY GUIDELINES[2]

Neuroendocrine tumors are rare, slow-growing, hormone-secreting tumors that may occur in numerous locations in the body. Neuroendocrine tumors include the following:

- Carcinoid Tumors
- Islet Cell Tumors (also known as Pancreatic Endocrine Tumors)

- Neuroendocrine Unknown Primary
- Adrenal Gland Tumors
- Pheochromocytoma/paraganglioma
- Poorly Differentiated (High Grade or Anaplastic)/Small Cell
- Multiple Endocrine Neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple Endocrine Neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Neuroendocrine tumors may also be referred to by their location (e.g., pulmonary neuroendocrine tumors; gastroenteropancreatic neuroendocrine tumors)

Some appendiceal carcinoids, also called adeno carcinoids, goblet cell carcinoids or crypt cell carcinoids, have mixed histology, including elements of adenocarcinoma. While these biphasic tumors have both neuroendocrine and adenocarcinoma components, the National Comprehensive Cancer Network (NCCN) recommends they be managed according to colon cancer guidelines.

SCIENTIFIC EVIDENCE

Liver Tumors

Background

The primary treatment of liver tumors is surgical resection when possible. However, 80% of liver tumors are not resectable due to anatomic location, size, number of lesions, or underlying liver reserve. Radiofrequency ablation (RFA) may be considered a treatment option for certain unresectable liver tumors.

Primary Liver Tumors [Hepatocellular Carcinoma (HCC)]

Systematic Reviews and Meta-analyses

A number of systematic literature reviews have concluded that there is insufficient evidence to determine that RFA has demonstrated improved outcomes compared with liver resection when surgical criteria is met. However, there is sufficient evidence to determine that RFA has improved outcomes compared to other treatment molalities, including but not limited to percutaneous ethanol injection (PEI), percutaneous acetic acid infusion (PAI), and cryoablation for unresectable HCC. For example:

- In a Cochrane review, Weis et al reviewed studies on RFA for HCC versus other HCC interventions.[3] Moderate quality evidence demonstrated hepatic resection had superior survival outcomes than RFA, however, resection might have greater rates of complications and longer hospital stays. Other systematic reviews and meta- analyses have also found superior survival with hepatic resection but higher rates of complications than RFA.[4-7] This reinforces the use of RFA for only unresectable HCC. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over percutaneous ethanol injection (PEI). Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.
- In a comparative effectiveness review of local hepatic therapies for patients with unresectable primary hepatocellular carcinoma, the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare Program compared available treatment strategies using randomized,

nonrandomized comparative, and case-series studies.[8] The strength of evidence was insufficient when comparing RFA to RFA-transarterial chemoembolization (TACE) for overall survival, quality of life, outcomes related to progression, and local recurrence/local tumor progression, length of stay, and days missed of work. Evidence was insufficient when comparing RFA to PEI/percutaneous acetic acid infusion (PAI) following the analysis of 3 RCTs. One poor quality retrospective cohort study determined the two-year survival rate was not statistically significant for the comparison of RFA to TACE. Retrospective studies are limited by the accuracy of the medical records or the recall ability of patients and further there is no randomization or blinding in the study design.

- In a 2013, Shen and colleagues reported on a meta-analysis of 4 RCTs and quasi-RCTs, totaling 766 patients, to compare RFA to PEI for treatment of HCC nodules up to 3 cm.[9] Overall survival was significantly longer for RFA than PEI at 3 years (hazard ratios [HR]: 0.66, 95% confidence interval [CI]: 0.48-0.90, p=0.009), and local recurrence risk was lower with RFA (HR: 0.38, 95% CI: 0.15-0.96, p=0.040). However, there was no difference in distant intrahepatic recurrence and RFA resulted in more complications.
- In 2012, Xu et al. reported on a meta-analysis of 13 studies to compare RFA to surgical resection for early HCC.[10] Only 2 of the studies were RCTs. Surgical resection occurred in 1,233 patients and RFA was used in 1,302 patients. Surgical resection patients had significantly longer overall survival rates at 1, 3 and 5 years than RFA (odds ratio [OR]: 0.60, 95% confidence interval [CI]: 0.42 to 0.86, OR: 0.49, 95% CI: 0.36 to 0.65, and OR: 0.60, 95% CI: 0.43 to 0.84, respectively). When only HCC tumors <3 cm were analyzed, resection was still significantly better in overall survival than RFA at 1-, 3- and 5-years. Recurrence rates were also significantly lower in the surgical resection group at 1, 3 and 5 years than RFA (OR: 1.48, 95% CI: 1.05 to 2.08, OR: 1.76, 95% CI: 1.49 to 2.08, and OR: 1.68, (95% CI: 1.21 to 2.34, respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than RFA (OR: 6.25, 95% CI: 3.12 to 12.52; p=0.000), but in a subanalysis of HCC <3 cm, complication rates were significantly lower with resection than RFA.
- Tiong and Maddern conducted a systematic review and meta-analysis of studies published between 2000 and 2010 on patients with HCC who were treated with RFA, either in comparison or in combination with other interventions, such as surgery or PEI.[11] Outcome data collected were overall survival, disease-free survival, and disease recurrence rates. Only randomized controlled trials (RCTs), quasi-RCTs and non-randomized comparative studies with more than 12 months follow-up were included. Forty-three articles, including 12 RCTs, were included in the review. The majority of the articles reported the use of RFA for unresectable HCC, often in combination with other treatments such as PEI, transarterial chemoembolization, and/or surgery. The meta-analysis of 5 RCTs showed that RFA was superior to PEI, with higher overall and disease-free survival rates. Data on RFA compared with microwave ablation were inconclusive. The authors concluded that RFA can achieve good clinical outcomes for unresectable HCC. Similarly,
- Salhab and Canelo reviewed studies published from 2005 to 2010 on various medical and surgical treatments for HCC and found RFA to be superior to PEI in terms of overall survival at 3 years (p=0.002).[12] The authors concluded that RFA was appropriate for first-line treatment in patients with a single 3 cm or smaller HCC tumor.
- In a 2013 meta-analysis comparing RFA to cryoablation for HCC, Huang and colleagues evaluated 3 prospective studies and 1 retrospective study.[13] Included in the studies were 180 RFA and 253 cryoablation patients. RFA was found to be significantly superior to cryoablation in rates of complications (OR: 2.80, 95% CI: 1.54-5.09), local recurrence of patient (OR: 4.02, 95% CI: 1.93-8.39), and local recurrence of tumor (OR: 1.96, 95% CI: 1.12-3.42). However, mortality was not significantly different (OR 2.21, 95% CI: 0.45-10.8) between groups.

Randomized Controlled Trials

- Feng et al randomized patients with HCC with up to 2 nodules with nodular diameter of less than 4 cm to either surgical resection (n=84) or RFA (n=84).[14] This study population differed from that of many other RCTs in that the tumors were resectable. There were no statistically significant differences between the groups for overall survival or recurrence-free survival. The authors concluded that RFA provided therapeutic effects similar to surgical resection, but that RFA of small HCCs in certain sites was more likely to be incomplete, making surgical resection the better option in those cases.

Nonrandomized Trials

A large body of case series, meta-analyses, and retrospective evidence has been published on RFA as a treatment of unresectable primary liver tumors.[15-20] These articles reported disease-free survival rates consistent with those reported in the randomized controlled trials.

Clinical Practice Guidelines

- The 2014 National Comprehensive Cancer Network (NCCN) Guidelines stated that local hepatic therapies should not be used in place of liver resection or transplantation for patients who meet surgical criteria.[21] When liver tumors are not resectable due to location, size, number of lesions, or underlying liver disease, NCCN recommended the use of ablative techniques including RFA, for patients with certain unresectable HCC tumors 5 cm or smaller.[21] The optimal size for treatment with RFA is 3 cm or smaller. RFA may be used in combination with embolization for HCC tumors between 3 and 5 cm. This recommendation was based on category 2A evidence, defined as lower-level evidence with uniform NCCN consensus.
- In their 2009 position statement, the Society of Interventional Radiology (SIR) recommended use of RFA for the treatment of HCC for small tumors (<5 cm in diameter).[22] This statement indicated that superior results can be expected in tumors smaller than 3 cm in diameter, and intermediate results in 3-5 cm tumors. This document appears to be based on analysis of the available literature and panel consensus. While the statement reported the outcomes of numerous studies, the authors did not provide a critical analysis of the quality of the studies, and did not rate the strength of the evidence supporting their recommendations.
- The 2010 update of the practice guideline from the American Association for the Study of Liver Diseases (AASLD) considered RFA a safe and effective therapy for unresectable HCC or as a bridge to liver transplantation.[23]
- The 2011 American College of Radiology Appropriateness Criteria® considered RFA by percutaneous, open, or laparoscopic methods, effective for treatment of small (≤5 cm) HCC tumors.[24] While ablative therapy is most effective for these small HCCs, moderate success has also been described with tumors ≤7 cm. With larger tumor number and/or size, "the operator may want to focus on arterial-based therapies and adjuvant or neoadjuvant therapy."

Colorectal Cancer Metastases in the Liver

Systematic Reviews

In 2009 the American Society of Clinical Oncology (ASCO) published a clinical evidence review on RFA of colorectal cancer (CRC) metastases in the liver.[25] The evidence at that time was considered insufficient to form a practice guideline. Seventy-three articles from 46 studies met criteria for inclusion in the review. The evidence review reported a number of study design limitations that made comparisons difficult. These included the lack of randomized treatment allocation, lack of a control group, retrospective study designs, possible patient selection bias, heterogeneity of patient characteristics including tumor type, and differing procedure techniques, end points, and statistical analyses. There was a wide range of outcomes for 5-year survival (14-55%) and local tumor recurrence (3.6-60%). The rate of major complications was 6-9% and procedure-related mortality was 0-2%. The conclusion of the ASCO panel was that additional studies, preferably RCTs, are needed to determine the efficacy of RFA to increase overall survival, and local recurrence-free, progression-free, and disease-free survival in this patient population.

In several systematic reviews on RFA treatment of liver metastases from colorectal cancer, a number of limitations in the published studies made it difficult to compare the results.[26-29] The majority of the studies were single-arm, single-center, retrospective and prospective. There was wide variability in patient groups (e.g., lesion size, number, distribution, prior treatments), adjuvant therapies and management approaches within individual studies. Several studies combined results for colorectal and non-colorectal metastases, often reporting combined outcomes. End-points were not always reported uniformly, with varying definitions of “unresectable”, survival time, recurrence time, and complication rates.

