Clinical Policy Bulletin:  
Liver and Other Neoplasms - Treatment Approaches 

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Policy 

I. Percutaneous Ethanol Injection 

Aetna considers percutaneous ethanol injection (PEI) medically necessary for the treatment of hepatocellular cancers (HCC) without extra-hepatic spread. 

Aetna considers PEI for liver neoplasms experimental and investigational when criteria are not met. There is inadequate information to document the effectiveness of PEI as an alternative to surgical resection for the treatment of hepatic metastases. 

Aetna considers combined radiofrequency ablation and PEI experimental and investigational for the treatment of HCC because of insufficient evidence in the peer-reviewed literature. 

II. Chemoembolization 

Aetna considers chemoembolization (CE) medically necessary for any of the following: 

A. For treatment of neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver. For carcinoid tumors, CE is considered medically necessary only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea); or 
B. For unresectable, primary HCC; or 
C. For liver-only metastasis from uveal (ocular) melanoma; or 
D. Pre-operative hepatic artery chemoembolization followed by orthotopic liver transplantation for HCC. 

Aetna considers CE experimental and investigational for other indications including palliative treatment of liver metastases from other non-neuroendocrine primaries (e.g., breast cancer, cervical cancer, colon cancer, esophageal cancer, melanoma, rhabdomyosarcoma, or unknown primaries) and CE of the
pancreas for pancreatic cancer because there is inadequate evidence in the medical literature of the effectiveness of CE for these indications.

III. Intra-Hepatic Chemotherapy

Aetna considers intra-hepatic chemotherapy (infusion) medically necessary for members with liver metastases from colorectal cancer.

Aetna considers intra-hepatic chemotherapy experimental and investigational for other indications, including treatment of liver primaries or metastases from other primaries besides colorectal cancer because of insufficient evidence in the peer-reviewed literature.

Aetna considers "one-shot" arterial chemotherapy for members with liver metastases from colorectal cancer experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Aetna considers transarterially administered gene therapy experimental and investigational for primary and secondary liver malignancies because of insufficient evidence in the peer-reviewed literature.

IV. Intra-Hepatic Microspheres

Aetna considers intra-hepatic microspheres (e.g., TheraSphere, MDS Nordion Inc.; SIR-Spheres, Sirtex Medical Inc.) medically necessary for any of the following:

A. For treatment of neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver. For carcinoid tumors, intra-hepatic microspheres are considered medically necessary only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea); or

B. For unresectable, primary HCC; or

C. For unresectable liver tumors from primary colorectal cancer; or

D. Pre-operative use as a bridge to orthotopic liver transplantation for HCC.

Aetna considers intra-hepatic microspheres experimental and investigational for metastases from esophageal cancer and gallbladder cancer and other indications because of insufficient evidence in the peer-reviewed literature.

V. Drug-Eluting Beads Trans-Arterial Chemoembolization

Aetna considers drug-eluting beads trans-arterial chemoembolization experimental and investigational for leiomyosarcoma, and for primary and liver-dominant metastatic disease of the liver because of insufficient evidence in the peer-reviewed literature.

See also CPB 0274 - Ablation of Hepatic Lesions.

Background

Chemoembolization (CE) involves the periodic injection of chemotherapy mixed with embolic material into selected branches of the hepatic arteries feeding liver tumors. Chemoembolization has been successfully used as a palliative treatment of symptoms
associated with functioning neuroendocrine tumors involving the liver. The most common such tumor is the carcinoid tumor whose hormone production is associated with the carcinoid syndrome, characterized by debilitating flushing, wheezing and diarrhea. Pancreatic endocrine tumors that produce gastrin, insulin or other pancreatic hormones are unusual types of neuroendocrine tumors. Pancreatic endocrine (i.e., islet cell) tumors must be distinguished from the more common pancreatic epithelial tumors that arise from the exocrine portion of the pancreas.

The prognosis for patients with unresectable hepatocellular carcinoma (HCC) tumors is extremely poor. Even in the case of small nodular lesions detected by US screening, patients receiving no treatment showed a mean 3-year survival rate of 12%. Among non-surgical options, percutaneous ethanol injection (PEI) can be considered the treatment of choice for patients with small HCC tumors. Transcatheter arterial chemoembolization (TACE), most frequently performed by intra-arterially injecting an infusion of antineoplastic agents mixed with iodized oil (Lipiodol), has been extensively used in the treatment of large HCC tumors. However, although massive tumor necrosis can be demonstrated in most cases, a complete necrosis of the tumor has rarely been achieved with TACE, since residual tumor can be found in a non-negligible number of the treated lesions.

Transcatheter arterial chemoembolization was found mostly effective in nodules less than 4 cm in diameter, with a thick tumor capsule. In fact, small, encapsulated HCC are almost completely fed by hepatic arterial blood and therefore highly responsive to hepatic arterial embolization. On the contrary, in unencapsulated tumors or in tumors showing extracapsular invasion of neoplastic cells, TACE often fails to induce complete necrosis since tumor cells, either unimpeded by the absence of a capsule or spreading across the capsule itself, invade the adjacent liver parenchyma, thus obtaining additional blood supply from the sinusoidal portal system.

Large HCC lesions can be more effectively treated with combined TACE and PEI. In fact, alcohol diffusion is easier after the occurrence of the necrotic changes produced by TACE, thus allowing the intra-nodular injection of larger amounts of ethanol. Moreover, after arterial embolization, the normal wash-out of the injected ethanol is more difficult in the tumorous area, resulting in longer retention of the substance. The combination of TACE and PEI seems to be a highly effective treatment for large HCC also in the instances when daughter nodules are associated with a main tumor. The presence of the capsule significantly enhances the chances of success and should be considered an important requirement when selecting patients to be submitted to TACE and PEI.

According to available literature, TACE may be indicated for symptomatic treatment of functional neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver, in persons with adequate hepatic function (bilirubin less than 2 mg/dL, absence of ascites; no portal vein occlusion; and tumor involvement of less than 65 % of liver). For carcinoid tumors, TACE is indicated only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea). The safety and effectiveness of more than 4 TACE procedures is unknown.

For unresectable, primary HCC, TACE is indicated in persons with small encapsulated nodules (less than 4 cm in diameter), no evidence of extra-hepatic metastases, and with adequate hepatic (serum bilirubin concentration less than 2.9 mg/dL) and renal function (serum creatinine less than 2.0 mg/dL).
Pleguezuelo and colleagues (2008) stated that TACE improves survival in cirrhotic patients with HCC. The optimal schedule, best anti-cancer agent and best technique are still unclear. Transcatheter arterial chemoembolization may not be better than transarterial embolization (TAE). Hepatocellular carcinoma is very chemoresistant, thus embolization may be more important than chemotherapy. Lipiodol can not be considered as an embolic agent and there are no data to show that it can release chemotherapeutic agents slowly. It can mask residual vascularity on CT imaging and its use is not recommended. Both TACE and TAE result in hypoxia, which stimulates angiogenesis, promoting tumor growth; thus combination of TACE with anti-angiogenic agents may improve current results. To date, there is no evidence that TACE pre-liver transplantation or resection helps to expand current selection criteria for patients with HCC, nor results in less recurrence after surgery. Combination with other techniques, such as radiofrequency ablation (RFA) and drugs, may enhance the effect of TACE. New trials are being conducted to clarify these issues.

