Clinical Policy Bulletin: Ablation of Hepatic Lesions

Number: 0274

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers cryosurgery, microwave, or radiofrequency ablation medically necessary for members with isolated colorectal cancer liver metastases or isolated hepatocellular cancer who are not candidates for open surgical resection when the selection criteria specified below are met.

Members must fulfill all of the following criteria. Particular emphasis should be placed on criteria B and C, which ensure that cryosurgery, microwave, or radiofrequency ablation is performed with curative intent.

A. Members must either have hepatic metastases from a colorectal primary cancer or have a hepatocellular cancer; and
B. Members must have isolated liver disease. Members with nodal or extra-hepatic systemic metastases are not considered candidates for these procedures; and
C. All tumors in the liver, as determined by pre-operative imaging, would be potentially destroyed by cryotherapy, microwave, or radiofrequency ablation; and
D. Because open surgical resection is the preferred treatment, members must be unacceptable open surgical candidates due to the location or extent of the liver disease or due to co-morbid conditions such that the member is unable to tolerate an open surgical resection; and
E. Liver lesions must be 4 cm or less in diameter and occupy less than 50 % of the liver parenchyma. Lesions larger than this may not be adequately treated by these procedures.

Aetna considers cryosurgery, microwave, or radiofrequency ablation of hepatic lesions experimental and investigational when these criteria are not met.

II. Aetna considers cryosurgery, microwave, or radiofrequency ablation medically necessary for unresectable neuroendocrine tumors metastatic to the liver.

III. Aetna considers cryosurgery, microwave, or radiofrequency ablation as a treatment of hepatic metastases from non-colonic primary cancers experimental and investigational. Additionally, cryosurgical, microwave or radiofrequency ablation as a palliative treatment of either hepatic metastases from colorectal cancer or hepatocellular cancer is also considered experimental and investigational because the effectiveness of these approaches for these indications has not been established.

IV. Aetna considers combinational treatment of radiofrequency ablation and transcatheter arterial...
V. Aetna considers combinational treatment of high-intensity focused ultrasound (HIFU) and transcatheter arterial chemo-embolization for the treatment of hepatoblastoma experimental and investigational because the effectiveness of this approach has not been established.

See also CPB 0268 - Liver and Other Neoplasms - Treatment Approaches, and CPB 0492 - Radiofrequency Tumor Ablation.

Background

The liver is the most common site of distant metastasis from colorectal cancer. About 25% of patients with liver metastases from colorectal cancer have no other sites of metastasis and can be treated with regional therapies directed toward their liver tumors. Based on a preponderance of uncontrolled studies for hepatic metastatic colorectal carcinoma, surgical resection offers the only potential for cure of selected patients with completely resected disease, with 5-year survival rates of 25% to 46%; however, the majority of patients with primary or metastatic malignancies confined to the liver are not candidates for resection because of tumor size, location, or multi-focality or inadequate functional hepatic reserve. For the treatment of patients with non-resectable liver metastases, alternative local ablative therapeutic modalities have been developed. For most patients with spread of metastatic colorectal cancer beyond the liver, systemic chemotherapy rather than regional therapy is a more appropriate option.

Cryotherapy is an effective and precise technique for inducing tumor necrosis, but it is currently performed via laparotomy. Recent results suggest that ultrasound-guided radiofrequency thermal ablation may be an effective, minimally invasive technique for treating malignant hepatic tumors. Both interventional therapeutic techniques have been shown to result in a remarkable local tumor control rate with improved survival results for patients with liver metastases from colorectal cancer.

The National Institute for Clinical Excellence (NICE, 2004) guidance on radiofrequency ablation (RFA) for the treatment of colorectal metastases to the liver stated that: "Current evidence on the safety of radiofrequency ablation of colorectal metastases in the liver appears adequate. However, the evidence of its effect on survival is not yet adequate to support the use of this procedure without special arrangements for consent and for audit or research". In patients who are not eligible for traditional surgery, RFA can be used to destroy liver tumors. However, existing evidence does not conclusively support the effectiveness of RFA in improving patient survival.

The NICE guidance on cryotherapy of liver tumors concludes (NICE, 2010) that "current evidence on the safety of cryotherapy for the treatment of liver metastases appears adequate in the context of treating patients whose condition has such a poor prognosis, but the evidence on efficacy is inadequate in quality. Therefore cryotherapy for the treatment of liver metastases should only be used with special arrangements for clinical governance, consent and audit or research."

Jungraithmayr et al (2005) stated that local ablative procedures such as cryosurgery and thermo-ablation are increasingly employed as a supplement to liver resection for the treatment of primary and secondary liver tumors. However, it is still unclear whether the survival time can be extended through local ablative procedures. In this prospective study (n = 19), these investigators reported operative actions, complications and long-term follow-up of patients with malignant liver tumors undergoing cryotherapy. Subjects underwent cryotherapy due to a non-resectable malignant liver tumor (17 subjects with metastases of a colon carcinoma, and 2 subjects with a hepatocellular carcinoma). A total of 12 patients (63.2%) received cryotherapy only, and 7 patients (36.8%) received a combination of resection and cryotherapy. The median follow-up period was 23 months. The 30-day mortality was
0% and the rate of major complications was 21%. After 1 year, 27.3% of the patients were still recurrence-free. The recurrence rate for all tumors treated was 58.8%. The median survival time for all patients was 21 months. The 1- and 3-year survival rates were 62.5% and 15.8%, respectively. The authors concluded that the mortality for cryotherapy is low, but there is a high rate of complications and long-term tumor control is insufficient. If local ablative procedures of hepatic lesions are to be performed, not laparotomy but percutaneous, percutaneous thermoablation should be discussed as an alternative therapeutic measure.