- A 2012 Cochrane review found different types of variability in all reviewed studies. The main concern was the imbalance of patient characteristics in the studies reviewed, as well as heterogeneity in the interventions, comparisons and outcomes.[28] Therefore the authors concluded the evidence was insufficient to recommend RFA for CRC liver metastasis.
- In a 2014 Health Technology Assessment, Loveman et al. also found insufficient evidence to draw conclusions on the clinical effectiveness of ablative therapies, including RFA, for liver metastases.[30]
- In 2013, Weng and colleagues reported on a systematic review and meta-analysis to compare RFA to liver resection for the treatment of CRC liver metastases.[29] One prospective study and 12 retrospective studies were included in the analysis. Overall survival at 3 and 5 years was significantly longer in liver resection than RFA (risk ratio [RR]: 1.377, 95% CI: 1.246-1.522 and RR: 1.474, 95% CI: 1.284-1.692, respectively). Disease-free survival was also significantly longer in liver resection than RFA at 3 and 5 years (RR: 1.735, 95% CI: 1.483-2.029 and RR: 2.227, 95% CI: 1.823-2.720). While postoperative morbidity with liver resection was significantly higher than with RFA (RR: 2.495, 95% CI: 1.881-3.308), mortality was not significantly different between liver resection and RFA. Liver resection also still performed significantly better than RFA when data were analyzed in 3 subgroups: tumors <3 cm, solitary tumor and open or laparoscopic approach. However, hospital stays were significantly shorter (9.2 + 0.6 vs. 3.9 + 0.4, p<0.01) and rates of complications lower (18.3% vs. 3.9%, p<0.01) with RFA over liver resection. Interpretation of the meta-analysis is limited by the retrospective nature of the majority of studies.
- In an additional systematic review published in 2011 by Pathak et al., the long-term outcomes and complication rates of various ablative therapies used in the management of liver metastases from colorectal cancer (CRC) were assessed.[27] The literature search was from 1994 to 2010 and study inclusion criteria included a minimum 1-year follow-up and at least 10 patients. Of the 75 trials that met the inclusion criteria, 36 studied RFA which was found to have a local recurrence rate of 10-31%, with a mean 1-, 3- and 5-year survival of 85%, 36% and 24%, with major complication rates ranging from 0% to 33%. The authors concluded that ablative therapies including RFA offer significantly improved survival compared with palliative chemotherapy alone with 5-year survival rates of 17-24%, and that complication rates of commonly used techniques are low.

Randomized Controlled Trials

There are no published randomized controlled trials comparing RFA to conventional therapy for metastatic tumors in the liver from CRC.

Nonrandomized Trials

As noted in the above systematic reviews there are numerous published case series and retrospective reviews of RFA for treatment of CRC metastases in the liver.[26,31-37] Although evidence from case series and retrospective reviews is considered unreliable for the reasons noted previously, overall the outcomes from these studies consistently suggested that RFA may result in higher 1-, 3-, and 5-year survival rates than currently available chemotherapy. Further, evidence does not support RFA as a replacement for resection in patients who are eligible for resection.

Clinical Practice Guidelines

- The 2014 NCCN guidelines for CRC metastases to the liver list RFA as a treatment option in conjunction with surgical resection or alone for patients who cannot undergo resection.[38,39] This recommendation was based on category 2A evidence, defined as lower-level evidence with uniform NCCN consensus. The following guidelines apply:
    - Resection is the treatment of choice for resectable liver metastases from colorectal cancer. RFA is not considered to be a substitute for resection in patients with completely resectable disease.
    - Ablation therapy may be an option for those patients who cannot undergo resection due to comorbidities, location of lesion(s), or an estimate of inadequate liver volume following resection.
    - Resection and RFA should be reserved for patients with disease that is completely amenable to local therapy; “debulking procedures” with a goal of less than complete resection/ablation are not recommended.
- In their 2009 position statement, the Society of Interventional Radiology listed RFA for CRC metastases to the liver in patients who cannot undergo resection.[22] They noted that small tumors of 4 cm or less in diameter are more likely to have favorable outcomes. This document appears to be based on analysis of current literature and panel consensus. While the statement reported the outcomes of numerous studies, the authors did not provide a critical analysis of the quality of the studies and did not rate the strength of the evidence supporting their recommendations.
- The 2011 ACR Appropriateness Criteria® consider resection to be the gold standard in the management of CRC metastases in the liver.[24] For unresectable tumors, “[a]blation is most successful in patients with a limited number of smaller tumors. Larger tumors may be treated with a combination of ablation and TAE [transarterial embolization] or TACE [transarterial chemoembolization].”

<u>Neuroendocrine Tumor Metastases in the Liver</u>

Unlike the above liver tumors, the treatment benefit for RFA of neuroendocrine metastases in the liver is related to symptom control rather than survival or local recurrence. Therefore, patient selection and outcome measures in related studies focused on the level of symptoms rather than lesion size, number, and location. The primary treatment of symptomatic neuroendocrine tumor (NET) metastases is chemotherapy.

Randomized Controlled Trials

There are no published randomized controlled trials comparing RFA to conventional therapy for metastatic neuroendocrine tumors in the liver. Since these tumors are fairly rare, it is unlikely that large randomized trials will be conducted.

Nonrandomized Trials

Evidence from case series and retrospective studies have consistently suggested that RFA may provide a benefit in both survival and symptom control. For example, one large case series of various metastatic tumors included 295 neuroendocrine tumor metastases in the liver.[40] Local tumor recurrence rates were significantly lower for neuroendocrine tumors than for any of the other tumors in the study including HCC and metastatic CRC. Another case series included 63 patients with neuroendocrine metastases which included 36 carcinoid, 18 pancreatic islet cell, and 9 medullary thyroid tumors.[41] The authors reported that 92% of patients had at least partial symptom relief one week after surgery; 70% had complete relief at that time. Mean duration of symptom control was 11 months.

Clinical Practice Guidelines

- The 2014 NCCN guidelines listed ablative therapies, including RFA, as a treatment option for patients with clinically significant progression of unresectable metastatic carcinoid or other neuroendocrine tumors in the liver if near-complete treatment of tumor burden can be achieved.[2]
- The 2011 ACR Appropriateness Criteria® considered the following treatment options for control of tumor growth and symptom management:[24]
    - Typically, medical therapy is the initial treatment for symptom control.
    - For tumors that become refractory to medical therapy, thermal ablation "may be feasible in certain cases," though often suboptimal since most patients present with multiple bilobar metastases. However, ablation "can still play a meaningful role as an adjunctive intraoperative therapy or as an alternative treatment for poor surgical candidates."

<u>Metastases to the Liver from Organ Tumors Other Than Colorectal or Neuroendocrine Tumors</u>

Randomized Controlled Trials

There are no randomized, controlled trials comparing the effects of RFA with standard treatments for these tumors.

Nonrandomized Trials

Metastatic tumors in the liver other than CRC and neuroendocrine have not been well-studied. Evidence is currently absent, or limited to small case series and retrospective reviews.[40,42-45] These preliminary studies are difficult to compare because they are few in number, have small study populations, have no control group for comparison, and patient selection was not randomized. In addition, there were protocol differences that could affect results, such as how "unresectable" was defined, patient inclusion criteria (e.g., tumor size, number, distribution; prior treatments), RFA technology, and physician experience.[46,47]

Clinical Practice Guidelines

There are no clinical practice guidelines or position statements from U.S. professional associations that recommend radiofrequency ablation for treatment of metastases to the liver from tumors other than CRC or neuroendocrine tumors. There is no consensus among practitioners as to the best approach, i.e., via laparotomy, laparoscopy, or percutaneously, or patient selection criteria.

RFA of Unresectable HCC Tumors in the Transplant Setting

The goal of RFA prior to transplantation is to maintain a patient's eligibility for liver transplant by either downsizing a large tumor or by preventing progression of a smaller tumor. The literature related to locoregional therapy for HCC in the transplant setting can be divided into 3 objectives:

- Prevention of tumor progression while on the waiting list
- Downgrading HCC prior to transplantation
- To reduce risk of post-transplantation tumor recurrence in patients with T3 tumors

Assessment of the effects of pre-transplantation RFA on these objectives would, ideally, include clinical trials that compare the recurrence-free survival of patients who received pretransplant locoregional therapies with those who did not and to study recurrence-free survival in patients who received locoregional therapies to downsize larger tumor(s) or to prevent progression of smaller tumor(s) in order to meet transplant waiting list criteria.

The current published evidence is limited to case series and retrospective reviews which are considered unreliable due to methodologic limitations such as lack of randomization and lack of a control group for comparison.[48-56] In addition to these limitations, current studies targeted only a subset of candidates for liver transplant to treat HCC. Because only patients with adequate liver reserves were offered treatment, it cannot be determined whether any reported increase in recurrence-free survival was related to the pretransplant locoregional therapy or liver reserve status. It is unknown whether patients with adequate liver reserves have improved outcomes regardless of pretransplant management.

United Network for Organ Sharing policy

The United Network for Organ Sharing (UNOS) recognizes pretransplant locoregional therapies including RFA as a component of patient management during the waiting period for a donor liver.[57] In allocating donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. For HCC, part of this balance included tumor size and number of nodules as follows:

- T1: 1 nodule 1.9 cm or smaller
- T2: 1 nodule between 2.0–5.0 cm, or 2 or 3 nodules each smaller than 3.0 cm
- T3: 1 nodule larger than 5.0 cm, or 2 or 3 nodules with at least 1 larger than 3.0 cm

Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions were considered at high risk of post-transplant recurrence. Patients with T2 tumors were considered to have an increased risk of dying while on the waiting list compared with T1 lesions, and an acceptable risk of post-transplant tumor recurrence. Therefore, the UNOS criteria prioritized T2 HCC. In addition, patients could be removed from the waiting list if they were determined to be unsuitable for transplantation based on progression of HCC. Thus these criteria provide incentives to use locoregional therapies to maintain T2 classification.

The UNOS allocation system provides incentives to use locoregional therapies in 2 different settings:

- To downsize T3 tumors to T2 status to meet the UNOS criteria for additional allocation points; or
- To prevent progress of T2 tumors while on the waiting list to maintain the UNOS allocation points.

These 2 indications are discussed further here. It should be noted that the UNOS policy addresses the role of locoregional therapy in the pretransplant setting as follows:

> Organ Procurement and Transplant Network (OPTN) Class 5T (Treated) nodules are defined as any OPTN Class 5 or biopsy-proven HCC lesion that was automatically approved upon initial application or extension and has subsequently undergone loco-regional treatment. OPTN Class 5T nodules qualify for continued priority points predicated on the pre-treatment classification of the nodule(s) and are defined as:
>
> 1. Past loco-regional treatment for HCC (OPTN class 5 lesion or biopsy proven prior to ablation).
> 2. Evidence of persistent/recurrent HCC such as nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present.

OPTN guidelines also indicate "candidates whose tumors have been ablated after previously meeting the criteria for additional MELD/PELD points (OPTN Class 5T) will continue to receive additional MELD/PELD points (equivalent to a 10-percentage point increase in candidate mortality) every 3 months without RRB review, even if the estimated size of residual viable tumor falls below stage T2 criteria."

Candidates with HCC not meeting transplant criteria, "including those with downsized tumors whose original/presenting tumor was greater than a stage T2, must be referred to the applicable RRB [Regional Review Board] for prospective review in order to receive additional priority."[58]

Clinical Practice Guidelines

- The 2014 NCCN Guidelines recommended that ablative techniques including RFA be considered as bridge therapy to decrease HCC tumor progression and the dropout rate from liver transplantation waiting lists.[21]
- The 2010 update of the practice guideline from the AASLD considered RFA safe and effective for use as a bridge to liver transplantation.[23]
- The 2011 ACR Appropriateness Criteria® considered RFA effective to downstage or bridge patients to transplant or resection.[24] While ablative therapies have been found to decrease the waiting list dropout rate for liver transplant, "published evidence is inconclusive as to whether this effectively improves patient survival."