Biolato et al (2010) provided an overview on the loco-regional therapy performed by TACE in patients with HCC, either as sole, either as neoadjuvant to surgery or bridge therapy to orthotopic liver transplantation (OLT). Chemoembolization combines de-arterialization of the tumor and selective delivery of chemotherapeutic agents into tumor's feeding vessels during angiography. Tumor ischemia raises the drug concentration compared to infusion alone and extends the retention of the chemotherapeutic drug. As loco-regional therapy, TACE allows a complete local tumor control of 25 to 35 % and permits an increase of survival in patients with intermediate HCC according to Barcelona-Clinic Liver Cancer (BCLC) classification. Excellent results were also achieved by combined therapies, such as with PEI or RFA, as neoadjuvant therapy prior to liver resection and in some circumstances as a bridging tool before liver transplantation. Drug eluting beads are microspheres that can be loaded with doxorubicin and induce toxic and ischemic necrosis with the same device; that allows an increase of drug selectively exposed to tumor cells and simultaneously a reduction of systemic toxicity. Tumor embolization induces a neoangiogenic reaction with a significant growth of adjacent satellites, so the association with sorafenib has a strong rationale for a combined therapy and is currently under investigation. The authors concluded that TACE is the standard of care for treatment of intermediate HCC.

Percutaneous ethanol injection has been shown to be effective only in primary HCC with a limited number (fewer than 4) of small foci (less than 5 cm in diameter) and with no evidence of extra-hepatic metastasis. According to the medical literature, PEI is not suitable for persons with coagulopathy or ascites. The National Comprehensive Cancer Network practice guidelines (NCCN, 2010) on hepatobiliary cancers stated that the 2 most commonly used methods of ablation therapy are PEI and RFA.

In a randomized controlled study, Brunello and colleagues (2008) compared PEI and RFA for the treatment of early HCC. A total of 139 cirrhotic patients in Child-Pugh classes A/B with 1 to 3 nodes of HCC (diameter 15 to 30 mm), for a total of 177 lesions were included in this study. Patients were randomized to receive RFA (n = 70) or PEI (n = 69). The primary end-point was complete response (CR) 1 year after the percutaneous ablation of all HCC nodes identified at baseline. Secondary end-points were: early (30 to 50 days) CR, complications, survival and costs. In an intention-to-treat analysis, 1-year CR was achieved in 46/70 (65.7 %) and in 25/69 (36.2 %) patients treated by RFA and PEI, respectively (p = 0.0005). For lesions greater than 20 mm in diameter, there was a larger CR rate in the RFA-treated subjects (68.1 % versus...
An early CR was obtained in 67/70 (95.7%) patients treated by RFA compared with 42/64 (65.6%) patients treated by PEI (p = 0.0001). Complications occurred in 10 and 12 patients treated by RFA and PEI, respectively. The overall survival (OS) rate was not significantly different in the RFA versus PEI arm (adjusted hazard ratio = 0.88, 95% confidence interval [CI]: 0.50 to 1.53). There was an incremental health-care cost of 8,286 Euro for each additional patient successfully treated by RFA. The authors concluded that the 1-year CR rate after percutaneous treatment of early HCC was significantly better with RFA than with PEI, but did not provide a clear survival advantage in cirrhotic patients.

Wong et al (2008) examined if combining PEI with RFA in the management of HCC in high-risk locations improves treatment outcomes. These researchers compared the outcome of management of high-risk tumors with PEI and RFA (n = 50) or RFA alone (n = 114) with the outcome of RFA of non-high-risk tumors (n = 44). They also compared the survival rates of patients with and those without high-risk HCC. Percutaneous ethanol injection was performed into the part of the tumor closest to a blood vessel or vital structure before RFA. The study included 142 patients with 208 HCCs managed with RFA. Despite larger tumor sizes (2.8 +/- 1 cm versus 1.9 +/- 0.7 cm versus 2.5 +/- 0.1 cm for the high-risk RFA plus PEI, non-high-risk RFA, and high-risk RFA groups, respectively; p < 0.001), the primary effectiveness rate of high-risk RFA and PEI (92%) was similar to that of non-high-risk RFA (96%). The primary effectiveness rate of high-risk RFA and PEI was slightly higher (p = 0.1) than that of high-risk RFA (85%). The local tumor progression rates (21% versus 33% versus 24% at 18 months) of the 3 respective groups were not statistically different (p = 0.91). Patients with and those without high-risk tumors had equal survival rates (p = 0.42) after 12 (87% versus 100%) and 24 (77% versus 80%) months of follow-up. Independent predictors of primary effectiveness were a tumor size of 3 cm or less (p = 0.01) and distinct tumor borders (p = 0.009). Indistinct borders (p = 0.033) and non-treatment-naive status of HCC (p = 0.002) were associated with higher local tumor progression rates. The only predictor of survival was complete ablation of all index tumors (p = 0.001). The authors concluded that the combination of RFA and PEI in the management of HCC in high-risk locations has a slightly higher primary effectiveness rate than does RFA alone. They stated that a randomized controlled study is warranted.

In a Cochrane review, Schoppmeyer (2009) evaluated the beneficial and harmful effects of PEI or percutaneous acetic acid injection (PAI) in adults with early HCC. A systematic search was performed in the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, and ISI Web of Science in May 2009. Meeting abstracts of 6 oncological and hepatological societies (ASCO, ESMO, ECCO, AASLD, EASL, APASL) and references of articles were hand-searched. Researchers in the field were contacted. Randomized trials comparing PEI or PAI with no intervention, sham intervention, other percutaneous interventions or surgery for the treatment of early HCC were considered regardless of blinding, publication status, or language. Studies comparing RFA or combination treatments were excluded. Two authors independently selected trials for inclusion, and extracted and analyzed data. The hazard ratios (HRs) for median OS and recurrence-free survival were calculated using the Cox regression model with Parmar’s method. Type and number of adverse events were reported descriptively. Three randomized trials with a total of 261 patients were eligible for inclusion. The risk of bias was high in all trials. Two of the trials compared PEI with PAI. Overall survival (HR 1.47; 95% CI: 0.68 to 3.19) and recurrence-free survival (HR 1.42; 95% CI: 0.68 to 2.94) were not significantly different. Data on the
duration of hospital stay were inconclusive. Data on quality of life were not available. There were only mild adverse events in both treatment modalities. The other trial compared PEI with surgery. There was no significant difference in overall survival (HR 1.57; 95% CI: 0.53 to 4.61) and recurrence-free survival (HR 1.35; 95% CI: 0.69 to 2.63). No serious adverse events were reported in the PEI group. Three post-operative deaths occurred in the surgery group. The authors concluded that PEI and PAI does not differ significantly regarding benefits and harms in patients with early HCC, but only a limited number of patients have been examined and the bias risk was high in all trials. There is also insufficient evidence to determine whether PEI or segmental liver resection is more effective, although PEI may seem safer.