Microwave energy can also be used to destroy liver neoplasms. Microwave ablation destroys tumor cells by heat, resulting in localized areas of necrosis and tissue destruction. Guidance from the National Institute for Health and Clinical Excellence (NICE, 2006) concluded that there is sufficient evidence of the safety and effectiveness of microwave ablation of hepatocellular carcinoma. This conclusion was based upon the results of non-randomized controlled studies of microwave ablation of hepatocellular carcinoma that found similar outcomes to liver resection (Midorikawa et al, 2005), percutaneous ethanol injection (Seki et al, 1999), and radiofrequency ablation (Lu et al, 2005). However, NICE (2007) found insufficient evidence of the safety and effectiveness of microwave ablation of colorectal cancer metastatic to the liver and other liver metastases. One small randomized controlled clinical trial (n = 30) found similar overall and disease-free survival with liver resection and microwave ablation of liver metastases (Shibata et al, 2000). Other uncontrolled case series reported similar results with microwave ablation of liver metastases (Liang et al, 2003; Morikawa et al, 2002).

National Comprehensive Cancer Network (NCCN, 2007) hepatocellular carcinoma guidelines state that microwave ablation, cryotherapy, RFA, and percutaneous ethanol injection may be used in the treatment of unresectable non-metastatic hepatocellular carcinoma, for patients with non-metastatic hepatocellular carcinoma who do not agree to surgery, and to treat hepatocellular carcinoma which is local but inoperable (e.g., due to poor performance status or presence of comorbidity). The NCCN guidelines make no distinction with respect to these different ablative methods. The guidelines state that ablative therapy of colorectal cancer metastases to the liver using RFA or cryosurgery at the time of colon resection can also be considered when all measurable metastatic disease can be treated.

Kornprat et al (2007) examined the role of intra-operative thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. Patients with colorectal hepatic metastases underwent hepatic resection combined with thermoablation, either cryosurgical ablation (CSA) or RFA. Main outcome measures included local recurrence rates at ablation sites, overall survival, disease-free survival, and hepatic disease-free survival. A total of 665 patients were enrolled in this study. Of these, 39 (5.9%) had additional intra-operative thermoablative procedures (19 RFA, 20 CSA). There was 1 (3%) post-operative death not directly associated with the ablation, and the total morbidity rate was 41% (16 of 39). No RFA-related complication occurred; however, 3 patients developed an abscess at cryoablation sites. Actuarial 3-year survival was 47% for the entire group, with a median follow-up of 21.1 months (range of 0.5 to 71.4 months). The median disease-free survival was 12.3 months (range of 8.4 to 16.2 months). Overall, the local in situ recurrence rate according to number of ablated tumors was 14% for RFA and 12% for CSA. Tumor size correlated directly with recurrence (p = 0.02) in RFA-treated lesions. The authors concluded that ablation combined with hepatic resection is rarely necessary or applicable. However, in selected patients whose tumors were otherwise unresectable, additional use of ablation allows effective clearance of disease. In these patients with extensive bilobar disease, recurrence rates are high, but long-term survival is encouraging and may be improved with aggressive post-operative chemotherapy.

Siperstein et al (2007) evaluated factors affecting long-term survival of patients undergoing RFA of colorectal hepatic metastases, with attention to evolving chemotherapy regimens. A total of 235 patients with colorectal metastases who were not candidates for resection and/or failed chemotherapy underwent laparoscopic RFA. Pre-operative risk factors for survival and pre- and post-operative chemotherapy exposure were analyzed. A total of 234 patients underwent 292 RFA sessions at an average of 8 months after initiation of chemotherapy. Twenty-three percent had extra-hepatic disease pre-operatively. Patients averaged 2.8 lesions, with a dominant diameter of 3.9 cm. Kaplan-Meier
actuarial survival was 24 months, with actual 3 and 5 years survival of 20.2 % and 18.4 %, respectively. Median survival was improved for patients with less than or equal to 3 versus greater than 3 lesions (27 versus 17 months, p = 0.0018); dominant size less than 3 versus greater than 3 cm (28 versus 20 months, p = 0.07); chorioembryonic antigen less than 200 versus greater than 200 ng/ml (26 versus 16 months, p = 0.003). Presence of extra-hepatic disease (p = 0.34) or type of pre-/post-operative chemotherapy (5-FU-leucovorin versus FOLFOX/FOLFIRI versus bevacizumab) (p = 0.11) did not alter median survival. The authors concluded that the number and dominant size of metastases, and pre-operative chorioembryonic antigen value are strong predictors of survival. Despite classic teaching, extra-hepatic disease did not adversely affect survival. They stated that in this group of patients who failed chemotherapy, newer treatment regimens (pre- or post-operatively) had no survival benefit. The actual 5-year survival of 18.4 % in these patients versus near zero survival for chemotherapy alone argues for a survival benefit of RFA.

In a review on the use of RFA for the treatment of primary and metastatic liver tumors, Garrean et al (2008) concluded that although RFA has been readily adopted into treatment paradigms, more rigorous trials are needed to solidify its place in the armamentarium of therapeutic strategies for hepatic malignancy.

In a systematic review on the current role of RFA in the management of hepatocellular carcinoma, Lau and Lai (2009) concluded that the evidence in the medical literature showed RFA was more effective than other local ablative therapies, and supported its use in the treatment of unresectable small hepatocellular carcinoma, recurrent small hepatocellular carcinoma, and as bridging therapy before liver transplantation, and as a primary treatment in competition with partial hepatectomy for resectable small hepatocellular carcinoma.

Stang et al (2009) performed a systematic review on the clinical benefit and role of RFA as treatment of colorectal liver metastases (CLMs). A PubMed literature search for original articles published until August 2008 was performed. Studies with 40 patients, 18-month median follow-up and reported 3 year overall survival (OS) rates after RFA of CLM were selected for analysis. A total of 13 clinical series and 8 non-randomized comparative studies were analyzed. Median progression-free survival (PGS) after RFA ranged between 6 and 13 months. Median and 5-year OS after RFA (RFA plus resection) ranged between 24 to 59 months and 18 to 40 % (36 to 46 months and 27 to 30 %). Comparative studies indicated significantly improved OS after RFA versus chemotherapy alone, RFA plus chemotherapy versus RFA alone and up-front RFA versus RFA following second-line chemotherapy. The authors concluded that these findings support that RFA prolongs time without toxicity and survival as an adjunct to hepatectomy and/or chemotherapy in well-selected patients, but not as an alternative to resection.