<u>Adverse Effects of RFA of Liver Tumors</u>

Complication rates for RFA of liver tumors are reported in approximately 7% of patients, as compared with that of open liver resection which may be as high as 22%.[22]

Specific complications reported in the literature to date include the following:[22,25,36,59-61]

- Hemorrhage

- Liver Abscess
- Liver infarction
- Liver failure
- Cutaneous burn
- Diaphragm perforation
- Bowel perforation
- Seeding of the needle tract with cancer cells
- Hydrothorax or hemothorax requiring drainage
- Bile duct injury
- Death

Renal Cell Carcinoma (RCC)

Background

- Radical nephrectomy, partial nephrectomy, or nephron-sparing surgery remains the principal treatments of RCC.
- RFA may be considered a treatment option when surgical excision is not an option such as the following:
    - When preservation of renal function is necessary (e.g., in patients with marginal renal function, a solitary kidney, bilateral tumors)
    - In patients with comorbidities that would render them unfit for surgery.
    - In patients at high risk of developing additional renal cancers (as in von Hippel-Lindau disease).

Systematic Reviews and Meta-Analysis

- Van Poppel et al. conducted a review of the literature published between 2004 and May 2011.[62] The authors reported sufficient evidence to determine that RFA was a reasonable treatment option in certain patients. However, due to insufficient long-term data comparing ablative therapies with surgical excision, the authors recommended that use of RFA be limited to low-grade renal tumors less than 4 cm in patients who were not candidates for surgical resection or active surveillance. The authors also noted the need for long-term prospective studies to compare ablative techniques for renal ablation such as RFA versus cryoablation.

- In 2012, El Dib and colleagues conducted a meta-analysis evaluating RFA and cryoablation for small renal masses.[63] 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 from 2 to 4.3 cm) in the RFA group and 2.5 cm (range from 2 to 4.2 cm) in the cryoablation group. Mean follow-up times for the RFA and cryoablation groups were 18.1 and 17.9 months, respectively. Clinical efficacy, defined as cancer-specific survival rate, radiographic success, no evidence of local tumor progression, or distant metastases, was not significantly different between groups. The pooled proportion of clinical efficacy for RFA was 90% (95% CI: 0.86–0.93) and 89% (95% confidence interval [CI]: 0.83–0.94) for cryoablation.

Randomized Controlled Trials

There are no randomized, controlled trials comparing the effects of RFA with standard treatments for RCC.

Nonrandomized Trials

- Published studies have consistently reported fairly high success rates at up to six years follow-up; two to five re-ablation sessions were often necessary to achieve 95% tumor necrosis.[64-86]
- Numerous case series, while unreliable, consistently suggest that the benefits of RFA outweigh the risks in patients for whom nephrectomy is not possible.
- Current studies suggest that physician specialty (i.e., interventional radiology, urology) and experience, and procedure approach (i.e., percutaneous, open, laparoscopic) may impact tumor recurrence and patient survival outcomes, and authors have recommended further study on these variables.

Clinical Practice Guidelines

- The 2014 NCCN guidelines stated that thermal ablative techniques (e.g., cryosurgery or radiofrequency ablation) can be considered for selected small tumors in patients who are not surgical candidates.[87] The guidelines also noted that "comparison with surgical resection (i.e., total or partial nephrectomy by open or laparoscopic techniques) has not been done", and that "ablative techniques are associated with a higher local recurrence rate than conventional surgery."
- The 2009 consensus guidelines for stage I renal masses from the American Urological Association Education and Research, Inc. considered thermal ablation (cryoablation or RFA) an option for patients at high risk for surgery. The guidelines noted that patients should be made aware of the need for long-term radiographic surveillance after ablation, and that reintervention may be needed for local recurrence.[88]

<u>Adverse Effects of RFA for RCC</u>

Reported complication rates have been low.[64-86,89]

Complications reported in the literature to date have included the following:

- Perinephric hematomas
- Hemorrhage
- Ureteral strictures
- Percutaneous urinary fistula
- Appendiceal perforation

Breast Tumors

<u>Background</u>

- The standard treatment for breast cancer is surgical excision by lumpectomy or mastectomy. Adjuvant radiation therapy, chemotherapy, and/or hormone therapy may also be used.
- If treated, fibroadenomas, benign tumors of the breast, are typically surgically excised.

<u>Literature Appraisal</u>

Systematic Reviews

- In 2010, Zhao et al. conducted a systematic review of 38 studies on ablation techniques for breast cancer treatment published from 1994 to 2009.[90] Nine of the studies reviewed focused on RFA for 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. These studies were limited to feasibility or pilot studies that were difficult to compare due to heterogeneous patient and tumor characteristics and energy sources. In addition, the studies were conducted in the research setting rather than in clinical practice. The authors concluded that RFA for breast cancer tumors was feasible but further studies with longer follow-up on survival, tumor recurrence and cosmetic outcomes are needed.
- Similarly, another 2010 review of 17 studies by Soukup and colleagues reported that RFA for the treatment of breast tumors was feasible and promising.[91] However, while minimal adverse effects and complications occurred with breast RFA, the authors noted that incomplete tumor ablation remained a concern. Additional studies of health outcomes and refinement of the procedure were recommended.

Randomized Controlled Trials

There are no randomized trials comparing survival and local recurrence rates following RFA compared with standard breast cancer treatments.

Nonrandomized Trials

- Current published evidence is limited to preliminary nonrandomized pilot and feasibility studies with small numbers of patients.[92-105] These studies are considered unreliable due to methodologic limitations such as non-random allocation of treatment and a lack of appropriate comparison groups.
- The bulk of the published studies measured secondary outcomes such as tissue analysis for viable cancer cells less than one month following RFA.
- No long-term follow-up data has been reported on local control and survival rates for RFA of breast cancer compared with conventional breast-conserving treatment.
- Small study populations limit the ability to rule out the role of chance as an explanation of study findings.
- The heterogeneity of the patient selection criteria between studies limits meaningful comparison of outcomes. The role of various patient characteristics (e.g., tumor size and location; number of tumors) cannot be ruled out as an explanation for study findings.

Clinical Practice Guidelines

The 2014 NCCN guidelines do not address RFA in the management of breast cancer.[106]

<u>Adverse Effects</u>

No major complications have been reported, though long-term data is limited.

Lung (Pulmonary) Tumors

<u>Background</u>

- Surgery is the current treatment of choice in patients with stage 1 (early stage) primary non-small cell lung carcinoma (NSCLC). (Stage 1 includes 1a: T1N0M0 and 1b: T2N0M0).
- Patients with early stage NSCLC who are not surgical candidates may be candidates for radiation treatment with curative intent.
- RFA is being investigated as a treatment of small primary lung cancers or lung metastases in patients who are not surgical candidates.

Literature Appraisal

Systematic Reviews

- In a 2013 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review on local nonsurgical therapies for stage I non–small-cell lung cancer (NSCLC), no comparative RFA studies were identified.[107] 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 of RFA, surgical excision and stereotactic radiotherapy (SBRT) 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.[108]
- A 2008 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 OS.[109] Seventeen studies were included for a total of 707 patients (range: 12–142). All of the studies were observational case series with no control groups and were classified as poor quality by the authors of the systematic review. No RCTs or comparative studies were found. The definition of nonsurgical 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 3-year survival rates. One-, 2-, and 3-year survival rates ranged from 63–85%, 55–65%, and 15–45%, respectively. There was a wide range in results of local recurrence rates, heterogeneity of patient and tumor characteristics, and relatively short follow-up in most. The authors of the systematic review concluded that there is limited evidence reporting clinical outcomes of RFA treatment of lung tumors, and that the quality of the evidence is relatively low, with no RCTs or case-control trials comparing the use of RFA with conventional treatment for nonsurgical patients.
- More recently, a 2011 systematic review also reported low quality evidence consisting of nonrandomized observational case series with no control group. The review included 46 studies with a total of 2,905 ablations in 1,584 patients.[110] The mean tumor size of 2.8 ± 1.0 cm. Local recurrence occurred in 282 cases (12.2%) and ranged from 0% to 64% as reported in 24 studies. Overall survival rates ranged from 25% to 100% with a mean of 59.4% as reported in 21 studies with a mean of 17.7 ± 12.4 months follow-up. 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, pleural effusion and pain. Mortality related to the RFA procedure was 0.21% overall. The authors concluded RFA for the treatment of lung tumors demonstrated promise but that higher quality studies comparing RFA to other local treatment options "are urgently needed."
- In a 2012 review of evidence from 16 studies, Bilal and colleagues compared RFA to stereotactic ablative radiotherapy (SABR) in patients with inoperable early stage non-small cell lung cancer (NSCLC).[111] The authors found overall survival rates for RFA and SABR were similar in patients

at 1 year (68.2–95% vs. 81–85.7%) and 3 years (36–87.5% vs. 42.7–56%). However, survival rates at 5 years were lower with RFA (20.1–27%) than with SABR (47%). Caution must be used in interpreting these findings drawn from comparisons of results from uncontrolled, case series and retrospective reviews.

Randomized Controlled Trials

There are no randomized trials comparing survival and local recurrence rates following RFA compared with standard treatment of primary or metastatic lung tumors.

Nonrandomized Trials

- Current studies consist of small case series, retrospective reviews, or uncontrolled cohort studies which focused primarily on technical feasibility and initial tumor response.[109,112-142]
- One larger nonrandomized case series was published in 2011. Huang and colleagues prospectively followed 329 consecutive patients treated with RFA for lung tumors.[143] Complications were experienced by 34.3% (113) patients and was 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 < 4 cm but became significant in tumors > 4 cm.
- Study quality concerns include lack of long-term follow-up; significant interstudy heterogeneity in terms of study design, patient populations and RFA methods used; and, non-uniformity of reporting and efficacy scoring criteria. These differences limit meaningful comparison between studies because they may significantly impact study findings.

Clinical Practice Guidelines and Other Considerations

- A 2008 public statement from the U.S. Food and Drug Administration (FDA), which is still in place, stated that FDA has not cleared any RF ablation 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 RF ablation devices in the treatment of lung tumors.[1]
- The 2014 NCCN practice guidelines for non-small cell lung cancer state that recent 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.[144] RFA is not recommended for tumors near major pulmonary vessels.[144] This recommendation was based on category 2A evidence, defined as lower-level evidence with uniform NCCN consensus.
- The 2015 NCCN practice guidelines for small cell lung cancer do not address ablative therapies for this type of cancer or for lung neuroendocrine tumors.[145]
- The 2014 NCCN colon cancer and rectal cancer practice guidelines state that RFA may be considered for treatment of unresectable colorectal metastases in the lung that are amenable to complete ablation.[39,146] This recommendation was based on category 2A evidence, defined as lower-level evidence with uniform NCCN consensus.
- The 2014 NCCN practice guidelines for kidney cancer do not include RFA as a treatment option for metastases in the lung.[87] 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.[147] 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.[148] These consensus guidelines indicate RFA is an alternative treatment option in patients who are not surgical candidates due to severe medical comorbidity.

- The 2011 ACR Appropriateness Criteria on nonsurgical treatment for non-small cell lung cancer stated,[149] "Recently, radiofrequency ablation (RFA) has been advocated as potential alternative to conventional RT for early-stage lung tumors. In RFA, a lesion is ablated with an RF electrode that is placed within the tumor through percutaneous techniques, typically CT guidance. A retrospective analysis at a single institution reported a 2-year local control of 64% in tumors smaller than 3 cm and 25% in tumors larger than 3 cm. The authors reported a 28% overall pneumothorax rate, and a 10% rate of chest tube insertions, similar to data reported by another study. A group of researchers have reported higher complication rates when accounting for delayed or recurrent pneumothoraces. Further work needs to be done to determine the role of RFA in early-stage NSCLC, as well as in recurrent disease and metastatic disease from other sites to the lung."