In a meta-analysis, Wang et al (2010) identified the survival benefits of TACE combined with percutaneous ablation (PA) therapy (RFA or PEI) for unresectable HCC compared with those of TACE or PA alone. Randomized-controlled trials (RCTs) published as full papers or abstracts were searched to assess the survival benefit or tumor recurrence for patients with unresectable HCC on electronic databases. The primary outcome was survival. The secondary outcomes were response to therapy and tumor recurrence. A total of 10 RCTs met the criteria to perform a meta-analysis including 595 participants. Transcatheter arterial chemoembolization combined with PA therapy, respectively improved, 1-, 2-, and 3-year OS compared with that of monotherapy [odds ratio (OR) = 2.28, 95% CI: 1.14 to 4.57; p = 0.020], (OR = 4.53, 95% CI: 2.62 to 7.82, p < 0.00001) and (OR = 3.50, 95% CI: 1.75 to 7.02, p = 0.0004). Sensitivity analysis demonstrated a significant benefit in 1-, 2- and 3-year OS of TACE plus PEI compared with that of TACE alone for patients with large HCC lesions, but not in TACE plus RFA versus RFA for patients with small HCCs. The pooled result of 5 RCTs showed that combination therapy decreased tumor recurrence compared with that of monotherapy (OR = 0.45, 95% CI: 0.26 to 0.78, p = 0.004). The authors concluded that TACE combined with PA therapy especially PEI improved the OS status for large HCCs.

Hepatic arterial infusion (HAI) of chemotherapy involves the use of an implanted subcutaneous pump to deliver continuous chemotherapy into the hepatic artery. Controlled trials have shown that this therapy is associated with higher tumor response rates and this approach is considered a potentially curative treatment of patients with colorectal cancer (CRC) with isolated liver metastases. Other applications of intrahepatic chemotherapy are unproven.

Mocellin et al (2007) stated that the treatment of unresectable liver-confined metastatic disease from CRC is a challenging issue. Although loco-regional treatments such as HAI claim the advantage of delivering higher doses of anti-cancer agents directly into the affected organ, the benefit in terms of OS is unclear. These investigators quantitatively summarized the results of RCTs comparing HAI with systemic chemotherapy (SCT). They reported that 10 RCTs have been published for a total of 1,277 patients. For tumor response rates, relative risks (RR) and their 95% CIs were obtained from raw data; for OS, HRs and their 95% CIs were extrapolated from the Kaplan-Meier survival curves. These researchers noted that HAI regimens were based on floxuridine (FUDR) in 9 of 10 RCTs, whereas in 1 RCT, fluorouracil (FU) + leucovorin was used. Systemic chemotherapy consisted of FUDR, FU, FU + leucovorin, or a miscellany of FU and best supportive care in 3, 1, 4, and 2 studies, respectively. Pooling the data, tumor response rate was 42.9% and 18.4% for HAI and SCT, respectively (RR = 2.26; 95% CI, 1.80 to 2.84; p < 0.0001). Mean weighted median OS times were 15.9 and 12.4 months for HAI and SCT, respectively; the meta-risk of death was not statistically different between the 2 study groups (HR = 0.90; 95% CI, 0.76 to 1.07; p = 0.24). The authors concluded that currently available evidence
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does not support the clinical or investigational use of fluoropyrimidine-based HAI alone for the treatment of patients with unresectable CRC liver metastases, at least as a first-line therapy.

In a review on recent advances in transarterial therapy of primary and secondary liver malignancies, Kalva and colleagues (2008) stated that transarterially administered gene therapy holds promise but is still in the early stages of investigation.

Despite various modalities available for the treatment of non-resectable HCC, such therapies have not resulted in marked impact on OS. A new approach in treating these patients is administration of microspheres via hepatic artery branches with subsequent deposition in the tumor terminal vasculature. This method could provide an approximately 3-fold or greater radiation dose in tumor nodules relative to normal liver. Previous studies have demonstrated that yttrium-90 embedded into non-biodegradable glass microspheres (TheraSphere, MDS Nordion Inc., Kanata, Ontario, Canada) can be administered safely by intra-hepatic arterial injection to patients with HCC and underlying cirrhosis at a dose of 100 Gy. A recent study (Dancey et al, 2000) reported that intra-hepatic yttrium-90 microspheres appears to be beneficial for patients with non-resectable HCC with less toxicity than systemic or hepatic arterial chemotherapy or hepatic arterial chemoembolization.

Dancey et al (2000) indicated that the following criteria be used to select appropriate patients for administration of intra-hepatic microspheres as an adjuvant to chemotherapy, surgery or transplantation for persons with unresectable HCC. These criteria are based on the selection criteria for clinical studies of the TheraSphere submitted for FDA approval, and contraindications to use of TheraSphere in the FDA-approved product labeling. These criteria may also be applied to persons with metastatic liver tumors from primary CRC (see discussion of SIR-Spheres below):

I. Histologically confirmed non-resectable lesion confined to the liver and at least 1 measurable lesion; and

II. Eastern Cooperative Oncology Group (ECOG) performance status score less than or equal to 3

- Absolute granulocyte count greater than or equal to 2.0 x 10^9/L
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) less than 5 x upper normal limit [AST = 5 to 40 IU/L, ALT = 5 to 35 IU/L, ALP = 42 to 128 U/L]
- Bilirubin less than 1.5 x upper normal limit [total bilirubin = 0.1 to 1.0 mg/dL or 5.1 to 17.0 mmol/L]
- Estimated life expectancy greater than or equal to 12 weeks
- Normal pulmonary function defined as within 30% of the expected values for each parameter (e.g., forced vital capacity, forced expiratory volume in 1 second, maximal mid-expiratory flow, maximal voluntary ventilation, and arterial blood gases);
- Platelet count greater than or equal to 100 x 10^9/L
- Prothrombin time (PT) and activated partial prothrombin time (APTT) within normal limits [PT = 11.0 to 12.5 seconds; APTT = 30 to 40 seconds]; and

III. Adequate bone marrow and hepatic function; and
IV. No contraindications to hepatic artery catheterization (e.g., vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis); and
V. No other concurrently planned oncotherapy; and
VI. At least 1 month post other chemotherapy or surgery.

The following exclusion criteria apply:

I. Previous chemotherapy or radiation therapy for hepatoma; or
II. Potential absorbed dose to lungs greater than 30 Gy; or
III. Any uncorrectable angiographic flow to the gastrointestinal tract; or
IV. Co-morbid disease that would preclude safe delivery of intra-hepatic microspheres treatment and place the member at undue risk.

Diagnostic work-up prior to the use of intra-hepatic microspheres includes (i) hepatic angiogram which entails placement of intra-hepatic catheter to assess vasculature and TheraSphere delivery route, and (ii) technetium-99 macroaggregated albumin (Tc-99 MAA) study to evaluate hepatic flow to gastrointestinal tract and/or pulmonary shunting. These studies are medically necessary and thus are eligible for coverage.

In the United States, SIR-Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary CRC with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (flouxuridine). The Food and Drug Administration (FDA) approval of SIR-Spheres was based on the results of a RCT involving 70 persons with CRC metastatic to the liver, 34 of whom received FUDR chemotherapy (control group), and 36 of whom received FUDR plus SIR-Spheres. Two of the patients receiving FUDR plus SIR-Spheres had a CR, and 16 had a partial response (PR). By comparison, 1 patient receiving FUDR alone achieved a CR and 7 had a PR. There is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres, when compared with the group treated with FUDR only.

The FDA-approved product labeling for SIR-Spheres states that treatment with SIR-Spheres may be indicated when the metastatic CRC in the liver is considered unresectable. According to the FDA-approved labeling, metastatic CRC may be considered non-resectable in any of the following circumstances:

I. Multiple liver metastases together with involvement of both lobes; or
II. Tumor invasion of the hepatic confluence where the 3 hepatic veins enter the inferior vena cava (IVC) such that none of the hepatic veins could be preserved if the metastases were resected; or
III. Tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; or
IV. Widespread metastases such that resection would require removal of more liver than is necessary to maintain life.