The American Society of Clinical Oncology (ASCO) published a systematic review on the effectiveness of RFA for hepatic metastases from colorectal cancer (CRHM). Because data were considered insufficient to form the basis of a practice guideline, ASCO has instead published a clinical evidence review. The evidence is from single-arm, retrospective, and prospective trials. No randomized controlled trials have been included. The following 3 clinical issues were considered by the panel: (i) the efficacy of surgical hepatic resection versus RFA for resectable tumors; (ii) the utility of RFA for unresectable tumors; and (iii) RFA approaches (open, laparoscopic, or percutaneous). Evidence suggested that hepatic resection improves OS, particularly for patients with resectable tumors without extra-hepatic disease. Careful patient and tumor selection was discussed at length in the literature. Investigators who use RFA reported a wide variability in the 5-year survival rate (14 % to 55 %) and local tumor recurrence rate (3.6 % to 60 %). The reported mortality rate was low (0 % to 2 %), and the major complications rate was commonly reported to be between 6 % and 9 %. Radiofrequency ablation is currently performed with all 3 approaches. The authors concluded that there is a compelling need for more research to determine the efficacy and utility of RFA to increase local recurrence-free survival, PRS, and disease-free survival as well as OS for patients with CRHM. Clinical trials have established that hepatic resection can improve OS for patients with resectable CRHM (Wong et al, 2010).
Guidelines on neuroendocrine tumors from the National Comprehensive Cancer Network (NCCN, 2009) stated that, for unresectable liver metastases from carcinoid tumors and islet cell tumors, locally ablative therapy is recommended.

Furthermore, the 2010 NCCN practice guideline on "hepatobiliary cancers" stated that the 2 most commonly used methods of ablation therapy are percutaneous ethanol injection and RFA.

Gasparini and associates (2012) assessed the effectiveness of a combination of percutaneous RFA, stop-flow and transcatheter arterial chemo-embolization (TACE) in the treatment of hepatic neoplasms. From December 1997 to September 2000, a total of 34 patients with hepa-to-cellular carcinoma (HCC) underwent RF thermoablation treatment. The choice of method was based on the type of lesion (HCC versus metastasis) and the following dimensional criteria: (i) RF without stop-flow associated with the injection of diagnostic lipiodol in the case of a single nodule with a maximum diameter smaller than 3 cm; (ii) RF with stop-flow of the hepatic artery associated with TACE in the case of a single nodule with a diameter greater than 3 cm; and (iii) RF with stop-flow of the hepatic artery associated with TACE in the case of 2 to 3 nodules, a subdivision was made into 2 groups according to the volume: smaller or greater than 80 ml. Ten out of 34 patients affected by HCC with a diameter smaller than 3 cm, treated only with RF, demonstrated 100 % necrosis in the follow-up period, which varied between 6 and 24 months (average of 10 months). The remaining 24 patients affected by HCC and treated with RF associated with stop-flow and TACE showed responses related to the volume of the tumor: (i) patients with a single nodule with a diameter of 3 to 5 cm showed 100 % necrosis; (ii) patients affected by multi-focal HCC with a maximum of 3 nodules and/or total tumor mass smaller than 80 ml, for a total of 9 lesions, showed 95 % necrosis; and (iii) patients affected by multi-focal HCC with more than 3 nodules (total mass less than 40 % of liver volume) or tumor mass greater than 80 ml, for a total of 13 lesions, showed 90 % necrosis. In the group of patients affected by multiple nodules with volumes smaller than 80 ml, the technique did not show complete effectiveness, thus these patients cannot be considered cured. Such aspects were even clearer in the more advanced stages. The authors concluded that in this case study, RF proved effective with lesions up to 3 cm in diameter. By reducing thermal dispersion, the association of the stop-flow technique with RFA, determined a greater volume of necrosis, which allows effective treatment of single nodules with a diameter of up to 5 cm and/or multiple nodules. The association with TACE: (i) provided a way to highlight and treat lesions not recognizable through other imaging techniques; (ii) increased the accumulation of lipid contrast in the tissue surrounding the lesion and in the vessels not occluded by thermal ablation in the lesions with diameters greater than 3 cm; (iii) enabled further treatment of tumor residue possibly left untouched by thermal ablation in large tumors; and (iv) increased the amount of lipiodol accumulated in normal tissue surrounding the lesion, made evident through the comparison of the dimensions of the nodule's blush between angiography and lipiodol computed tomography (CT). These preliminary findings need to be validated by well-designed studies.

Peng et al (2013) compared RFA with or without TACE in the treatment of HCC. A randomized controlled trial was conducted on 189 patients with HCC less than 7 cm at a single tertiary referral center between October 2006 and June 2009. Patients were randomly assigned to receive TACE combined with RFA (TACE-RFA; n = 94) or RFA alone (n = 95). The primary end point was OS. The secondary end point was recurrence-free survival, and the tertiary end point was adverse effects. At a follow-up of 7 to 62 months, 34 patients in the TACE-RFA group and 48 patients in the RFA group had died. Thirty-three (35.1 %) patients and 52 (54.7 %) patients had developed recurrence in the TACE-RFA group and RFA group, respectively. The 1-, 3-, and 4-year OS for the TACE-RFA group and the RFA group were 92.6 %, 66.6 %, and 61.8 % and 85.3 %, 59 %, and 45.0 %, respectively. The corresponding recurrence-free survivals were 79.4 %, 60.6 %, and 54.8 % and 66.7 %, 44.2 %, and 38.9 %, respectively. Patients in the TACE-RFA group had better OS and recurrence-free survival than patients in the RFA group (hazard ratio, 0.525; 95 % confidence intervals [CI]: 0.335 to 0.822; p = 0.002; hazard ratio, 0.575; 95 % CI: 0.374 to 0.897; p = 0.009, respectively). There were no treatment-related deaths. On logistic regression analyses, treatment allocation, tumor size, and tumor number were significant prognostic factors for OS, whereas treatment allocation and tumor number were
significant prognostic factors for recurrence-free survival. The authors concluded that TACE-RFA was superior to RFA alone in improving survival for patients with HCC less than 7 cm. The main drawbacks of this study were: (i) small sample size, (ii) not double-blinded, (iii) single-center experience, and the results may not be generalizable, and (iv) the majority of subjects had 1 or 2 lesions, and almost 50% of them had a tumor of less than or equal to 3 cm.