Adverse Effects

Acute, delayed or recurrent pneumothorax is the most commonly reported complication of lung RFA for primary or metastatic tumors (30-56% of treatment sessions).[136,143,150-153] Most cases resolved without chest tube placement.

Other complications reported in the literature to date are considered uncommon and include the following:[152-157]

- Pleural effusion
- Intrathoracic hemorrhage with or without hemothorax
- Hemoptysis
- Pneumonia
- Fever
- Post procedure chest pain
- Exacerbation of interstitial pneumonia
- Bronchopleural fistula
- Seeding of the needle tract with cancer cells
- Lung inflammation; aseptic pleuritis
- Infection or abscess
- Cough
- Subcutaneous emphysema
- Pain duration ablation procedure
- Pleuritic chest pain
- Pneumonitis
- Stellate ganglion injury
- Brachial plexus injury
- Death

Osteoid osteomas

Background

- Osteomas usually heal spontaneously in three to four years and standard initial treatment includes medical management with NSAIDs.

- Invasive procedures including open surgery, laser photocoagulation, radiofrequency ablation, or core drill excision may be necessary if symptoms cannot be managed with NSAIDs.

Literature Appraisal

Randomized Controlled Trials

There are no randomized trials on the safety and effectiveness of RFA for treatment of osteomas, either as initial treatment or for tumors that have failed to respond to nonsurgical treatment.

Nonrandomized Trials

- Numerous nonrandomized uncontrolled case series have consistently suggested that the benefits of RFA outweigh the risks in patients who require treatment due to failed response to nonsurgical treatments.[158-163]
- Despite the weaknesses in the published clinical evidence, RFA of osteomas has become a standard of care for osteomas that have failed standard treatments. This was based on the lower morbidity and quicker recovery time associated with the procedure compared with open surgery. The risk of osteoma recurrence with RFA is 5–10%; recurrent tumors can be retreated with RFA.
- There are minimal clinical trial data on the risks and benefits of RFA as initial treatment of osteoid tumors. Since most of these tumors heal spontaneously with medical treatment, the necessity of surgical intervention as initial treatment is unclear.

Adverse Effects

- RFA treatment does not limit subsequent use of RFA should a tumor recur.
- RFA is not performed in many spinal osteomas because of possible thermal-related nerve damage.
- No other major complications or adverse events have been reported.

Palliation of Pain from Bone Metastases

Background

- External beam irradiation is often 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 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.
- RFA may be considered another alternative for palliating pain from bone metastases.

Literature Appraisal

Randomized Controlled Trials

There are no randomized trials on the safety and effectiveness of RFA for treatment of painful metastatic bone tumors. A randomized, sham controlled study on this population is unlikely to be conducted due to the level of pain these patients suffer and the lack of treatment options.

Nonrandomized Trials

- Current evidence is limited to data from small, poorly designed case series.[164-168] However, though small and uncontrolled, available studies consistently reported significant improvement in pain following RFA in patients who failed or were poor candidates for standard treatments.
- Clinical trial data is lacking for use of RFA as an alternative to conventional techniques for initial treatment of painful bony metastases.

<u>Adverse Effects</u>

No serious side effects of RFA have been reported in this population.

Head and Neck Tumors

<u>Background</u>

- Tumors of the head and neck arise in the lip, oral cavity, pharynx, larynx, paranasal sinuses and salivary glands.
- Treatment depends on the location and extent of the disease.[169]
    - Standard treatment for patients with early-stage disease (stage I or II) is single-modality with surgery or radiation therapy. The two modalities result in similar survival.
    - Combined modality therapy is required for locally advanced disease.
- In patients with recurrent head and neck cancer, surgical salvage attempts are poor in terms of local control, survival and quality of life, and these recurrent tumors are often untreatable with standard salvage therapies. Palliative chemotherapy or comfort measures may be offered.

<u>Literature Appraisal</u>

Randomized Controlled Trials

There are no randomized trials on the safety and effectiveness of RFA for treatment of head and neck tumors.

Nonrandomized Trials

- Current published evidence is limited to poorly designed case series, feasibility, and retrospective studies that are considered unreliable due to lack of a control group for comparison and lack of randomization to control for bias.[170-174]
- In addition to these methodological limitations, prospective case series included small numbers of patients. Small study populations limit the ability to rule out the role of chance as an explanation of study findings.

Clinical Practice Guidelines

No clinical practice guidelines were identified that recommend the use of RFA in the management of head and neck cancers, including the 2014 NCCN guidelines for head and neck cancers.[175,176]

Adverse Effects

Complications and adverse events are reported to be uncommon, but are often severe. They are generally related to burning of local soft tissue (e.g., fistula formation).[170-173,177]

Thyroid Tumors

Background[178]

- Thyroid carcinoma is uncommon, with a lifetime risk of being diagnosed with thyroid carcinoma less than 1%.
- Thyroid carcinoma occurs 2 to 3 times more often in women than men.
- The main histological types of thyroid carcinoma include: 1) differentiated (including papillary, follicular, and Hürthle); 2) medullary; 3) anaplastic (aggressive undifferentiated tumor).
- Treatment of thyroid cancer depends on the type of carcinoma diagnosed. Anaplastic thyroid cancer is uniformly lethal, however most deaths are from papillary, follicular, and Hürthle cell carcinomas.

Literature Appraisal

Randomized Controlled Trials

- In 2012, Huh and colleagues 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[179]. 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. This study is limited in size and the study did not include cancerous lesions.

Nonrandomized Trials

- Baek et al. reported on a retrospective review of RFA for 1543 benign thyroid nodules in 1459 patients at 13 thyroid centers.[180] 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. Retrospective studies are limited by the accuracy of the medical records reviewed or the recall ability of patients when filling out a study questionnaire. In addition there is no randomization or blinding in a retrospective study design and therefore it is difficult to control bias and confounders.
- In 2013 Lim et al. reported on a case series of 111 patients treated with RFA for 126 benign non-functioning thyroid nodules.[181] Patient follow-up was a mean duration of 49.4 ± 13.6 months. RFA 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.[182] 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% with toxic thyroid nodules). The authors observe that RFA is particularly attractive for elderly people for whom surgery and radioiodine therapy are often contraindicated or ineffective.
- A smaller series (n=33) found similar outcomes in terms of reduction in compressive symptoms and improvement in thyroid function.[183] Hyperfunction was fully controlled in 24% of patients and partially reduced in the others.

Clinical Practice Guidelines

NCCN 2013 guidelines for thyroid carcinoma indicate ablation techniques such as radiofrequency may be considered for palliative resection of symptomatic distant metastases.[178] Ablation may also be considered for asymptomatic distant metastases when there is progressive disease.

Miscellaneous Tumors

<u>Background</u>

- The standard treatment of miscellaneous tumors depends on the type, location, and extent of the cancer.
- A large number of phase II or III clinical trials involving the use of RFA in the treatment of primary or metastatic cancers are underway.[177]

<u>Literature Appraisal</u>

The current published evidence on RFA for other tumors is either absent or is limited to unreliable data from small case series and retrospective reviews. Evidence from these studies is considered unreliable due to methodological limitations such as non-random allocation of treatment and a lack of appropriate comparison groups.[170,182-195]

Summary

<u>Liver Tumors</u>

- Resectable primary liver tumors [hepatocellular carcinoma (HCC)]
  There is insufficient evidence to determine that radiofrequency ablation (RFA) has improved outcomes compared with liver resection when surgical criteria is met based on the current literature and guidelines.
- Unresectable primary liver tumors [hepatocellular carcinoma (HCC)]
  Randomized controlled trials, nonrandomized trials, and clinical practice guidelines have suggested that radiofrequency ablation (RFA) of unresectable HCC may result in improved survival outcomes compared with percutaneous ethanol injections and chemotherapy. In light of this evidence and the lack of treatment options for unresectable primary liver tumors, the current evidence is considered sufficient to suggest that RFA may be beneficial in the short- to mid-term for treatment of no more

than 3 primary liver tumors that are no larger than 5 cm in diameter. Therefore, RFA may be medically necessary as a treatment of these tumors when the goal of treatment is curative and the patient is not a candidate for liver transplantation.

- Unresectable hepatic metastases from colorectal cancer
  The current literature for radiofrequency ablation (RFA) as a treatment of unresectable CRC metastases in the liver is limited to nonrandomized, uncontrolled case series and retrospective reviews which are difficult to compare due to heterogenous patient characteristics, inclusion criteria, RFA techniques, study end-points, and statistical analyses. However, overall the outcomes from these studies have consistently reported low rates of morbidity and mortality and higher survival rates particularly in comparison with chemotherapy. In addition, clinical practice guidelines list RFA as a treatment option for selected patients. In light of this evidence and the lack of treatment options for these patients, RFA may be medically necessary in patients with 5 or fewer unresectable hepatic CRC metastases of 5 cm or smaller in the absence of extrahepatic metastases when the goal of treatment is curative.
- Hepatic metastases from neuroendocrine tumors
  The available evidence suggests that radiofrequency ablation (RFA) may be beneficial for patients with symptomatic neuroendocrine tumor metastases to the liver. Due to the rare nature of these tumors, it is unlikely that data from large randomized trials will ever become available. Data from case series and retrospective reviews have consistently reported durable tumor and symptom control. In addition, clinical practice guidelines list RFA as a treatment option in selected patients. Therefore, RFA may be medically necessary as a treatment of symptomatic neuroendocrine metastases in the liver when medical treatment has failed to control symptoms.
- Hepatic metastases from tumors other than CRC or neuroendocrine tumors
  The evidence is insufficient to permit conclusions about the benefits of radiofrequency ablation (RFA) on metastases in the liver from tumors other than colorectal cancer and neuroendocrine tumors. Therefore, RFA is considered investigational in this patient population.
- Unresectable HCC in the transplant setting
  Because of the lack of well-designed trials comparing post-transplantation survival and tumor recurrence rates of patients with versus without pre-transplant locoregional therapy, much remains unknown about the effect RFA has on the health outcomes of patients with HCC who are awaiting liver transplantation. However, the UNOS guidelines provide an incentive for use of locoregional therapies, including RFA, to maintain T2 status while on the waiting list. Therefore, RFA of HCC may be medically necessary as a bridge to liver transplantation when the intent is to prevent tumor progression or decrease tumor size to achieve or maintain a patient’s candidacy for liver transplant.

Renal Cell Carcinoma

- Although studies for this indication consist mainly of case series and retrospective reviews, the overall body of evidence suggests that radiofrequency ablation (RFA) may be beneficial in the short- to mid-term for small (≤4 cm), localized renal cell carcinomas (RCCs) in patients who are not considered candidates for nephrectomy. Therefore, RFA may be medically necessary for small RCCs in patients who are not surgical candidates or when preservation of kidney function is necessary.
- There is insufficient evidence to determine whether RFA is effective for treatment of resectable renal tumors. Therefore, RFA is considered investigational for treatment of RCC tumors for which surgical resection is an option.

Breast Tumors

There is insufficient evidence to determine the effectiveness of radiofrequency ablation for treatment of benign or malignant breast masses; therefore, this treatment is considered investigational for the treatment of these tumors.

Lung Tumors

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 have 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. Therefore, RFA treatment of isolated peripheral non-small cell lung cancer lesions limited to 3 cm in size in patients when medical co-morbidity renders the individual unfit for those interventions and the tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart may be considered medically necessary. Further, RFA treatment of malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when the patient is not considered a surgical candidate, there is no evidence of extrapulmonary metastases, and the tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart may be considered medically necessary.