The FDA-approved product labeling for SIR-Sphere’s states that resectability may be evaluated via imaging with a triple phase contrast angio-portal CT scan or MRI.

The FDA-approved labeling for SIR-Sphere states that the following tests are recommended before treatment.

I. A hepatic angiogram should be performed to establish arterial anatomy of the liver.
II. A nuclear medicine break-through scan (intra-hepatic technetium MAA Scan) to determine the percent lung shunting. If a port has been inserted, this test can be performed through the port.

III. Serologic tests of liver function should be performed to determine the extent of liver function/damage.

The FDA-approved product labeling for SIR-Spheres states that appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

The product labeling states that SIR-Spheres are contraindicated in patients who have

- Ascites or are in clinical liver failure, or
- Been treated with capecitabine within the 2 previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres, or
- Disseminated extra-hepatic malignant disease, or
- Greater than 20% lung shunting of the hepatic artery blood flow determined by technetium MAA scan, or
- Had previous external beam radiation therapy to the liver, or
- Markedly abnormal synthetic and excretory liver function tests (LTFs), or
- Portal vein thrombosis; or
- Pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel.

The manufacturer of SIR-Spheres recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres to confirm placement of the microspheres in the liver.

An assessment by the California Technology Assessment Forum (Tice, 2009) on selective internal radiation therapy or radioembolization for inoperable liver metastases from colorectal cancer reported that 22 case series with data on patients with metastatic CRC have demonstrated that it is feasible to deliver radiation therapy to liver tumors and achieve at least partial remission in a substantial proportion of patients with relatively few serious adverse events. The assessment stated that procedure-specific adverse events such as radiation pneumonitis, gastrointestinal ulceration and radiation-induced liver disease have been characterized and pre-treatment planning strategies have been developed to limit their frequency and severity. The CTAF assessment (Tice, 2009) reported that results of 2 RCTs (citing Gray et al, 2001; van Hazel et al, 2004) are encouraging, but not definitive. Both trials demonstrated improvements in disease-free survival and a trend towards longer OS. However, the trials were very small (less than 100 patients in total) and the response rates in the control groups were lower than expected. Furthermore, the assessment noted, the control groups did not use the standard first-line therapy for CRC metastatic only to the liver. The assessment stated that ongoing clinical trials that are randomizing over 800 newly diagnosed patients to first line chemotherapy with or without radioembolization should define the efficacy of combined therapy and the associated additional toxicity. Similarly, the data on the utility of radioembolization as salvage therapy for patients who have failed multiple rounds of chemotherapy is limited and immature.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2009) state that radioembolization is an acceptable alternative for management of unresectable liver only or liver dominant metastases from carcinoids or islet cell tumors.
Guidance from the National Institute for Health and Clinical Excellence (2011) concluded that current evidence on the safety of selective internal radiation therapy for non-resectable colorectal metastases in the liver is adequate. The report concluded, however, that the evidence on its efficacy in chemotherapy-naive patients is inadequate in quantity. The report found that, for patients who have previously been treated with chemotherapy, there is evidence that selective internal radiation therapy can prolong time to progression of hepatic metastases, but more evidence is required on survival and quality of life. Therefore for patients who have been previously treated with chemotherapy this procedure should be used with special arrangements for clinical governance, consent and audit. The NICE Committee considered selective internal radiation therapy a potentially beneficial treatment for patients with non-resectable colorectal metastases in the liver, but concluded that more research and data collection are required to demonstrate its efficacy. The Committee noted that observational studies report large numbers of patients previously treated by chemotherapy who have received selective internal radiation therapy, but that the number of these patients reported in comparative trials was very small. For patients who have previously been treated with chemotherapy, comparative trials are needed to determine whether selective internal radiation therapy prolongs survival compared with best standard treatment, and to determine its effect on quality of life. There is also a need to identify which subgroups of patients are likely to derive clinical benefit from selective internal radiation therapy. The NICE Committee noted that there have been a small number of reports of SIRT downstaging colorectal metastases to the extent that treatment by resection or ablation became possible. However, it considered that there was insufficient evidence to comment on the potential use of the procedure with this intent.

The advantage of chemoembolization of the liver as an anti-neoplastic treatment for HCC is that it achieves high intra-tumoral concentrations of the chemotherapeutic agent locally that can not be reached with systemic chemotherapy in non-toxic doses. However, chemotherapeutic release and local concentrations can not be standardized by this technique. Drug-eluting beads (DEB) are believed to have predictable pharmacokinetics and can achieve higher doses of the chemotherapeutic and prolonged contact time with cancer cells.

In a phase I/II clinical trial, Poon and colleagues (2007) assessed the safety and efficacy of TACE using doxorubicin-eluting beads (DC Beads) for HCC. Patients with incurable HCC and Child-Pugh class A cirrhosis were considered eligible. Two courses of TACE using DC Beads were given at an interval of 2 months, and tumor response was assessed by computerized tomography scan. The phase I trial was a dose-escalating study starting from 25 mg to 150 mg doxorubicin in cohorts of 3 patients. The 150-mg doxorubicin dose was used for the phase II study. Primary end points were treatment-related complications and deaths. Secondary end points included tumor response and pharmacokinetics of doxorubicin. In the phase I study involving 15 patients, no dose-limiting toxicity was observed for up to 150 mg doxorubicin, which was used for 20 patients in the phase II study. The pharmacokinetic study showed a low peak plasma doxorubicin concentration (49.4 +/- 23.7 ng/ml), and no systemic toxicity was observed. The treatment-related complication rate was 11.4 %. There was no treatment-related death. Among 30 patients who completed 2 courses of TACE, the PR rate and the CR rates were 50 % and 0 %, respectively, by response evaluation criteria in solid tumors (RECIST) criteria at computerized tomography scan 1 month after the second TACE. By modified RECIST criteria, taking into account the extent of tumor necrosis, 19 (63.3 %) patients had a PR and 2 (6.7 %) had a CR. The authors
concluded that these findings showed that TACE using DC Beads is a safe and effective treatment for HCC, supporting a phase III randomized trial to compare this novel treatment with conventional TACE using doxorubicin-lipiodol emulsion.

In an open-label, single-center, single-arm study, Malagari et al (2008) evaluated the safety and efficacy of DC Beads delivered by TACE for the treatment of unresectable HCC. A total of 62 cirrhotic patients with documented single unresectable HCC were included in this study. Mean tumor diameter was 5.6 cm (range of 3 to 9 cm) classified as Okuda stages 1 (n = 53) and 2 (n = 9). Patients received repeat embolizations with DC Beads every 3 months (maximum of 3). The maximum doxorubicin dose was 150 mg per embolization, loaded in DC Beads of 100 to 300 or 300 to 500 microm.

Regarding efficacy, overall, an objective response according to the European Association for the Study of the Liver (EASL) criteria was observed in 59.6 %, 81.8 %, and 70.8 % across 3 treatments. A CR was observed in 4.8 % after the first procedure and 3.6 % and 8.3 % after the second and third procedures, respectively. At 9 months a CR was seen in 12.2 %, an objective response in 80.7 %, progressive disease in 6.8 %, and 12.2 % showed stable disease. Mean tumor necrosis ranged from 77.4 % to 83.9 % (range of 28.6 % to 100 %) across 3 treatments. Alpha-fetoprotein levels showed a mean decrease of 1,123 ng/ml (95 % CI: 846 to 1399; p = 3 x 10(-11)) after the first session and remained stable after the second and third embolizations (42 and 70 ng/ml decrease, respectively). Regarding safety, bilirubin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase showed only transient increases during the study period. Severe procedure-related complications were seen in 3.2 % (cholecystitis, n = 1; liver abscess, n = 1). Post-embolization syndrome was observed in all patients. The authors concluded that CE using doxorubicin-loaded DC Beads is a safe and effective treatment of HCC as demonstrated by the low complication rate, increased tumor response, and sustained reduction of alpha-fetoprotein levels.