In an editorial that accompanied the afore-mentioned study, Zhu and Salem (2013) stated that “Findings from this study require confirmation by others globally …. because only approximately 50% of lesions were larger than 3 cm and there were no specification on the number of patients with lesion size from 3 to 7 cm, it remained unclear whether the benefits of TACE-RFA were only applicable to smaller lesions (i.e., less than 5 cm), as has been previously suggested. Likewise, because 62% to 67% of patients enrolled onto this study had only one lesion, the relative benefits of combined TACE-RFA in patients with multifocal disease remain to be defined. Finally, there was treatment cross-over in each arm, potentially confounding survival outcomes …. However, despite the available data on tolerability and safety, efficacy data for this combined approach is either negative or pending”.

In a pilot study, Iezzi and colleagues (2013) evaluated the feasibility, safety and effectiveness of a new combined single-step therapy in patients with unresectable multi-nodular unilobar HCC, with at least 1 lesion greater than 3 cm, with balloon-occluded RFA (BO-RFA) plus TACE of the main lesion and TACE of the other lesions. The second purpose of this study was to compare the initial effects in terms of tumor necrosis of this new combined therapy with those obtained in a matched population treated with TACE alone in a single-step treatment in the authors’ center in the previous year. This study was approved by the institutional review board, and informed consent was obtained from all patients. A total of 10 consecutive patients with multi-nodular (2 to 6 nodules) unilobar unresectable HCC and with a main target lesion of greater than 3 cm (range of 3.5 to 6 cm) not suitable for curative therapy were enrolled in this single-center multi-disciplinary pilot study. The schedule consisted of percutaneous RFA (single 3-cm monopolar needle insertion) of the target lesion during occlusion of the hepatic artery supplying the tumor, followed by selective TACE, plus lobar TACE for other lesions (450-mg carboplatin and lipiodol plus temporary embolization with SPONGOSTAN). Adverse events and intra- and peri-procedural complications were clinically assessed. Early local effectiveness was evaluated on 1-month follow-up multi-phasic CT on the basis of the Modified Response Evaluation Criteria in Solid Tumors (m-RECIST). A separate evaluation of target lesions in terms of enhancement, necrotic diameter and presence and distribution of lipiodol uptake was also performed. No major complications occurred. Overall technical success, defined as complete de-vascularization of all nodules during the arterial phase, was achieved in 7 of 10 patients, with 3 cases of partial response (persistence of small hypervascular nodules). When considering only target lesions, technical success was obtained in all patients, with a non-enhancing area corresponding in shape to the previously identified HCC (necrotic diameter, 3.5 to 5 cm) and with circumferential peripheral lipiodol uptake (safety margin) of at least 0.5 cm (0.5 to 1.3 cm). The authors concluded that TACE and BO-RFA, plus TACE in a single-step approach appears to be a safe and effective combined therapy for treating advanced, unresectable HCC lesions, allowing a high rate of complete local response to be achieved in large lesions also.

Wiggermann et al (2013) evaluated the reliability of ultrasound (US) elastography for delineating thermal ablation defects post- RFA by comparing lesion dimensions determined by real-time elastography (RTE) with the findings of contrast-enhanced US (CEUS). A total of 21 malignant liver tumors were percutaneously ablated using RFA. Color-coded elastography and CEUS were performed by 1 experienced examiner, using a 1 to 5 MHz multi-frequency convex transducer (LOGIQ E9, GE). Lesions were examined using CEUS and RTE to assess ablation defects. Measurements of lesions (long axis, short axis, and area) representing the same image plane used for elastography were taken during CEUS examination and compared to the measurements obtained from the elastograms. All measurements were performed by 2 independent observers. A statistically significant correlation in vivo between RTE and CEUS measurements with respect to the lesion’s principal axis and area ($r=0.876$ long axis, $r=0.842$ short axis and $r=0.889$ area) was found. Inter-rater reliability assessed with the concordance correlation coefficient was substantial for all measurements ($p \geq 0.96$). Overall, elastography slightly underestimated the lesion size, as judged by the CEUS images. The
authors concluded that these findings support that RTE could potentially be used for the routine assessment of thermal ablation therapies.