Osteoid Osteomas

- Although the published evidence is limited to nonrandomized uncontrolled case series, radiofrequency ablation (RFA) of osteomas has become a standard of care based on expert opinion that the potential benefits of RFA outweigh risks in patients with osteoid tumors who have failed nonsurgical treatments. Therefore, RFA may be medically necessary for selected patients.
- There is insufficient evidence to determine the effectiveness of radiofrequency ablation (RFA) for initial treatment of osteoid tumors and RFA is, therefore, considered investigational for initial treatment of these tumors.

Palliation of Pain for Bone Metastases

- The current evidence is limited to nonrandomized uncontrolled case series; however, these studies have consistently reported significant improvement in pain following radiofrequency ablation (RFA) in patients who have failed or are poor candidates for standard treatments. In light of this evidence, the unlikelihood of randomized controlled trials in these patients, and the lack of treatment options, the potential benefits of RFA appear to outweigh risks in these patients. Therefore, RFA may be medically necessary in patients with painful metastatic bone lesions who have failed or are poor candidates for standard treatments.
- Because of the lack of data on radiofrequency ablation (RFA) for initial treatment of painful bony metastases, this indication is considered investigational.

Head and Neck Cancers

There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective for treatment of tumors of the head and neck. Therefore, RFA is considered investigational for the treatment of head and neck cancers.

Thyroid Tumors

The evidence for radiofrequency ablation (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.

Miscellaneous Tumors

There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective for treatment of other tumors. Therefore RFA is considered investigational for all other tumors.

REFERENCES

1. FDA Public Health Notification: Radiofrequency Ablation of Lung Tumors - Clarification of Regulatory Status. 2008. [cited 07/21/2011]; Available from: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061985.htm
2. National Cancer Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Neuroendocrine Tumors v.2.2014. [cited 07/25/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
3. Weis, S, Franke, A, Mossner, J, Jakobsen, JC, Schoppmeyer, K. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2013;12:CD003046. PMID: 24357457
4. Feng, Q, Chi, Y, Liu, Y, Zhang, L, Liu, Q. Efficacy and safety of percutaneous radiofrequency ablation versus surgical resection for small hepatocellular carcinoma: a meta-analysis of 23 studies. *J Cancer Res Clin Oncol*. 2014 Jun 3. PMID: 24889505
5. Wang, Y, Luo, Q, Li, Y, Deng, S, Wei, S, Li, X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. *PLoS One*. 2014;9:e84484. PMID: 24404166
6. Qi, X, Tang, Y, An, D, et al. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *J Clin Gastroenterol*. 2014 May-Jun;48(5):450-7. PMID: 24172183
7. Duan, C, Liu, M, Zhang, Z, Ma, K, Bie, P. Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. *World J Surg Oncol*. 2013;11:190. PMID: 23941614
8. Agency for Healthcare Research and Quality. Effectivene Health Care Program. Local Thearpies for Unresectable Primary Hepatocellular Carcinoma. Executive Summary. Comparative Effectiveness Review. Number 114. [cited 07/2013]; Available from: http://effectivehealthcare.ahrq.gov/ehc/products/360/1511/liver-cancer-unresectable-executive-130524.pdf
9. Shen, A, Zhang, H, Tang, C, et al. A systematic review of radiofrequency ablation versus percutaneous ethanol injection for small hepatocellular carcinoma up to 3 cm. *J Gastroenterol Hepatol*. 2013 May;28(5):793-800. PMID: 23432154
10. Xu, G, Qi, FZ, Zhang, JH, Cheng, GF, Cai, Y, Miao, Y. Meta-analysis of surgical resection and radiofrequency ablation for early hepatocellular carcinoma. *World J Surg Oncol*. 2012;10:163. PMID: 22897815

11. Tiong, L, Maddern, GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. *Br J Surg*. 2011 Sep;98(9):1210-24. PMID: 21766289
12. Salhab, M, Canelo, R. An overview of evidence-based management of hepatocellular carcinoma: a meta-analysis. *Journal of cancer research and therapeutics*. 2011 Oct-Dec;7(4):463-75. PMID: 22269411
13. Huang, YZ, Zhou, SC, Zhou, H, Tong, M. Radiofrequency Ablation versus Cryosurgery Ablation for Hepatocellular Carcinoma: A Meta-Analysis. *Hepatogastroenterology*. 2013 Jan 16;60(127). PMID: 23321123
14. Feng, K, Yan, J, Li, X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol*. 2012 May 23. PMID: 22634125
15. Galandi, D, Antes, G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2004(2):CD003046. PMID: 15106188
16. Mulier, S, Ni, Y, Jamart, J, Ruers, T, Marchal, G, Michel, L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg*. 2005 Aug;242(2):158-71. PMID: 16041205
17. Morimoto, M, Numata, K, Sugimori, K, et al. Successful initial ablation therapy contributes to survival in patients with hepatocellular carcinoma. *World J Gastroenterol*. 2007 Feb 21;13(7):1003-9. PMID: 17373733
18. Bouza, C, Lopez-Cuadrado, T, Alcazar, R, Saz-Parkinson, Z, Amate, JM. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol*. 2009;9:31. PMID: 19432967
19. Hsieh, CB, Chang, HM, Chen, TW, et al. Comparison of transcatheter arterial chemoembolization, laparoscopic radiofrequency ablation, and conservative treatment for decompensated cirrhotic patients with hepatocellular carcinoma. *World J Gastroenterol*. 2004 Feb 15;10(4):505-8. PMID: 14966906
20. Park, MJ, Kim, TH, Lee, KM, Cheong, JY, Kim, JK. Radiofrequency Ablation of Metastatic Liver Masses: Recurrence Patterns and Prognostic Factors based on Radiologic Features. *Hepatogastroenterology*. 2012 Oct 29;60(123). PMID: 23108077
21. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Hepatobiliary Cancers. v.2.2014. [cited 08/04/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
22. Gervais, DA, Goldberg, SN, Brown, DB, Soulen, MC, Millward, SF, Rajan, DK. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. *J Vasc Interv Radiol*. 2009 Jan;20(1):3-8. PMID: 18948025
23. Bruix J, Sherman M. AASLD Practice Guideline. Management of Hepatocellular Carcinoma: An Update. [cited 07/26/2012]; Available from: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf
24. Kouri BE, Funaki BS, Ray CE Jr, et al. ACR Appropriateness Criteria® radiologic management of hepatic malignancy. [cited 07/25/2014]; Available from: http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/68FFA493F4994FAF88191F8CD36D6834.pdf
25. Wong, SL, Mangu, PB, Choti, MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol*. 2010 Jan 20;28(3):493-508. PMID: 19841322
26. McKay, A, Dixon, E, Taylor, M. Current role of radiofrequency ablation for the treatment of colorectal liver metastases. *Br J Surg*. 2006 Oct;93(10):1192-201. PMID: 16983740

27. Pathak, S, Jones, R, Tang, JM, et al. Ablative therapies for colorectal liver metastases: a systematic review. *Colorectal Dis*. 2011 Sep;13(9):e252-65. PMID: 21689362
28. Cirocchi, R, Trastulli, S, Boselli, C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. *Cochrane Database Syst Rev*. 2012;6:CD006317. PMID: 22696357
29. Weng, M, Zhang, Y, Zhou, D, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. *PLoS One*. 2012;7(9):e45493. PMID: 23029051
30. Loveman, E, Jones, J, Clegg, AJ, et al. The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. *Health Technol Assess*. 2014 Jan;18(7):vii-viii, 1-283. PMID: 24484609
31. 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 Jun;239(6):818-25; discussion 25-7. PMID: 15166961
32. Lencioni, R, Crocetti, L, Cioni, D, Della Pina, C, Bartolozzi, C. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. *Invest Radiol*. 2004 Nov;39(11):689-97. PMID: 15486530
33. Kemeny, N. Management of liver metastases from colorectal cancer. *Oncology (Williston Park)*. 2006 Sep;20(10):1161-76, 79; discussion 79-80, 85-6. PMID: 17024869
34. Ruers, TJ, Joosten, JJ, Wiering, B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. *Ann Surg Oncol*. 2007 Mar;14(3):1161-9. PMID: 17195903
35. de Jong, MC, Pulitano, C, Ribero, D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg*. 2009 Sep;250(3):440-8. PMID: 19730175
36. Van Tilborg, AA, Meijerink, MR, Sietses, C, et al. Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. *Br J Radiol*. 2011 Jun;84(1002):556-65. PMID: 21159807
37. Guenette, JP, Dupuy, DE. Radiofrequency ablation of colorectal hepatic metastases. *J Surg Oncol*. 2010 Dec 15;102(8):978-87. PMID: 21166002
38. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon cancer. v.3.2014. [cited 05/05/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
39. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Rectal Cancer. v.3.2014. [cited 08/04/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf
40. Berber, E, Ari, E, Herceg, N, Siperstein, A. Laparoscopic radiofrequency thermal ablation for unusual hepatic tumors: operative indications and outcomes. *Surg Endosc*. 2005 Dec;19(12):1613-7. PMID: 16247574
41. Mazzaglia, PJ, Berber, E, Milas, M, Siperstein, AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. *Surgery*. 2007 Jul;142(1):10-9. PMID: 17629995
42. Meloni, MF, Andreano, A, Laeseke, PF, Livraghi, T, Sironi, S, Lee, FT, Jr. Breast cancer liver metastases: US-guided percutaneous radiofrequency ablation--intermediate and long-term survival rates. *Radiology*. 2009 Dec;253(3):861-9. PMID: 19709994
43. Jakobs, TF, Hoffmann, RT, Schrader, A, et al. CT-guided radiofrequency ablation in patients with hepatic metastases from breast cancer. *Cardiovasc Intervent Radiol*. 2009 Jan;32(1):38-46. PMID: 18575933