Carter and Martin (2009) stated that DEB-TACE is a novel therapy for the treatment of hyper-vascularized tumors. Through the intra-arterial delivery of microspheres, DEB-TACE allows for embolization as well as local release of chemotherapy in the treatment of hepatic malignancy, providing an alternative therapeutic option in unresectable tumors. Its role as an adjunct to surgical resection or RFA is less clear. These researchers summarized recent studies investigating DEB-TACE in order to better define safety, efficacy and outcomes associated with its use. A systematic review of all published articles and trials identified 9 clinical trials and 23 abstracts. These were reviewed for tumor histology, stage of treatment, delivery technique, outcome at follow-up, complications and mortality rates. Publications involved treatment of HCC, metastatic colorectal carcinoma (MCRC), metastatic neuroendocrine (MNE) disease and cholangiocarcinoma (CCA). Using RECIST or EASL criteria, studies treating HCC reported CR rates of 5 % (5/101) at 1 month, 9 % (8/91) at 4 months, 14 % (19/138) at 6 months and 25 % (2/8) at 10 months; PR was reported as 58 % (76/131) at 1 month, 50 % (67/119) at 4 months, 57 % (62/108) at 6-7 months and 63 % (5/8) at 10 months.

Studies involving MCRC, CCA and MNE disease were less valuable in terms of response rate because there is a lack of comparative data. The most common procedure-associated complications included fever (46 to 72 %), nausea and vomiting (42 to 47 %), abdominal pain (44 to 80 %) and liver abscess (2 to 3 %). Rather than reporting individual symptoms, 2 studies reported rates of post-embolic syndrome, consisting of fever, abdominal pain, and nausea and vomiting, at 82 % (75/91). Six of 8 studies reported length of hospital stay, which averaged 2.3 days per procedure. Mortality was reported as occurring in 10 of 456 (2 %) procedures, or 10 of 214 (5 %) patients. The authors concluded that drug-eluting bead TACE is becoming more widely
utilized in primary and liver-dominant metastatic disease of the liver. Outcomes of success must be expanded beyond response rates because these are not a reliable surrogate for progression-free survival or OS. Ongoing clinical trials will further clarify the optimal timing and strategy of this technology.

In a phase II clinical trial, Fiorentini et al (2009) evaluated the safety and efficacy of TACE. A total of 10 patients with liver metastases (LM) from uveal melanoma (UM) were treated with TACE-containing beads pre-loaded with irinotecan (IRI, 100 mg). All patients had an objective response, 3 presented a very good PR and 7 obtained a PR. The median follow-up time from the beginning of therapy was 6.5 months (range of 4 to 9 months); 8 patients were alive at the time of this analysis. The most important adverse event was abdominal pain during the procedure. Adequate supportive treatment with antibiotic and anti-emetic prophylaxis, desametazone and intravenous hydration is strictly necessary until stabilization of serum levels of transaminases and to prevent infections. A major analgesic such as morphine must be used before and after the procedure. The authors concluded that TACE containing beads pre-loaded with IRI is effective in the treatment of LM from UM. This approach seems to have better efficacy than previous TACE regimens adopted.

In an open-label, multi-center, single-arm study, Martin et al (2009) examined the value of DEB in patients with unresectable colorectal hepatic metastasis who had failed standard therapy. Patients received repeat embolizations with IRI-loaded beads (max 100 mg per embolization) per treating physician's discretion. A total of 55 patients underwent 99 treatments using IRI-DEB. The median number of total treatments per patient was 2 (range of 1 to 5). Median length of hospital stay was 23 hours (range of 23 hours to 10 days). There were 30 (30 %) sessions associated with adverse reactions during or after the treatment. The median disease free and OS from the time of first treatment was 247 days and 343 days. Six patients (10 %) were down-staged from their original disease status. Of these, 4 were treated with surgery and 2 with RFA. Neither number of liver lesions, size of liver lesions or extent of liver replacement (less than or equal to 25 % versus greater than 25 %) were predictors of OS. Only the presence of extra-hepatic disease (p = 0.001), extent of prior chemotherapy (failed 1st and 2nd line versus greater than 2 line failure) (p = 0.007) were predictors of OS in multi-variate analysis. The authors concluded that the findings in this interim report indicated that CE using IRI-loaded beads was safe and effective in the treatment of patients as demonstrated by a minimal complication rate and acceptable tumor response.

In a pilot study, Guiu et al (2009) evaluated efficacy and toxicity of a TACE procedure using a combination of pirarubicin, amiodarone, lipiodol, and gelatin sponge. A total of 43 patients were included in this study and they underwent TACE for unresectable HCC. Computed tomography scans were performed to assess tumor response (RECIST) and lipiodol uptake after the first session. Median follow-up lasted 30 months. Endpoints were OS and progression-free survival. Survival was estimated using Kaplan Meier estimations and compared using log-rank tests. Uni-variate and multi-variate Cox analyses were used to calculate HRs with their 95 % CI. Twenty-seven (67.5 %) patients had alcoholic cirrhosis. Mean tumor size was 9.5 cm (1 to 20 cm) and 37/43 were multi-focal or diffuse. Cancer of the liver Italian program score was 0 in 7/40 and 1 in 16/40. Mean number of TACE sessions was 3.5 (1 to 11). There were 3 treatment-related deaths (2 severe sepsis, 1 bowel perforation). A PR and a stable disease were observed in 12 (28 %) and 29 (67 %) patients, respectively. Median OS and progression-free survival were 29 months (95 % CI: 13.8 to 45) and 15 months (95 % CI: 11.5 to 20.8), respectively. Cancer of the liver Italian program
score less than or equal to 1 ($p = 0.042$) and lipiodol uptake greater than 25 % ($p = 0.003$) were independent prognostic factors for better OS. The authors concluded that this new TACE procedure is safe with a high OS rate and certainly deserves phase III investigation to compare it with classic treatments such as doxorubicin-lipiodol TACE.