Westwood et al (2013) stated that medical imaging techniques are important in the management of many patients with liver disease. Unenhanced US examinations sometimes identify focal abnormalities in the liver that may require further investigation, primarily to distinguish liver cancers from benign abnormalities. One important factor in selecting an imaging test is the ability to provide a rapid diagnosis. Options for additional imaging investigations include CT and/or magnetic resonance imaging (MRI) and biopsy when the diagnosis remains uncertain. Computed tomography and MRI usually require referral with associated waiting time and are sometimes contraindicated. The use of contrast agents may improve the ability of US to distinguish between liver cancer and benign abnormalities and, because it can be performed at the same appointment as unenhanced US, more rapid diagnoses may be possible. These investigators compared the clinical effectiveness and cost-effectiveness of CEUS using SonoVue® with that of contrast-enhanced CT (CECT) and contrast-enhanced MRI (CEMRI) for the assessment of adults with focal liver lesions (FLLs) in whom previous liver imaging is inconclusive. A total of 8 bibliographic databases including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects were searched from 2000 to September/October 2011. Research registers and conference proceedings were also searched. Systematic review methods followed published guidance. Risk of bias was assessed using a modified version of the QUADAS-2 tool. Results were stratified by clinical indication for imaging (characterization of FLLs detected on US surveillance of cirrhosis patients, detection of liver metastases, characterization of incidentally detected FLLs, assessment of treatment response). For incidental FLLs, pooled estimates of sensitivity and specificity, with 95 % CIs, were calculated using a random-effects model. For other clinical indications a narrative summary was used. The cost-effectiveness of CEUS was modelled separately for the 3 main clinical applications considered [characterization of FLLs detected on US surveillance of cirrhosis patients, detection of liver metastases in patients with colorectal cancer (CRC), characterization of incidentally detected FLLs]. Of the 854 references identified, 19 (describing 18 studies) were included in the review. Hand-searching of conference proceedings identified a further 3 studies; 20 of the 21 studies included in the systematic review were diagnostic test accuracy studies. Studies in cirrhosis patients reported varying estimates of test performance. There was no consistent evidence of a significant difference in performance between imaging modalities. It was unclear whether or not CEUS alone is adequate to rule out HCC for FLLs of less than 30 mm; 1 study indicated that CEUS may be better at ruling out HCC for FLLs of 11 to 30 mm [very small FLLs (less than 10 mm) excluded]. There was no consistent evidence of a difference in test performance between imaging modalities for the detection of metastases; CEUS alone may be adequate to rule out liver metastases in CRC. In patients with incidentally detected FLLs, the pooled estimates of sensitivity for any malignancy using CEUS and CECT were 95.1 % and 94.6 %, respectively, and the corresponding specificity estimates were 93.8 % and 93.1 % respectively. One study comparing CEUS with CEMRI reported similar sensitivity and lower specificity for both modalities. In the surveillance of cirrhosis, CEUS was as effective as but £379 less costly than CECT; CEMRI was £1063 more costly than CEUS and gained 0.022 quality-adjusted life years (QALYs). In the detection of liver metastases from CRC, CEUS cost £1 more than CECT, and at a lifetime time horizon they yielded equal QALYs; CEMRI was dominated by CECT. In the characterization of incidentally detected FLLs, CEUS was slightly more effective than CECT and CEMRI (by 0.0002 QALYs and 0.0026 QALYs, respectively) and less costly (by £52 and £131, respectively). The authors concluded that SonoVue CEUS could provide similar diagnostic performance to other imaging modalities (CECT and CEMRI) for the assessment of FLLs. Economic analyses indicated that CEUS was a cost-effective replacement for CEMRI. The use of CEUS instead of CECT was considered cost-effective in the surveillance of cirrhosis and the characterization of incidentally detected FLLs, with similar costs and effects for the detection of liver metastases from CRC. Moreover, they stated that further research is needed to compare the effects of different imaging modalities (SonoVue CEUS, CECT, CEMRI) on therapeutic planning, treatment and clinical outcomes. Furthermore, they stated that future test accuracy studies should provide standardized definitions of a
positive imaging test, and compare all 3 imaging modalities in the same patient group.

Alzaraa et al (2013) noted that the use of contrast agents (CA) with liver US has gained recently an established role for the diagnosis of various hepatic diseases due to their safety, high versatility and low costs (CEUS). These researchers provided a state-of-the-art summary of the available evidence for their use in the characterization of focal liver lesions. A published work search was conducted for all pre-clinical and clinical studies involving CA on hepatic US imaging. Contrast-enhanced US increased the sensitivity for lesion detection and the specificity to differentiate between benign and malignant diseases due to the enhanced visualization of the tumor microcirculation. Results achieved seem at least equivalent to those of spiral CT or MRI. The association of CA with intra-operative US has changed the surgical approach in 25 % of patients and guarantees complete ablations by a single session in most of them. The authors concluded that CEUS provides detailed information about tumor vasculature, improves the pre-operative characterization and therefore the therapeutic strategy, and can evaluate the intra-operative completeness of the ablation.

The National Comprehensive Cancer Network’s clinical practice guideline on “Hepatobiliary cancers” (Version 2.2013) states that “Diagnostic HCC imaging involves the use of one or more of the following modalities: 4-phase helical CT; 4-phase dynamic contrast-enhanced MRI; or contrast-enhanced ultrasound (CEUS) .... Liver lesions less than 1 cm should be evaluated by at least a 3-phase contrast-enhanced CT or MRI or CEUS every 3 to 6 months, with enlarging lesions evaluated according to size. Patients with lesions stable in size should be followed with imaging every 3 to 6 months using the same imaging modality that was first used to identify the nodules”.

Wang et al (2014) evaluated the effectiveness of high-intensity focused ultrasound (HIFU) combined with TACE in treating pediatric hepatoblastoma. A total of 12 patients with initially unresectable hepatoblastoma were enrolled in the study. All patients received chemotherapy, TACE and HIFU ablation. Follow-up materials were obtained in all patients. The tumor response, survival rate and complication were analyzed. Completely ablation was achieved in 10 patients (83.3 %), and the alphafetoprotein level was also decreased to normal in these patients. The mean follow-up time was 13.3 ± 1.8 months (range of 2 to 25 months). At the end of follow-up, 2 patients died from tumor progression, the rest 10 patients were alive. One patient was found to have lung metastasis after HIFU and had an operation to remove the lesion. The median survival time was 14 months, and the survival rates of 1, 2-year were 91.7 % and 83.3 %, respectively. Complication included fever, transient impairment of hepatic function and mild malformation of rib. The authors concluded that HIFU combined with TACE is a safe and promising method with a low rate of severe complications. As a non-invasive approach, it may provide a novel locally therapy for patients with unresectable hepatoblastoma.