44. Jones, RL, McCall, J, Adam, A, et al. Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. *Eur J Surg Oncol*. 2010 May;36(5):477-82. PMID: 20060679
45. Pawlik, TM, Vauthey, JN, Abdalla, EK, Pollock, RE, Ellis, LM, Curley, SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg*. 2006 Jun;141(6):537-43; discussion 43-4. PMID: 16785353
46. BlueCross BlueShield Association Medical Policy Reference Manual 2003. "Radiofrequency Ablation of Unresectable Liver Tumors." Vol. 18, Tab 13.
47. Garrean, S, Hering, J, Saied, A, Helton, WS, Espat, NJ. Radiofrequency ablation of primary and metastatic liver tumors: a critical review of the literature. *Am J Surg*. 2008 Apr;195(4):508-20. PMID: 18361927
48. Heckman, JT, Devera, MB, Marsh, JW, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. *Ann Surg Oncol*. 2008 Nov;15(11):3169-77. PMID: 18696158
49. Fisher, RA, Maluf, D, Cotterell, AH, et al. Non-resective ablation therapy for hepatocellular carcinoma: effectiveness measured by intention-to-treat and dropout from liver transplant waiting list. *Clin Transplant*. 2004 Oct;18(5):502-12. PMID: 15344951
50. Yamashiki, N, Tateishi, R, Yoshida, H, et al. Ablation therapy in containing extension of hepatocellular carcinoma: a simulative analysis of dropout from the waiting list for liver transplantation. *Liver Transpl*. 2005 May;11(5):508-14. PMID: 15838878
51. Mazzaferro, V, Battiston, C, Perrone, S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg*. 2004 Nov;240(5):900-9. PMID: 15492574
52. Lu, DS, Yu, NC, Raman, SS, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology*. 2005 May;41(5):1130-7. PMID: 15841454
53. Yao, FY, Hirose, R, LaBerge, JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl*. 2005 Dec;11(12):1505-14. PMID: 16315294
54. Sauer, P, Kraus, TW, Schemmer, P, et al. Liver transplantation for hepatocellular carcinoma: is there evidence for expanding the selection criteria? *Transplantation*. 2005 Sep 27;80(1 Suppl):S105-8. PMID: 16286885
55. Merli, M, Nicolini, G, Gentili, F, et al. Predictive factors of outcome after liver transplantation in patients with cirrhosis and hepatocellular carcinoma. *Transplant Proc*. 2005 Jul-Aug;37(6):2535-40. PMID: 16182736
56. Yao, FY, Kinkhabwala, M, LaBerge, JM, et al. The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. *Am J Transplant*. 2005 Apr;5(4 Pt 1):795-804. PMID: 15760404
57. Transplant.hrsa.gov website; 3.6 Allocation of Livers policy. [cited 11/09/2009]; Available from: http://www.unos.org/PoliciesandBylaws2/policies/pdfs/policy_8.pdf
58. Organ Procurement and Transplantation Network (OPTN). Organ Distribution: Allocation of Livers. (3.6.4.4). [cited 03/04/2014]; Available from: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf
59. Berber, E, Siperstein, A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Ann Surg Oncol*. 2008 Oct;15(10):2757-64. PMID: 18618182
60. Kong, WT, Zhang, WW, Qiu, YD, et al. Major complications after radiofrequency ablation for liver tumors: analysis of 255 patients. *World J Gastroenterol*. 2009 Jun 7;15(21):2651-6. PMID: 19496197

61. Snoeren, N, Jansen, MC, Rijken, AM, et al. Assessment of viable tumour tissue attached to needle applicators after local ablation of liver tumours. *Dig Surg*. 2009;26(1):56-62. PMID: 19169031
62. Van Poppel, H, Becker, F, Cadeddu, JA, et al. Treatment of localised renal cell carcinoma. *Eur Urol*. 2011 Oct;60(4):662-72. PMID: 21726933
63. El Dib, R, Touma, NJ, Kapoor, A. Cryoablation vs radiofrequency ablation for the treatment of renal cell carcinoma: a meta-analysis of case series studies. *BJU Int*. 2012 Aug;110(4):510-6. PMID: 22304329
64. Memarsadeghi, M, Schmook, T, Remzi, M, et al. Percutaneous radiofrequency ablation of renal tumors: midterm results in 16 patients. *Eur J Radiol*. 2006 Aug;59(2):183-9. PMID: 16725292
65. Gupta, A, Raman, JD, Leveillee, RJ, et al. General anesthesia and contrast-enhanced computed tomography to optimize renal percutaneous radiofrequency ablation: multi-institutional intermediate-term results. *J Endourol*. 2009 Jul;23(7):1099-105. PMID: 19530948
66. Long, L, Park, S. Differences in patterns of care: reablation and nephrectomy rates after needle ablative therapy for renal masses stratified by medical specialty. *J Endourol*. 2009 Mar;23(3):421-6. PMID: 19260799
67. Mylona, S, Kokkinaki, A, Pomoni, M, Galani, P, Ntai, S, Thanos, L. Percutaneous radiofrequency ablation of renal cell carcinomas in patients with solitary kidney: 6 years experience. *Eur J Radiol*. 2009 Feb;69(2):351-6. PMID: 18313248
68. Carey, RI, Leveillee, RJ. First prize: direct real-time temperature monitoring for laparoscopic and CT-guided radiofrequency ablation of renal tumors between 3 and 5 cm. *J Endourol*. 2007 Aug;21(8):807-13. PMID: 17867933
69. Ahrar, K, Matin, S, Wood, CG, et al. Percutaneous radiofrequency ablation of renal tumors: technique, complications, and outcomes. *J Vasc Interv Radiol*. 2005 May;16(5):679-88. PMID: 15872323
70. Boss, A, Clasen, S, Kuczyk, M, et al. Magnetic resonance-guided percutaneous radiofrequency ablation of renal cell carcinomas: a pilot clinical study. *Invest Radiol*. 2005 Sep;40(9):583-90. PMID: 16118551
71. Chiou, YY, Hwang, JI, Chou, YH, Wang, JH, Chiang, JH, Chang, CY. Percutaneous radiofrequency ablation of renal cell carcinoma. *J Chin Med Assoc*. 2005 May;68(5):221-5. PMID: 15909727
72. Gervais, DA, McGovern, FJ, Arellano, RS, McDougal, WS, Mueller, PR. Radiofrequency ablation of renal cell carcinoma: part 1, Indications, results, and role in patient management over a 6-year period and ablation of 100 tumors. *AJR Am J Roentgenol*. 2005 Jul;185(1):64-71. PMID: 15972400
73. Mahnken, AH, Rohde, D, Brkovic, D, Gunther, RW, Tacke, JA. Percutaneous radiofrequency ablation of renal cell carcinoma: preliminary results. *Acta Radiol*. 2005 Apr;46(2):208-14. PMID: 15902899
74. Matsumoto, ED, Johnson, DB, Ogan, K, et al. Short-term efficacy of temperature-based radiofrequency ablation of small renal tumors. *Urology*. 2005 May;65(5):877-81. PMID: 15882715
75. McDougal, WS, Gervais, DA, McGovern, FJ, Mueller, PR. Long-term followup of patients with renal cell carcinoma treated with radio frequency ablation with curative intent. *J Urol*. 2005 Jul;174(1):61-3. PMID: 15947578
76. Merkle, EM, Nour, SG, Lewin, JS. MR imaging follow-up after percutaneous radiofrequency ablation of renal cell carcinoma: findings in 18 patients during first 6 months. *Radiology*. 2005 Jun;235(3):1065-71. PMID: 15914485

77. Varkarakis, IM, Allaf, ME, Inagaki, T, et al. Percutaneous radio frequency ablation of renal masses: results at a 2-year mean followup. *J Urol*. 2005 Aug;174(2):456-60; discussion 60. PMID: 16006864
78. Weizer, AZ, Raj, GV, O'Connell, M, Robertson, CN, Nelson, RC, Polascik, TJ. Complications after percutaneous radiofrequency ablation of renal tumors. *Urology*. 2005 Dec;66(6):1176-80. PMID: 16360436
79. Aron, M, Gill, IS. Minimally invasive nephron-sparing surgery (MINSS) for renal tumours. Part II: probe ablative therapy. *Eur Urol*. 2007 Feb;51(2):348-57. PMID: 17084513
80. Mouraviev, V, Joniau, S, Van Poppel, H, Polascik, TJ. Current status of minimally invasive ablative techniques in the treatment of small renal tumours. *Eur Urol*. 2007 Feb;51(2):328-36. PMID: 17069964
81. Wingo, MS, Leveillee, RJ. Central and deep renal tumors can be effectively ablated: radiofrequency ablation outcomes with fiberoptic peripheral temperature monitoring. *J Endourol*. 2008 Jun;22(6):1261-7. PMID: 18484892
82. Zagoria, RJ, Traver, MA, Werle, DM, Perini, M, Hayasaka, S, Clark, PE. Oncologic efficacy of CT-guided percutaneous radiofrequency ablation of renal cell carcinomas. *AJR Am J Roentgenol*. 2007 Aug;189(2):429-36. PMID: 17646471
83. Breen, DJ, Rutherford, EE, Stedman, B, et al. Management of renal tumors by image-guided radiofrequency ablation: experience in 105 tumors. *Cardiovasc Intervent Radiol*. 2007 Sep-Oct;30(5):936-42. PMID: 17573550
84. Abdellaoui, A, Watkinson, AF. Radiofrequency ablation of renal tumors. *Future Oncol*. 2008 Feb;4(1):103-11. PMID: 18241005
85. Stern, JM, Svatek, R, Park, S, et al. Intermediate comparison of partial nephrectomy and radiofrequency ablation for clinical T1a renal tumours. *BJU Int*. 2007 Aug;100(2):287-90. PMID: 17617136
86. Kunkle, DA, Uzzo, RG. Cryoablation or radiofrequency ablation of the small renal mass : a meta-analysis. *Cancer*. 2008 Nov 15;113(10):2671-80. PMID: 18816624
87. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Kidney Cancer v.3.2014. [cited 08/04/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
88. American Urological Association Education and Research, Inc. Guideline for management of the clinical stage 1 renal mass. 2009. [cited 07/28/2012]; Available from: http://www.guideline.gov/content.aspx?id=14573&search=%22radiofrequency+ablation%22+kidney
89. Boone, J, Bex, A, Prevoo, W. Percutaneous radiofrequency ablation of a small renal mass complicated by appendiceal perforation. *Cardiovasc Intervent Radiol*. 2012 Jun;35(3):695-9. PMID: 22011782
90. Zhao, Z, Wu, F. Minimally-invasive thermal ablation of early-stage breast cancer: a systemic review. *Eur J Surg Oncol*. 2010 Dec;36(12):1149-55. PMID: 20889281
91. Soukup, B, Bismohun, S, Reefy, S, Mokbel, K. The evolving role of radiofrequency ablation therapy of breast lesions. *Anticancer Res*. 2010 Sep;30(9):3693-7. PMID: 20944155
92. Kontos, M, Felekouras, E, Fentiman, IS. Radiofrequency ablation in the treatment of primary breast cancer: no surgical redundancies yet. *Int J Clin Pract*. 2008 May;62(5):816-20. PMID: 18412934
93. Singletary, SE. Breast cancer surgery for the 21st century: the continuing evolution of minimally invasive treatments. *Minerva Chir*. 2006 Aug;61(4):333-52. PMID: 17122766
94. Noguchi, M. Radiofrequency ablation therapy for small breast cancer. *Semin Ultrasound CT MR*. 2009 Apr;30(2):105-12. PMID: 19358441