Tokh et al (2010) noted that conventional TACE uses a combination of chemotherapy, lipiodol, and an embolic agent. Drug-eluting bead therapy is a potentially less toxic and therapeutically equivalent form of intra-arterial drug delivery. These researchers assessed the safety, efficacy and survival among patients with HCC treated with DEB after a long experience with traditional TACE. A total of 63 sequential patients with unresectable HCC were treated over an 18-month period. Subjects received 2 courses of DEB-CE, using 100 mg doxorubicin in DEB ranging from 300 to 700 microns in diameter. They retrospectively analyzed patient demographics, etiologies of liver disease, Child Pugh status, CLIP scores, size of largest tumor, baseline alpha-fetoprotein (AFP), toxicity, change in size of largest tumor, change in AFP, and survival from first treatment. A total of 63 patients (51 men; median age of 62 years) were treated; 53 had cirrhosis (30 Hepatitis C, 12 from alcohol); 6 had portal vein thrombosis; median tumor size was 4.8 cm (range of 2 to 12 cm); 37 had elevated AFP (median 471 ng/ml, range of 21 to 54,860). 37 were Child's A and 26 B; 9 had CLIP scores greater than 2. 51 remain alive, and 30-day mortality was zero. Most common adverse reactions were abdominal pain (71 %), nausea (52 %), and fatigue (18 %). Overall, 81 % of evaluable patients had tumor regression; AFP decreased in 79 % of patients with elevated levels, with a median fall of 78.5 %. Poor prognostic indicators for survival following the procedure included cirrhosis, elevated bilirubin and elevated AFP; CLIP score, Child's status, etiology and size did not significantly impact outcome. Actuarial survival was 18.2 months. The authors concluded that outcomes following treatment of HCC using DEB compare favorably with historic results using conventional CE. Patients experience substantially less fever, a shorter duration of pain, but more nausea within 24 hours. There were no early deaths. Survival appears to be at least equivalent, with milder toxicity, compared with the authors' historic experience. They noted that RCTs of the 2 modalities of CE are currently under way.

Malagari et al (2010) evaluated the added role of a chemotherapeutic in TACE of intermediate-stage HCC. The issue is of major importance since, as suggested by recent evidence, hypoxia or incomplete de-vascularization of the tumor is a potent stimulator of angiogenesis, and there are not many papers supplying level one evidence confirming the value of a chemotherapeutic. The hypothesis was that since DEB-TACE is standardized and reproducible, a comparison with bland TACE can readily reveal the potential value of the chemotherapeutic. In this prospective study, 2 groups were randomized: group A ($n = 41$) was treated with doxorubicin DEB-TACE, and group B ($n = 43$) with bland embolization. Patients were randomized for tumor diameter; they were embolized at set time intervals (2 months), with a maximum of 3 embolizations. Tumor response was evaluated using the EASL criteria and AFP levels. At 6 months a CR was seen in 11 patients (26.8 %) in the DEB-TACE group and in 6 patients (14 %) in the bland embolization group; a PR was achieved in 19 patients (46.3 %) and 18 (41.9 %) patients in the DEB-TACE and bland embolization groups, respectively. Recurrences at 9 and 12 months were higher for bland embolization (78.3 % versus 45.7 %) at 12 months. Time to progression (TTP) was longer for the DEB-TACE group (42.4 +/- 9.5 and 36.2 +/- 9.0 weeks), at a statistically significant level ($p = 0.008$). The authors concluded that DEB-TACE presents a better local response, fewer recurrences, and a longer TTP than bland embolization with BeadBlock. However, survival benefit and bland embolization with smaller particles must be addressed in future papers to better assess the clinical value.
Nicolini et al (2010) retrospectively compared radiological tumor response and degree of necrosis in explanted livers after CE with epirubicin-loaded DC Bead versus bland embolization in patients on a transplant waiting list. From 2003 to 2007, 49 patients with HCC underwent transplantation at a single center. Sixteen patients were treated with bland embolization (n = 8) with 100-300-microm Embosphere particles or CE with epirubicin-loaded 100-300-microm DC Bead particles (n = 8) every other month until complete tumor de-vascularization. Computed tomography was performed every 3 months until recurrence. Explanted livers were analyzed to evaluate the degree of necrosis in the nodules. After orthotopic liver transplantation (OLT), patients were followed-up for survival and disease status. The groups were comparable for baseline characteristics. Most patients had Child-Pugh class A disease. Solitary HCC was found in 75% of patients. Mean target lesion size was 32 mm +/- 15.4.

Chemoembolization with DEB achieved complete necrosis in 77% of lesions whereas bland embolization achieved complete necrosis in 27.2% of lesions. There was a significant difference between bland embolization and CE with DEB with regard to histological necrosis (p = 0.043). No significant treatment-related complications were observed for either group. Fifteen patients are alive with no tumor recurrence. The authors concluded that CE with DEB before OLT achieved higher rates of complete histological response than bland embolization, with no serious adverse events observed. Because of the retrospective data analyses and small sample size, further studies are warranted to confirm these promising results.

Current NCCN guidelines on cervical cancer include no recommendation to use chemoembolization for cervical cancer, including cervical cancers metastatic to the liver. In addition, National Cancer Institute (PDQ) guidance includes no recommendation for chemoembolization for liver cancer. ClinicalTrials.gov lists dozens of trials of chemoembolization, primarily for hepatocellular carcinoma and for colorectal cancers metastatic to the liver. However, there are no trials listed in ClinicalTrials.gov for chemoembolization for persons with cervical cancer. Peer-reviewed published evidence for chemoembolization for cervical cancer consists of 3 retrospective case-series studies (in Chinese – Liu et al, 2009; Yu et al, 2009; and Tian et al, 2010). The largest of these (Tian et al, 2010) found no improvements in survival with the addition of chemoembolization to radiotherapy for cervical cancer. The study concluded that “Compared with the simple radiotherapy, there are a similar short-term survival rate and significant poor 5-year, 8-year survival rate in the patients treated with the uterine arterial interventional chemoembolization combined with radiotherapy, which also may be strong dangerous factor for the occurrence of tardive bladder injury. The results shown that the uterine arterial interventional chemoembolization do not recommend to be routine adjuvant therapy for the radical radiotherapy of cervical cancer”.

Cannon et al (2012) assessed the safety and effectiveness of chemoembolization with doxorubicin-eluting beads (DEBDOX) in the treatment of multi-nodular (greater than or equal to 10 lesions) HCC. A 503-patient prospective multi-national DC Bead registry database from 6/2007 to 2/2010 identified 176 patients treated for HCC with DEBDOX. There were 42 patients with multi-nodular HCC compared to 134 with non-multinodular HCC. After a median follow-up of 12 months, the multi-nodular group response rate according to modified RECIST criteria was 56% and median overall survival was 7.6 months, compared to 57% and 15 months in the non-multinodular group (p = 0.08). The authors concluded that multi-nodular HCC represents a more advanced stage of disease; however, DEBDOX treatment is safe and effective when compared to historical controls and current best systemic therapy. They stated that continued
hepatic arterial therapy and evaluation is needed in this clinical subset to further confirm these results.

Lencioni et al (2013) stated that TACE is the current standard of care for patients with intermediate-stage HCC and relatively preserved liver function. In a meta-analysis of RCTs comparing conventional TACE regimens including the administration of an anticancer-in-oil emulsion followed by embolic agents versus best supportive care, TACE was shown to improve median survival from 16 to 20 months. Various strategies to improve outcomes for this patient group have become the subject of much ongoing clinical research. The introduction of an embolic DEB has been shown to substantially improve the pharmacokinetic profile of TACE, providing levels of consistency and repeatability not available with conventional regimens while concomitantly significantly diminishing systemic drug exposure. In randomized trials, DEB-TACE significantly reduced liver toxicity and drug-related adverse events compared with conventional TACE. These investigators reviewed technique, indications and contraindications, and clinical outcomes of conventional and DEB-TACE in the management of HCC. In addition, scientific background and early clinical experience with the use of combination regimens including TACE and systemically active molecular-targeted agents with anti-angiogenic properties were discussed. The authors concluded that the combination of DEB-TACE and anti-angiogenic therapy represents a potentially powerful approach that is currently undergoing clinical investigation in a phase III setting.