Groeschl et al (2014) hypothesized that tumor size, number of tumors, surgical approach, and tumor histology significantly affected microwave ablation (MWA) success and recurrence-free survival. Consecutive patients with hepatic malignancy treated by MWA were included from 4 high-volume institutions (2003 to 2011) and grouped by histology into 4 groups: (i) HCC, (ii) colorectal liver metastases, (iii) neuroendocrine liver metastases, and (iv) other cancers. Independent significance of outcome variables was established with logistic regression and Cox proportional hazards models. A total of 450 patients were treated with 473 procedures (139 HCC, 198 colorectal liver metastases, 61 neuroendocrine liver metastases, and 75 other) for a total of 875 tumors. Median follow-up was 18 months. Concurrent hepatectomy was performed in 178 patients (38 %), and when performed was associated with greater morbidity. Complete ablation was confirmed for 839 of 865 tumors (97.0 %) on follow-up cross-sectional imaging (10 were un-evaluable). A surgical approach (open, laparoscopic, or percutaneous) had no significant impact on complication rates, recurrence, or survival. The local recurrence rate was 6.0 % overall and was highest for HCC (10.1 %, p = 0.045) and percutaneously treated lesions (14.1 %, p = 0.014). In adjusted models, tumor size 3 cm or more predicted poorer recurrence-free survival (hazard ratio [HR]: 1.60, 95 % CI: 1.0 to -2.50, p = 0.039). The authors concluded that in this large data set, patients with 3 cm or more tumors showed a propensity for early recurrence, regardless of histology. Higher rates of local recurrence were noted in HCC patients, which may reflect underlying liver disease. There were no significant differences in morbidity or
survival based on the surgical approach; however, local recurrence rates were highest for percutaneously ablated tumors.

Lei et al (2014) compared the safety and effectiveness of hepatic resection and RFA for small HCCs less than 5 cm in diameter. A total of 289 patients were diagnosed with a small HCC (a single tumor no larger than 5 cm). Among these patients, 133 underwent hepatic resection, and 156 received RFA. Demographic data, intra-operative data, post-operative recovery data, and the baseline characteristics of the 2 groups of patients were compared. The incidence of post-operative complications; 1-, 3-, and 5-year survival rates; and tumor recurrence were determined. No statistically significant differences in the baseline characteristics were noted between the 2 groups. By contrast, operation time (p = 0.003), intra-operative blood loss (p = 0.000), and the length of post-operative hospital stay (p = 0.000) were significantly lower in the RFA group compared with the surgical resection group. The 2 groups displayed similar post-operative complication rates (12 % or 16/133 in the liver resection group versus 8.3 % or 13/156 in the RFA group, p = 0.395). The 1-, 3-, and 5-year OS rates of the patients in the liver resection group were 88.7 %, 78.2 %, and 66.2 %, respectively; whereas the rates in the RFA group were 90.4 %, 76.3 %, and 66.0 %, respectively (p = 0.722). The 1-, 3-, and 5-year tumor-free survival rates of patients in the resection group were 87.2 %, 69.9 %, and 58.6 %, respectively, whereas the rates in the RFA group were 85.9 %, 66.0 %, and 54.5 %, respectively (p = 0.327). In addition, among HCC patients receiving RFA, patients with tumors no greater than 3 cm in diameter exhibited no significant differences regarding OS and tumor-free survival rates compared with patients with tumors 3 to 5 cm in diameter (all p > 0.05). The authors concluded that RFA is a safe and effective therapeutic option for small HCCs and may be a preferred choice for HCC patients with small lesions.

**Combinational Treatment of Radiofrequency Ablation and Transcatheter Arterial Chemo-Embolization:**

Guo and colleagues (2013) evaluated the safety and effectiveness of TACE plus CT-guided percutaneous RFA for small HCC in special locations. From June 2008 to December 2011, a total of 36 patients with small HCC (39 lesions) received TACE plus CT-guided percutaneous RFA at the authors’ hospital. The follow-up period was over 6 months. They were divided into 2 groups according to the locations of HCC: (i) special location (located at hepatic subcapsular, portal area, next to large blood vessels or other organs) and (ii) non-special location groups. All patients underwent TACE at 1 month pre-RFA. Follow-up imaging with enhanced CT or MRI was performed 1 month after combined treatment to evaluate the complete ablation rate in the 2 groups. If a complete ablation was achieved, enhanced CT or MRI was performed every 1 to 3 months to evaluate the local tumor progression. The occurrence rate of complications, complete ablation rate, local tumor progression and time to tumor progression (TTP) were compared between 2 groups. In the special location group, a total of 24 TACE and 26 ablations were performed in 20 patients with 22 lesions while there were 18 TACE and 17 ablations in 16 patients with 17 lesions in the non-special location group. In the special location group, 12 patients (46.2 %) suffered procedure-related complications, including a major complication (n = 1, left ventricular failure) and a minor complication (n = 11) of vascular injury (n = 6), subcapsular hemorrhage (n = 3) and arterial-portal vein fistula (n = 2); whereas only 3 patients (17.6 %) suffered a minor complication of subcapsular hemorrhage (n = 1) and arterial-portal vein fistula (n = 2) in the special location group. The occurrence rate of complications was similar between 2 groups (p = 0.101). The complete ablation rate after 1 month was 68.2 % (15/22) in the special location group and it was significantly higher than that of the non-special location group (100 %, p = 0.012). In the special location group, the 6-month, 1-, 2-, 3-year local tumor progression rates were 31.8 %, 40.9 %, 45.5 %, 45.5 % versus 0, 0, 0, 5.9 % in the non-special location group, respectively. The mean TTP of 14.4 months in the special location group was markedly shorter than that in the non-special location group (31.5 months, p = 0.001). The authors concluded that the combined regimen of TACE and percutaneous RFA was safe and feasible for small HCC in special location; and the rate of local tumor progression was significantly higher than that of non-special location tumor.