95. Fornage, BD, Sneige, N, Ross, MI, et al. Small (< or = 2-cm) breast cancer treated with US-guided radiofrequency ablation: feasibility study. *Radiology*. 2004 Apr;231(1):215-24. PMID: 14990810
96. van der Ploeg, IM, van Esser, S, van den Bosch, MA, et al. Radiofrequency ablation for breast cancer: a review of the literature. *Eur J Surg Oncol*. 2007 Aug;33(6):673-7. PMID: 17369003
97. Noguchi, M. Is radiofrequency ablation treatment for small breast cancer ready for "prime time"? *Breast Cancer Res Treat*. 2007 Dec;106(3):307-14. PMID: 17972173
98. Susini, T, Nori, J, Olivieri, S, et al. Radiofrequency ablation for minimally invasive treatment of breast carcinoma. A pilot study in elderly inoperable patients. *Gynecol Oncol*. 2007 Feb;104(2):304-10. PMID: 17070572
99. Oura, S, Tamaki, T, Hirai, I, et al. Radiofrequency ablation therapy in patients with breast cancers two centimeters or less in size. *Breast Cancer*. 2007;14(1):48-54. PMID: 17244994
100. van Esser, S, van den Bosch, MA, van Diest, PJ, Mali, WT, Borel Rinkes, IH, van Hillegersberg, R. Minimally invasive ablative therapies for invasive breast carcinomas: an overview of current literature. *World J Surg*. 2007 Dec;31(12):2284-92. PMID: 17957404
101. Imoto, S, Wada, N, Sakemura, N, Hasebe, T, Murata, Y. Feasibility study on radiofrequency ablation followed by partial mastectomy for stage I breast cancer patients. *Breast*. 2009 Apr;18(2):130-4. PMID: 19324550
102. Garbay, JR, Mathieu, MC, Lamuraglia, M, Lassau, N, Balleyguier, C, Rouzier, R. Radiofrequency thermal ablation of breast cancer local recurrence: a phase II clinical trial. *Ann Surg Oncol*. 2008 Nov;15(11):3222-6. PMID: 18709415
103. Athanassiou, E, Sioutopoulou, D, Vamvakopoulos, N, et al. The fat content of small primary breast cancer interferes with radiofrequency-induced thermal ablation. *Eur Surg Res*. 2009;42(1):54-8. PMID: 18987475
104. Kinoshita, T, Iwamoto, E, Tsuda, H, Seki, K. Radiofrequency ablation as local therapy for early breast carcinomas. *Breast Cancer*. 2011 Jan;18(1):10-7. PMID: 20072824
105. Klimberg, VS, Ochoa, D, Henry-Tillman, R, et al. Long-term results of phase II ablation after breast lumpectomy added to extend intraoperative margins (ABLATE l) trial. *J Am Coll Surg*. 2014 Apr;218(4):741-9. PMID: 24655863
106. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer. v.3.2014. [cited 07/25/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
107. Ratko, TA, Vats, V, Brock, J, Ruffner, BW, Aronson, N. Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non-Small-Cell Lung Cancer. *AHRQ Comparative Effectiveness Reviews*. 2013. PMID: 23865091
108. Schlijper, RC, Grutters, JP, Houben, R, et al. What to choose as radical local treatment for lung metastases from colo-rectal cancer: surgery or radiofrequency ablation? *Cancer Treat Rev*. 2014 Feb;40(1):60-7. PMID: 23768754
109. Zhu, JC, Yan, TD, Morris, DL. A systematic review of radiofrequency ablation for lung tumors. *Ann Surg Oncol*. 2008 Jun;15(6):1765-74. PMID: 18368456
110. Chan, VO, McDermott, S, Malone, DE, Dodd, JD. Percutaneous radiofrequency ablation of lung tumors: evaluation of the literature using evidence-based techniques. *J Thorac Imaging*. 2011 Feb;26(1):18-26. PMID: 20829720
111. Bilal, H, Mahmood, S, Rajashanker, B, Shah, R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interact Cardiovasc Thorac Surg*. 2012 Aug;15(2):258-65. PMID: 22581864
112. Akeboshi, M, Yamakado, K, Nakatsuka, A, et al. Percutaneous radiofrequency ablation of lung neoplasms: initial therapeutic response. *J Vasc Interv Radiol*. 2004 May;15(5):463-70. PMID: 15126656

113. Belfiore, G, Moggio, G, Tedeschi, E, et al. CT-guided radiofrequency ablation: a potential complementary therapy for patients with unresectable primary lung cancer--a preliminary report of 33 patients. *AJR Am J Roentgenol*. 2004 Oct;183(4):1003-11. PMID: 15385294
114. Gadaleta, C, Catino, A, Ranieri, G, et al. Radiofrequency thermal ablation of 69 lung neoplasms. *J Chemother*. 2004 Nov;16 Suppl 5:86-9. PMID: 15675488
115. Jin, GY, Lee, JM, Lee, YC, Han, YM, Lim, YS. Primary and secondary lung malignancies treated with percutaneous radiofrequency ablation: evaluation with follow-up helical CT. *AJR Am J Roentgenol*. 2004 Oct;183(4):1013-20. PMID: 15385295
116. Kang, S, Luo, R, Liao, W, Wu, H, Zhang, X, Meng, Y. Single group study to evaluate the feasibility and complications of radiofrequency ablation and usefulness of post treatment position emission tomography in lung tumours. *World J Surg Oncol*. 2004;2:30. PMID: 15350201
117. King, J, Glenn, D, Clark, W, et al. Percutaneous radiofrequency ablation of pulmonary metastases in patients with colorectal cancer. *Br J Surg*. 2004 Feb;91(2):217-23. PMID: 14760671
118. Lee, JM, Jin, GY, Goldberg, SN, et al. Percutaneous radiofrequency ablation for inoperable non-small cell lung cancer and metastases: preliminary report. *Radiology*. 2004 Jan;230(1):125-34. PMID: 14645875
119. Steinke, K, Glenn, D, King, J, et al. Percutaneous imaging-guided radiofrequency ablation in patients with colorectal pulmonary metastases: 1-year follow-up. *Ann Surg Oncol*. 2004 Feb;11(2):207-12. PMID: 14761926
120. Yasui, K, Kanazawa, S, Sano, Y, et al. Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. *Radiology*. 2004 Jun;231(3):850-7. PMID: 15105453
121. Bojarski, JD, Dupuy, DE, Mayo-Smith, WW. CT imaging findings of pulmonary neoplasms after treatment with radiofrequency ablation: results in 32 tumors. *AJR Am J Roentgenol*. 2005 Aug;185(2):466-71. PMID: 16037522
122. Fernando, HC, De Hoyos, A, Landreneau, RJ, et al. Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates. *J Thorac Cardiovasc Surg*. 2005 Mar;129(3):639-44. PMID: 15746749
123. Nguyen, CL, Scott, WJ, Young, NA, Rader, T, Giles, LR, Goldberg, M. Radiofrequency ablation of primary lung cancer: results from an ablate and resect pilot study. *Chest*. 2005 Nov;128(5):3507-11. PMID: 16304306
124. VanSonnenberg, E, Shankar, S, Morrison, PR, et al. Radiofrequency ablation of thoracic lesions: part 2, initial clinical experience--technical and multidisciplinary considerations in 30 patients. *AJR Am J Roentgenol*. 2005 Feb;184(2):381-90. PMID: 15671350
125. Simon, CJ, Dupuy, DE, DiPetrillo, TA, et al. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology*. 2007 Apr;243(1):268-75. PMID: 17392258
126. Ambrogi, MC, Lucchi, M, Dini, P, et al. Percutaneous radiofrequency ablation of lung tumours: results in the mid-term. *Eur J Cardiothorac Surg*. 2006 Jul;30(1):177-83. PMID: 16723242
127. de Baere, T, Palussiere, J, Auperin, A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. *Radiology*. 2006 Aug;240(2):587-96. PMID: 16864679
128. Yamakado, K, Hase, S, Matsuoka, T, et al. Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. *J Vasc Interv Radiol*. 2007 Mar;18(3):393-8. PMID: 17377185
129. Yan, TD, King, J, Sjarif, A, et al. Treatment failure after percutaneous radiofrequency ablation for nonsurgical candidates with pulmonary metastases from colorectal carcinoma. *Ann Surg Oncol*. 2007 May;14(5):1718-26. PMID: 17285398

130. Haasbeek, CJ, Senan, S, Smit, EF, Paul, MA, Slotman, BJ, Lagerwaard, FJ. Critical review of nonsurgical treatment options for stage I non-small cell lung cancer. *Oncologist*. 2008 Mar;13(3):309-19. PMID: 18378542
131. Onishi, H, Shirato, H, Nagata, Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol*. 2007 Jul;2(7 Suppl 3):S94-100. PMID: 17603311
132. Lencioni, R, Crocetti, L, Cioni, R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol*. 2008 Jul;9(7):621-8. PMID: 18565793
133. Zhu, JC, Yan, TD, Glenn, D, Morris, DL. Radiofrequency ablation of lung tumors: feasibility and safety. *Ann Thorac Surg*. 2009 Apr;87(4):1023-8. PMID: 19324122
134. Pennathur, A, Abbas, G, Gooding, WE, et al. Image-guided radiofrequency ablation of lung neoplasm in 100 consecutive patients by a thoracic surgical service. *Ann Thorac Surg*. 2009 Nov;88(5):1601-6; discussion 7-8. PMID: 19853119
135. Beland, MD, Wasser, EJ, Mayo-Smith, WW, Dupuy, DE. Primary non-small cell lung cancer: review of frequency, location, and time of recurrence after radiofrequency ablation. *Radiology*. 2010 Jan;254(1):301-7. PMID: 20032160
136. Lanuti, M, Sharma, A, Digumarthy, SR, et al. Radiofrequency ablation for treatment of medically inoperable stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2009 Jan;137(1):160-6. PMID: 19154919
137. Yamakado, K, Inoue, Y, Takao, M, et al. Long-term results of radiofrequency ablation in colorectal lung metastases: single center experience. *Oncol Rep*. 2009 Oct;22(4):885-91. PMID: 19724869
138. Soga, N, Yamakado, K, Gohara, H, et al. Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. *BJU Int*. 2009 Sep;104(6):790-4. PMID: 19338555
139. Zemlyak, A, Moore, WH, Bilfinger, TV. Comparison of survival after sublobar resections and ablative therapies for stage I non-small cell lung cancer. *J Am Coll Surg*. 2010 Jul;211(1):68-72. PMID: 20610251
140. Lee, H, Jin, GY, Han, YM, et al. Comparison of survival rate in primary non-small-cell lung cancer among elderly patients treated with radiofrequency ablation, surgery, or chemotherapy. *Cardiovasc Intervent Radiol*. 2012 Apr;35(2):343-50. PMID: 21626257
141. Ambrogi, MC, Fanucchi, O, Cioni, R, et al. Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. *J Thorac Oncol*. 2011 Dec;6(12):2044-51. PMID: 22052222
142. von Meyenfeldt, EM, Prevoo, W, Peyrot, D, et al. Local progression after radiofrequency ablation for pulmonary metastases. *Cancer*. 2011 Aug 15;117(16):3781-7. PMID: 21319158
143. Huang, L, Han, Y, Zhao, J, et al. Is radiofrequency thermal ablation a safe and effective procedure in the treatment of pulmonary malignancies? *Eur J Cardiothorac Surg*. 2011 Mar;39(3):348-51. PMID: 20663679
144. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. v.4.2014. [cited 06/20/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
145. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Small Cell Lung Cancer. v.1.2015. [cited 07/16/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf

146. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon Cancer. v.3.2014. [cited 08/04/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
147. Howington, JA, Blum, MG, Chang, AC, Balekian, AA, Murthy, SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013 May;143(5 Suppl):e278S-313S. PMID: 23649443
148. Donington, J, Ferguson, M, Mazzone, P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest*. 2012;142:1620-35. PMID: 23208335
149. Gewanter, RM, Rosenzweig, KE, Chang, JY, et al. ACR Appropriateness Criteria: nonsurgical treatment for non-small-cell lung cancer: good performance status/definitive intent. *Curr Probl Cancer*. 2010 May-Jun;34(3):228-49. PMID: 20541060. [cited 07/2013]; Available from: http://www.guideline.gov/content.aspx?id=23840&search=imrt+and+lung
150. Yoshimatsu, R, Yamagami, T, Terayama, K, Matsumoto, T, Miura, H, Nishimura, T. Delayed and recurrent pneumothorax after radiofrequency ablation of lung tumors. *Chest*. 2009 Apr;135(4):1002-9. PMID: 19017870
151. Hiraki, T, Tajiri, N, Mimura, H, et al. Pneumothorax, pleural effusion, and chest tube placement after radiofrequency ablation of lung tumors: incidence and risk factors. *Radiology*. 2006 Oct;241(1):275-83. PMID: 16908680
152. Sano, Y, Kanazawa, S, Gobara, H, et al. Feasibility of percutaneous radiofrequency ablation for intrathoracic malignancies: a large single-center experience. *Cancer*. 2007 Apr 1;109(7):1397-405. PMID: 17315166
153. Okuma, T, Matsuoka, T, Yamamoto, A, et al. Frequency and risk factors of various complications after computed tomography-guided radiofrequency ablation of lung tumors. *Cardiovasc Intervent Radiol*. 2008 Jan-Feb;31(1):122-30. PMID: 17985181
154. Hiraki, T, Mimura, H, Gobara, H, et al. Two cases of needle-tract seeding after percutaneous radiofrequency ablation for lung cancer. *J Vasc Interv Radiol*. 2009 Mar;20(3):415-8. PMID: 19167247
155. Nomura, M, Yamakado, K, Nomoto, Y, et al. Complications after lung radiofrequency ablation: risk factors for lung inflammation. *Br J Radiol*. 2008 Mar;81(963):244-9. PMID: 18208852
156. Hiraki, T, Gobara, H, Kato, K, Toyooka, S, Mimura, H, Kanazawa, S. Bronchiolitis obliterans organizing pneumonia after radiofrequency ablation of lung cancer: report of three cases. *J Vasc Interv Radiol*. 2012 Jan;23(1):126-30. PMID: 22221477
157. Palussiere, J, Cannella, M, Gomez, F, Ferron, S, Descat, E. Stellate ganglion injury after percutaneous radiofrequency ablation of a lung tumor. *Cardiovasc Intervent Radiol*. 2011 Aug;34(4):873-6. PMID: 21153414
158. Rosenthal, DI, Hornicek, FJ, Torriani, M, Gebhardt, MC, Mankin, HJ. Osteoid osteoma: percutaneous treatment with radiofrequency energy. *Radiology*. 2003 Oct;229(1):171-5. PMID: 12944597
159. Cioni, R, Armillotta, N, Bargellini, I, et al. CT-guided radiofrequency ablation of osteoid osteoma: long-term results. *Eur Radiol*. 2004 Jul;14(7):1203-8. PMID: 15014976
160. Martel, J, Bueno, A, Ortiz, E. Percutaneous radiofrequency treatment of osteoid osteoma using cool-tip electrodes. *Eur J Radiol*. 2005 Dec;56(3):403-8. PMID: 15964164
161. Ghanem, I. The management of osteoid osteoma: updates and controversies. *Curr Opin Pediatr*. 2006 Feb;18(1):36-41. PMID: 16470160
162. Papagelopoulos, PJ, Mavrogenis, AF, Kyriakopoulos, CK, et al. Radiofrequency ablation of intra-articular osteoid osteoma of the hip. *J Int Med Res*. 2006 Sep-Oct;34(5):537-44. PMID: 17133784

163. Rimondi, E, Mavrogenis, AF, Rossi, G, et al. Radiofrequency ablation for non-spinal osteoid osteomas in 557 patients. *Eur Radiol*. 2012 Jan;22(1):181-8. PMID: 21842430
164. Goetz, MP, Callstrom, MR, Charboneau, JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol*. 2004 Jan 15;22(2):300-6. PMID: 14722039
165. Kojima, H, Tanigawa, N, Kariya, S, Komemushi, A, Shomura, Y, Sawada, S. Clinical assessment of percutaneous radiofrequency ablation for painful metastatic bone tumors. *Cardiovasc Intervent Radiol*. 2006 Nov-Dec;29(6):1022-6. PMID: 16988875
166. Proschek, D, Kurth, A, Proschek, P, Vogl, TJ, Mack, MG. Prospective pilot-study of combined bipolar radiofrequency ablation and application of bone cement in bone metastases. *Anticancer Res*. 2009 Jul;29(7):2787-92. PMID: 19596962
167. Thanos, L, Mylona, S, Galani, P, et al. Radiofrequency ablation of osseous metastases for the palliation of pain. *Skeletal Radiol*. 2008 Mar;37(3):189-94. PMID: 18030464
168. Gronemeyer, DH, Schirp, S, Gevargez, A. Image-guided radiofrequency ablation of spinal tumors: preliminary experience with an expandable array electrode. *Cancer J*. 2002 Jan-Feb;8(1):33-9. PMID: 11898806
169. NCCN Website: NCCN Guidelines™ & Clinical Resources. [cited 11/09/2009]; Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
170. Owen, RP, Silver, CE, Ravikumar, TS, Brook, A, Bello, J, Breining, D. Techniques for radiofrequency ablation of head and neck tumors. *Arch Otolaryngol Head Neck Surg*. 2004 Jan;130(1):52-6. PMID: 14732768
171. Brook, AL, Gold, MM, Miller, TS, et al. CT-guided radiofrequency ablation in the palliative treatment of recurrent advanced head and neck malignancies. *J Vasc Interv Radiol*. 2008 May;19(5):725-35. PMID: 18440462
172. Carney, AS, Timms, MS, Marnane, CN, Krishnan, S, Rees, G, Mirza, S. Radiofrequency coblation for the resection of head and neck malignancies. *Otolaryngol Head Neck Surg*. 2008 Jan;138(1):81-5. PMID: 18164998
173. Liukko, T, Makitie, AA, Markkola, A, Ylikoski, J, Back, L. Radiofrequency induced thermotherapy: an alternative palliative treatment modality in head and neck cancer. *Eur Arch Otorhinolaryngol*. 2006 Jun;263(6):532-6. PMID: 16565858
174. Owen, RP, Khan, SA, Negassa, A, et al. Radiofrequency ablation of advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2011 May;137(5):493-8. PMID: 21576561
175. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Head and Neck Cancer v.2.2014. [cited 07/16/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
176. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Head and Neck Cancers. v.2.2014. [cited 08/05/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
177. ClinicalTrials.gov website; Radiofrequency Ablation. [cited 11/09/2009]; Available from: http://www.clinicaltrials.gov/ct2/results?term=%22radiofrequency+ablation%22
178. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Thyroid Carcinoma. v.2.2014. [cited 08/13/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
179. Huh, JY, Baek, JH, Choi, H, Kim, JK, Lee, JH. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session--prospective randomized study. *Radiology*. 2012 Jun;263(3):909-16. PMID: 22438360
180. Baek, JH, Lee, JH, Sung, JY, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. *Radiology*. 2012 Jan;262(1):335-42. PMID: 21998044

181. Lim, HK, Lee, JH, Ha, EJ, Sung, JY, Kim, JK, Baek, JH. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. *Eur Radiol*. 2013 Apr;23(4):1044-9. PMID: 23096937
182. Spiezia, S, Garberoglio, R, Milone, F, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. *Thyroid*. 2009 Mar;19(3):219-25. PMID: 19265492
183. Deandrea, M, Limone, P, Basso, E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. *Ultrasound Med Biol*. 2008 May;34(5):784-91. PMID: 18207307
184. Mayo-Smith, WW, Dupuy, DE. Adrenal neoplasms: CT-guided radiofrequency ablation--preliminary results. *Radiology*. 2004 Apr;231(1):225-30. PMID: 14990812
185. Nair, RT, vanSonnenberg, E, Shankar, S, et al. Visceral and soft-tissue tumors: radiofrequency and alcohol ablation for pain relief--initial experience. *Radiology*. 2008 Sep;248(3):1067-76. PMID: 18710995
186. Locklin, JK, Mannes, A, Berger, A, Wood, BJ. Palliation of soft tissue cancer pain with radiofrequency ablation. *J Support Oncol*. 2004 Sep-Oct;2(5):439-45. PMID: 15524075
187. Arima, K, Yamakado, K, Suzuki, R, et al. Image-guided radiofrequency ablation for adrenocortical adenoma with Cushing syndrome: outcomes after mean follow-up of 33 months. *Urology*. 2007 Sep;70(3):407-11. PMID: 17905083
188. Wood, BJ, Abraham, J, Hvizda, JL, Alexander, HR, Fojo, T. Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. *Cancer*. 2003 Feb 1;97(3):554-60. PMID: 12548596
189. Spiliotis, JD, Datsis, AC, Michalopoulos, NV, et al. Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas. *Langenbecks Arch Surg*. 2007 Jan;392(1):55-60. PMID: 17089173
190. Liapi, E, Geschwind, JF. Transcatheter and ablative therapeutic approaches for solid malignancies. *J Clin Oncol*. 2007 Mar 10;25(8):978-86. PMID: 17350947
191. Rosenthal, DI. Radiofrequency treatment. *Orthop Clin North Am*. 2006 Jul;37(3):475-84, viii. PMID: 16846772
192. Rybak, LD, Rosenthal, DI, Wittig, JC. Chondroblastoma: radiofrequency ablation--alternative to surgical resection in selected cases. *Radiology*. 2009 May;251(2):599-604. PMID: 19304917
193. Vavra, P, Dostalik, J, Zacharoulis, D, Khorsandi, SE, Khan, SA, Habib, NA. Endoscopic radiofrequency ablation in colorectal cancer: initial clinical results of a new bipolar radiofrequency ablation device. *Dis Colon Rectum*. 2009 Feb;52(2):355-8. PMID: 19279436
194. Kameyama, S, Murakami, H, Masuda, H, Sugiyama, I. Minimally invasive magnetic resonance imaging-guided stereotactic radiofrequency thermocoagulation for epileptogenic hypothalamic hamartomas. *Neurosurgery*. 2009 Sep;65(3):438-49; discussion 49. PMID: 19687687
195. Zou, YP, Li, WM, Zheng, F, et al. Intraoperative radiofrequency ablation combined with 125 iodine seed implantation for unresectable pancreatic cancer. *World J Gastroenterol*. 2010 Oct 28;16(40):5104-10. PMID: 20976848
196. BlueCross BlueShield Association Medical Policy Reference Manual "Radiofrequency Ablation of Primary or Metastatic Liver Tumors." Policy No. 7.01.91
197. BlueCross BlueShield Association Medical Policy Reference Manual "Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors." Policy No. 7.01.95

CROSS REFERENCES

Radioembolization for Primary and Metastatic Tumors of the Liver, Medicine, Policy No. 140

Cryosurgical Ablation of Miscellaneous Solid Tumors, Surgery, Policy No. 132

Endoscopic Radiofrequency Ablation or Cryoablation for Barrett's Esophagus, Surgery, Policy No. 173

Microwave Tumor Ablation, Surgery, Policy No. 189

CODES	NUMBER	DESCRIPTION
CPT	20982	Ablation, bone tumor(s) (e.g., osteoid osteoma, metastasis) radiofrequency, percutaneous, including computed tomographic guidance
	31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)
	32998	Ablation therapy for reduction or eradication of one or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, radiofrequency, unilateral
	47370	Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
	47380	Ablation, open, of one or more liver tumor(s); radiofrequency
	47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
	50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed
	50592	Ablation, one or more renal tumor(s), percutaneous, unilateral, radiofrequency
	76940	Ultrasound guidance for, and monitoring of, parenchymal tissue ablation
	77013	Computerized tomography guidance for, and monitoring of, parenchymal tissue ablation
	77022	Magnetic resonance guidance for, and monitoring of, parenchymal tissue ablation
HCPCS	No code	