In a meta-analysis, Gao and associates (2013) evaluated the effectiveness of DEB-TACE compared with conventional TACE (cTACE). These researchers included 7 studies (a total of 693 patients) to compare DEB-TACE with cTACE. The pooled (OR were calculated using a random or fixed effects model. MEDLINE, EMBASE and the Cochrane Database were searched for articles published from dates of inceptions up to February 20, 2012. Sensitivity analysis and publication bias estimate were also performed to evaluate the potential risk bias in the overall results of pooled analysis. The pooled estimates for tumor response of DEB-TACE were not significantly different from those of cTACE, with CR (OR: 1.18; 95 % CI: 0.81 to 1.71; p = 0.394), PR (OR: 1.37; 95 % CI: 0.94 to 1.99; p = 0.101), stable disease (SD) (OR: 0.88; 95 % CI: 0.51 to 1.51; p = 0.637), PD (OR: 0.85; 95 % CI: 0.52 to 1.38; p = 0.512), DC (OR: 1.37, 95 % CI: 0.95 to 1.98; p = 0.089) and OR (OR: 1.40; 95 % CI: 0.97 to 2.00; p = 0.070). The authors concluded that the current evidence suggests that DEB-TACE is able to accomplish the same tumor response as cTACE. Moreover, they stated that although this analysis provided a comprehensive look at published data involving the clinical effectiveness of DEB-TACE compared with conventional TACE, additional large scale of RCTs are still needed.

An UpToDate review on “Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization” (Curley et al, 2013) states that “A newer approach to TACE uses drug-eluting beads (DEBs) that slowly release chemotherapy, thus diminishing systemic toxicity. Early results from retrospective reports and several small prospective randomized trials suggest similar rates of tumor control as with conventional TACE, with lower rates of serious hepatobiliary toxicity, although follow-up is short in most series:

A meta-analysis of seven studies comparing conventional TACE versus DEB-TACE (five prospective randomized trials and two retrospective comparative reports, totaling 693 patients) concluded that the pooled estimates for tumor response with DEB-TACE were not significantly different from those of
conventional TACE (odds ratio [OR] for disease control 1.37, 95% CI 0.95-1.98).

Comparative toxicity was addressed in the largest randomized trial, the PRECISION V trial, in which conventional TACE using doxorubicin (50 to 75 mg/m²) was directly compared to DEB-TACE (150 mg doxorubicin per procedure) in 212 patients with Child-Pugh A/B cirrhosis and unresectable HCC. The DEB group had lower rates of treatment-emergent adverse events in the hepatobiliary system (16 versus 25 percent). The mean maximum postchemoembolization alanine transaminase increase with DEB-TACE was 50 percent less than in the conventional TACE group (p < 0.001), and the mean maximum aspartate transaminase increase was 41 percent lower. Furthermore, despite a higher mean total dose of doxorubicin in the DEB-TACE group (295 versus 233 mg), there was a small but statistically significant difference in mean change from baseline in left ventricular ejection fraction (LVEF) of 4 percentage points that favored DEB-TACE group. The incidence of postembolization syndrome was similar between both groups (25 versus 26 percent for DEB-TACE and conventional TACE). On the other hand, treatment-emergent gastrointestinal adverse events occurred more often in patients treated with DEB-TACE (61 versus 45 percent).

The authors noted that “Where available, TACE using drug-eluting beads may be preferred, although long-term experience with this modality is limited”.

Furthermore, the NCCN clinical practice guideline on “Hepatobiliary cancers” (Version 1.2013) notes that “Recent studies have evaluated TACE with drug-eluting beads in patients with unresectable HCC … These results need to be confirmed in larger prospective studies”.

Idilman et al (2013) determined the effect of trans-arterial chemo-embolization (TACE) treatment on survival in patients with HCC and examined the efficacy and tolerability of 2 different TACE procedures: (i) conventional TACE and (ii) drug-eluting beads (DEB), in these patients. A total of 40 patients with HCC treated with TACE between January 2007 and March 2011 were included. Thirty-seven patients had Child-Pugh class A and the remaining 3 had class B. Intra-arterial administration of doxorubicin with lipiodol-based conventional TACE or DEB-TACE was performed. Eighty sessions were performed with a median of 2 sessions. Sixteen patients were treated with conventional TACE and 11 with DEB-TACE, and 13 were treated with both treatment procedures in separate sessions. Primary outcome was defined as patient survival after treatment. The median follow-up was 19 months. The median overall survival of patients was 23.2 months. The survival of patients with Child-Pugh class A was significantly better than that of patients with class B (24 versus 6 months, p = 0.004). No statistically significant difference in survival was observed between conventional TACE and DEB-TACE treatments (p > 0.05). Baseline low serum albumin level (p = 0.003) and the presence of portal vein thrombosis (p = 0.011) negatively affected patient survival. Side effects of conventional TACE and DEB-TACE were similar. The authors concluded that based on the results of this study and in comparison with the findings in the literature, TACE treatment was seen to improve overall survival and provide better outcome in selected patients with HCC. They stated that no differences in survival or side effects were observed between the 2 TACE treatment modalities (conventional TACE and DEB-TACE).

Liver and Other Neoplasms - Treatment Approaches

carcinoma undergoing TACE as a primary therapy or as a bridge to liver transplantation (LT). A total of 45 consecutive patients underwent TACE with M1 DEB loaded with doxorubicin (DEBDOX/M1). Clinical data were recorded at 12, 24, and 48 hours, 7 and 30 days after treatment. Response was assessed by computed tomographic scan according to the modified response evaluation criteria in solid tumors criteria, and a second DEBDOX/M1 TACE was scheduled within 6 weeks in case of a non-complete response. All patients had well-compensated cirrhosis (97.7 % Child A, 44.4 % hepatitis C virus, median age of 61 years). Twenty patients (44.4 %) had Barcelona Clinic for Liver Cancer class B disease; the median number of nodules and their sum of diameters were 2 (range of 1 to 6) and 43 mm (range of 10 to 190), respectively. The mean number of TACE procedures per patient was 1.4. Objective response rate (complete + partial response) was 77.7 % with a median time to best response of 3 months (95 % confidence interval [CI]: 2 to 4). In 13 patients, DEBDOX/M1 TACE served as a bridge/down-staging to LT/surgery. Pathology showed that more than 90 % necrosis was achieved in 10 of 28 nodules. DEBDOX/M1 TACE was well-tolerated, and the grade 3/4 adverse event rate was low (1 of 65 procedures). The authors concluded that DEBDOX/M1 TACE is an effective procedure with a favorable safety profile and promising results in terms of objective response rate, tumor down-staging, and necrosis.

An UpToDate review on “Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization” (Curley et al, 2014) states that “Drug-eluting beads -- A newer approach to TACE uses drug-eluting beads (DEBs) that slowly release chemotherapy, thus diminishing systemic toxicity. Early results from retrospective reports and several small prospective randomized trials suggest similar rates of tumor control as with conventional TACE, with lower rates of serious hepatobiliary toxicity, although follow-up is short in most series”.

Furthermore, the NCCN’s clinical practice guideline on “Hepatobiliary cancers” (Version 1.2015) notes that “DEB-TACE has also been evaluated in patients with unresectable HCC .... Malagari et al also showed that DEB-TACE resulted in higher response rates, lower recurrences, and longer TTP compared to TAE in patients with intermediate-state HHC; however, this study also did not show any OS benefit for DEB-TACE .... Dhanasekaran et al reported a survival advantage for DEB-TACE over conventional TACE in a prospective randomized study of 71 patients with unresectable HCC. However, these results need to be confirmed in large prospective studies”.