Ni and colleagues (2013) compared RFA and TAC) with RFA monotherapy in HCC. These investigators searched PubMed, Medline, Embase and Chinese databases (CBMdisc and Wanfang data) for randomized controlled trials (RCTs) comparing RFA plus TACE and RFA alone for treatment
of HCC from January 2000 to December 2012. The OS rate, recurrence-free survival rate, tumor progression rate, and safety were analyzed and compared. The analysis was conducted on dichotomous outcomes and the standard meta-analytical techniques were used. Pooled odds ratios (ORs) with 95% CIs were calculated using either the fixed-effects or random-effects model. For each meta-analysis, the \( \chi^2 \) and I\(^2 \) tests were first calculated to assess the heterogeneity of the included trials. For \( p < 0.05 \) and I\(^2 \) > 50%, the assumption of homogeneity was deemed invalid, and the random-effects model was used; otherwise, data were assessed using the fixed-effects model. All statistical analysis was conducted using Review manager (version 4.2.2.) from the Cochrane collaboration. A total of 8 RCTs were identified as eligible for inclusion in this analysis and included 598 patients with 306 treated with RFA plus TACE and 292 with RFA alone. Data analysis indicated that RFA plus TACE was associated a significantly higher OS rate (OR 1-year = 2.96, 95% CI: 1.84 to 7.74, \( p < 0.001 \); OR 2-year = 3.72, 95% CI: 1.24 to 11.16, \( p = 0.02 \); OR 3-year = 2.65, 95% CI: 1.81 to 3.86, \( p < 0.001 \)) and recurrence-free survival rate (OR 3-year = 3.00, 95% CI: 1.75 to 5.13, \( p < 0.001 \); OR 5-year = 2.26, 95% CI: 1.43 to 3.57, \( p = 0.0004 \)) versus that of RFA alone. The tumor progression rate in patients treated with RFA alone was higher than that of RFA plus TACE (OR = 0.60, 95% CI: 0.42 to 0.88, \( p = 0.008 \)) and there was no significant difference on major complications between 2 different kinds of treatment (OR = 1.20, 95% CI: 0.31 to 4.62, \( p = 0.79 \)). Additionally, the meta-analysis data of subgroups revealed that the survival rate was significantly higher in patients with intermediate- and large-size HCC underwent RFA plus TACE than in those underwent RFA monotherapy; however, there was no significant difference between RFA plus TACE and RFA on survival rate for small HCC. The authors concluded that the combination of RFA with TACE had advantages in improving OS rate, and provided better prognosis for patients with intermediate- and large-size HCC.

Cao et al (2014) evaluated the safety and effectiveness of TACE combined with RFA and TACE alone for HCC. PubMed, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang Databases were searched for RCTs and retrospective cohort studies from the establishment of the databases to January 2014. The bibliographies of the included studies were searched, too. After study selection, assessment, data collection and analysis were undertaken, these researchers performed a meta-analysis by using the RevMan5.2 software. A total of 17 studies involving 1,116 patients met the inclusion criteria with 530 treated with RFA-plus-TACE and 586 with TACE alone. The results of meta-analysis showed that the combination of TACE and RFA was obviously associated with higher 1-, 2- and 3-year OS rates (OR 1-year = 3.98, 95% CI: 2.87 to 5.51, \( p <0.00001 \); OR 2-year = 3.03, 95% CI: 2.10 to 4.38, \( p < 0.00001 \); OR 3-year = 7.02, 95% CI: 4.14 to 11.92, \( p < 0.00001 \)) than TACE alone. The tumor complete necrosis rate in patients treated with TACE and RFA was higher than that of TACE alone (OR = 13.86, 95% CI: 8.04 to 23.89, \( p < 0.00001 \)). There was a significant difference in local recurrence rate between 2 different kinds of treatment (OR = 0.24, 95% CI: 0.14 to 0.44, \( p < 0.00001 \)). Additionally, combination of TACE and RFA was associated with higher complete tumor necrosis rates than TACE mono-therapy in the treatment of HCC. However, RFA plus TACE was found to be associated with a lower local recurrence rate than TACE monotherapy. TACE-plus-RFA treatment was associated with a higher response rate (RR) than the TACE-alone treatment (OR = 3.90, 95% CI: 2.37 to 6.42, \( p < 0.00001 \)). TACE-plus-RFA treatment did not differ from the TACE-alone treatment in terms of stable disease (SD) rate (OR = 0.38, 95% CI: 1.11 to 1.26, \( p = 0.11 \)). Meta-analyses showed that the combination of RFA and TACE was associated with a significantly lower progressive disease (PD) rate (OR = 0.15, 95% CI: 0.05 to 0.43, \( p = 0.0005 \)). The rate of AFP reducing or returning to normal in serum in RFA plus TACE group was obviously lower than TACE alone group (OR = 4.62, 95% CI: 2.56 to 8.34, \( p < 0.00001 \)). The effect of TACE plus RFA for HCC was better than TACE mono-therapy. The authors concluded that the combined therapy could elevate the patients’ OS rate, tumor necrosis rate and the rate of AFP reducing or returning to normal in serum and decrease local recurrence rate, PD rate compared with TACE alone.

Liang et al (2015) examined the clinical application of sequential therapy with TACE and CT-guided RFA in treating HCC of different sizes. The study included patients (n = 46) with HCC who had received TACE and RFA from November 2012 to November 2013. Eligible patients had an Eastern
Cooperative Oncology Group (ECOG) score of 0 to 1, a Child-Pugh grade of A-B, and no contradictions for TACE and/or RFA; 51 hepatic lesions of varying sizes were treated with TACE followed by RFA. Clinical response and 1- and 2-year survival rates were assessed. The frequency of complete and incomplete ablation following therapy was significantly different across the varying RFA pin numbers and the maximum diameter of the lesion (p ≤ 0.001). A greater percentage (97.3 %) of lesions that were less than or equal to 3 cm in diameter were completely ablated compared with lesions that were 3 to 5 cm (88.9 %) and greater than 5 cm in diameter (20 %). The median survival time of patients was 16.5 months, and the 1- and 2-year survival rates were 95.7 % and 69.3 %, respectively. There were only a limited number of complications, all of which were minor. These included hemothorax (4.3 %), abdominal hemorrhage (10.9 %), and abdominal hemorrhage with minor pneumothorax (2.2 %). The authors concluded that the findings of this study showed that the sequential treatment with TACE and CT-guided RFA was effective and well-tolerated in patients with HCC and that the effectiveness of treatment is dependent on tumor size.