In a prospective, single-center, phase I study, Cohen et al (2014) documented the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and the recommended phase II dose for future study of capecitabine in combination with radio-embolization. Patients with advanced unresectable liver-dominant cancer were enrolled in a 3+3 design with escalating doses of capecitabine (375 to 1,000 mg/m²) b.i.d.) for 14 days every 21 days. Radio-embolization with (90)Y-resin microspheres was administered using a sequential lobar approach with 2 cycles of capecitabine. A total of 24 patients (17 colorectal) were enrolled. The MTD was not reached. Hematologic events were generally mild. Common grade 1/2 non-hematologic toxicities included transient transaminitis/alkaline phosphatase elevation (9 (37.5 %) patients), nausea (9 (37.5 %)), abdominal pain (7 (29.0 %)), fatigue (7 (29.0 %)), and hand-foot syndrome or rash/desquamation (7 (29.0 %)). One patient experienced a partial gastric antral perforation with a capecitabine dose of 750 mg/m². The best response was PR in 4 (16.7 %) patients, SD in 17 (70.8 %) and progression in 3 (12.5 %). Median time to progression and OS of the metastatic CRC cohort was 6.4 and 8.1 months, respectively. The authors concluded that this combined modality treatment was
generally well-tolerated with encouraging clinical activity. Capecitabine 1,000 mg/m\(^2\) b.i.d. is recommended for phase II study with sequential lobar radio-embolization.

An UpToDate review on “Management of locally advanced unresectable and inoperable esophageal cancer” (Heron and Gibson, 2014) and NCCN’s clinical practice guideline on “Esophageal and esophagogastric junction cancers” (Version 1.2015) do not mention chemoembolization as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-9 Codes
CPT codes covered if selection criteria are met:

- 36245 Placement, arterial system; each first order abdominal, pelvic, or lower extremity artery branch, within a vascular family
- 36260 Insertion of implantable intra-arterial infusion pump (e.g., for chemotherapy of liver)
- 37242 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)
- 37243 for tumors, organ ischemia, or infarction
- 75894 Transcatheter therapy, embolization, any method, radiological supervision and interpretation
- 75896 Transcatheter therapy, infusion, other than for thrombolysis, radiological supervision and interpretation
- 77750 Infusion or instillation of radioelement solution (includes three months of follow-up care)
- 77776 - 77778 Interstitial radiation source application
- 96446 Chemotherapy administration into peritoneal cavity via indwelling port or catheter

Other CPT codes related to the CPB:

- 96522 Refilling and maintenance of implantable pump or reservoir for drug delivery, systemic (e.g., intravenous, intra-arterial)

HCPCS codes covered if selection criteria are met:

- C2616 Brachytherapy source, nonstranded, yttrium-90, per source [microspheres]
- Q3001 Radioelements for brachytherapy, any type, each
- S2095 Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres
Other HCPCS codes related to the CPB:

J2353  Injections, octreotide, depot form for intramuscular injection, 1 mg

J2354  Injections, octreotide, non-depot form for subcutaneous intravenous injection, 25 mcg

Percutaneous Ethanol Injection:

ICD-9 codes covered if selection criteria are met:

155.0  Malignant neoplasm of the liver, primary [hepatocellular cancers (HCC) without extrahepatic spread]

ICD-9 codes not covered for indications listed in the CPB:

155.2  Malignant neoplasm of the liver, not specified as primary or secondary

197.7  Secondary malignant neoplasm of liver, specified as secondary

Chemoembolization:

ICD-9 codes covered if selection criteria are met:

155.0 - 155.2  Malignant neoplasm of the liver and intrahepatic bile ducts [unresectable]

157.0 - 157.9  Malignant neoplasm of pancreas [endocrine involving the liver] [in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing, and diarrhea)]

190.0  Malignant neoplasm of eyeball except conjunctiva, cornea, retina, and choroid [with liver-only metastases]

209.00 - 209.29  Malignant carcinoid tumors

209.72  Secondary neuroendocrine tumor of liver

V49.83  Awaiting organ transplant status [Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for HCC]

ICD-9 codes not covered for indications listed in the CPB:

153.0 - 153.9  Malignant neoplasm of colon

171.0 - 171.9  Malignant neoplasm of connective tissue and other soft tissue [rhabdomyosarcoma]

172.0 - 172.9  Malignant melanoma of skin

174.1-174.9  Malignant Neoplasm of Female Breast

175.0-175.9  Malignant Neoplasm of Male Breast
Secondary malignant neoplasm of liver, specified as secondary [palliative treatment of liver metastases from other non-neuroendocrine primaries (e.g., colon cancer, melanoma, or unknown primaries)]

Other malignant neoplasm without specification of site [unknown primary]

Personal history of malignant neoplasm of breast

**Intra-hepatic chemotherapy:**

**ICD-9 codes covered if selection criteria are met:**

153.0 - 154.8 Malignant neoplasm of colon, rectum, rectosigmoid junction, and anus [not covered for "one-shot" arterial chemotherapy or transarterial gene therapy]

**ICD-9 codes not covered for indications listed in the CPB:**

155.0 - 155.2 Malignant neoplasm of the liver and intrahepatic bile ducts [liver primary]

**Intra-hepatic microspheres:**

**ICD-9 codes covered if selection criteria are met:**

153.0 - 154.8 Malignant neoplasm of colon, rectum, rectosigmoid junction, and anus [unresectable liver tumors from primary colorectal cancer]

155.0 - 155.2 Malignant neoplasm of the liver and intrahepatic bile ducts [unresectable primary HCC]

156.0 Malignant neoplasm of gallbladder

157.0 - 157.9 Malignant neoplasm of pancreas [endocrine tumors involving the liver and functional neuroendocrine cancers] [carcinoid tumors in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea)]

197.8 Secondary malignant neoplasm of other digestive organs and spleen

209.00 - 209.29 Malignant carcinoid tumors [functional neuroendocrine cancers in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea)]

209.72 Secondary neuroendocrine tumor of liver

**Drug-Eluting Beads Trans-Arterial Chemoembolization:**

**ICD-9 codes not covered for indications listed in the CPB:**

155.0 - 155.2 Malignant neoplasm of the liver and intrahepatic bile ducts
171.0 - 171.9  Malignant neoplasm of connective tissue and other soft tissue [leiomyosarcoma]

197.7  Secondary malignant neoplasm of liver, specified as secondary [liver dominant]

Other ICD-9 codes related to the CPB:

259.2  Carcinoid syndrome
782.62  Flushing
786.07  Wheezing
787.91  Diarrhea

The above policy is based on the following references:

Percutaneous Ethanol Injection


Chemoembolization


41. Heron DE, Gibson MK. Management of locally advanced unresectable and inoperable esophageal cancer. UpToDate Inc., Waltham, MA. Last reviewed December 2014.

**Intra-hepatic Chemotherapy (Infusion) for Liver Malignancies**

8. Rougier P. Are there indications for intraarterial hepatic chemotherapy or isolated liver perfusion? The case of liver metastases from colorectal cancer. Recent Results Cancer Res. 1998;147:3-12.

Intrahepatic Microspheres (TheraSphere, SIR-Sphere)


Drug-Eluting Beads Trans-Arterial Chemoembolization


15. Curley SA, Stuart KE, Schwartz JM, Carithers RL, Jr. Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy,
radioembolization. Last reviewed December 2013. UpToDate Inc., Waltham, MA.