Chevallier et al (2015) noted that local tumor recurrence after thermal ablation of HCC can impact on OS and are very closely linked to partial treatment of the primary lesion or to potential microvascular invasion or satellite micro-nodules located close to the main lesion. The diagnosis of these liver metastases close to the primary lesion on CT and MRI is difficult and their incidence, number, and spread throughout the liver correlates with diameter of primary tumor. Tumor diameter is currently the key factor to predict whether or not thermal ablation of HCC will be complete or not. It has now been shown for mono-polar RFA that this therapy alone is sufficient to effectively treat single HCCs less than 3 cm in diameter provided that liver micro-metastases are not present. If the HCC is greater than 3 cm in size, multi-focal or in the case of tumor recurrence, OS and recurrence-free survival results are better if mono-polar RFA is combined with hepatic TACE.

Wang et al (2016a) compared the safety and effectiveness of combined RFA and TACE with RFA alone for HCC. Randomized controlled trial that compared the clinical or oncologic outcomes of combination therapy of TACE and RFA versus RFA for the treatment of HCC were identified through literature searches of electronic databases (PubMed, Embase, Cochrane Library, China Biology Medicine disc, China National Knowledge Infrastructure, and Google Scholar). Hazard ratios or odds ratios with their corresponding 95 % CI were combined as the effective value to assess the summary effects. The strength of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation system. A total of 6 RCTs with 534 patients were eligible for inclusion in this meta-analysis. The meta-analysis showed that the combination of TACE and RFA is associated with a significantly longer OS (HR = 0.62, 95 % CI: 0.49 to 0.78, p < 0.001) and recurrence-free survival (HR = 0.55, 95 % CI: 0.40 to 0.76, p < 0.001) in contrast with RFA monotherapy. The seemingly higher incidence of major complications in the combination group compared with RFA group did not reach statistical significance (OR = 1.17, 95 % CI: 0.39 to 3.55, p = 0.78). The authors concluded that in patients with HCC, the combination of TACE and RFA is associated with significantly higher OS and recurrence-free survival, as compared with RFA monotherapy, without significant difference in major complications.

Wang et al (2016b) examined the safety and effectiveness of RFA and TACE for treatment of patients with HCC. All eligible studies were collected from PubMed, the Cochrane Libraries and Embase. The evaluation indices included OS rate, recurrence-free survival rate, local tumor progression rate and major complications. All statistical analysis was performed by RevMan version 5.2 software. There were 21 studies with 3,073 patients included in this meta-analysis. The RFA monotherapy was associated with higher 3- and 5-year OS rates (OR 3-year = 2.33, 95 % CI: 1.34 to 4.05; OR 5-year = 2.05, 95 % CI: 1.48 to 2.85) compared with TACE alone. The combination of RFA and TACE was associated with higher 1-, 3- and 5-year OS rates (OR 1-year = 1.94, 95 % CI: 1.28 to 2.96; OR 3-year = 1.56, 95 % CI: 1.19 to 2.04; OR 5-year = 1.53, 95 % CI: 1.13 to 2.07) compared with RFA alone. The authors concluded that the combination of TACE with RFA could obviously improve the short- and long-term survival rates and significantly provide a better prognosis for patients with intermediate-size HCC. They stated that RFA was associated with a higher long-term OS rate than that of TACE-treated patients with HCC.
Furthermore, NCCN’s clinical practice guideline on “Hepatobiliary cancers” (Version 1.206) states that “The consensus of the panel is that ablation alone may be a curative treatment for tumors less than or equal to 3 cm …. Tumors between 3 and 5 cm may be treated with a combination of ablation (cryoablation, microwave, percutaneous alcohol injection, and radiofrequency) and arterially directed therapies (e.g., TACE) to prolong survival, as long as the tumor location is favorable to ablation”.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”.*

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>37243</td>
<td>Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction [covered for treatment of hepatocellular carcinomas]</td>
</tr>
<tr>
<td>47380</td>
<td>Ablation, open, of one or more liver tumor(s); radiofrequency</td>
</tr>
<tr>
<td>47381</td>
<td>cryosurgical</td>
</tr>
<tr>
<td>47382</td>
<td>Ablation, one or more liver tumor(s), percutaneous, radiofrequency</td>
</tr>
<tr>
<td>47383</td>
<td>Ablation, 1 or more liver tumor(s), percutaneous, cryoablation</td>
</tr>
<tr>
<td>75894</td>
<td>Transcatheter therapy, embolization, any method, radiological supervision and interpretation [not covered for combinational treatment of radiofrequency ablation, high-intensity focused ultrasound and transcatheter arterial chemo-embolization for the treatment of unresectable hepatocellular carcinoma, hepatoblastoma] [covered for treatment of hepatocellular carcinomas]</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>37242</td>
<td>Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, other than hemorrhage or tumor (eg, congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76940</td>
<td>Ultrasound guidance for, and monitoring of, parenchymal tissue ablation</td>
</tr>
<tr>
<td>77013</td>
<td>Computerized tomography guidance for, and monitoring of, parenchymal tissue ablation</td>
</tr>
<tr>
<td>77022</td>
<td>Magnetic resonance guidance for, and monitoring of, parenchymal tissue ablation</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9734</td>
<td>Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance [not covered for combinational treatment of high-intensity focused ultrasound and transcatheter arterial chemo-embolization for the treatment of hepatoblastoma]</td>
</tr>
</tbody>
</table>
Other HCPCS codes related to the CPB:

C1886 Catheter, extravascular tissue ablation, any modality (insertable)

ICD-10 codes covered if selection criteria are met:

C18.0 - C20 Malignant neoplasm of colon, rectosigmoid junction and rectum [isolated with liver metastases] (C78.7 also required) Secondary malignant neoplasm of liver and intrahepatic bile duct
C22.0 Malignant neoplasm of liver [hepatoblastoma]
C22.2 - C22.8
C7B.02 Secondary carcinoid tumors of liver [unresectable with liver metastases]
D01.5 Carcinoma in situ of liver, gallbladder and bile ducts [hepatocellular cancer]

The above policy is based on the following references:


83. Wiggermann P, Brünn K, Rennert J, et al. Monitoring during hepatic radiofrequency ablation (RFA): Comparison of real-time ultrasound elastography (RTE) and contrast-enhanced


Amendment to
Aetna Clinical Policy Bulletin Number: 0274 Ablation of Hepatic Lesions

There are no amendments for Medicaid.