Subject: Transarterial Chemoembolization (TACE) for Primary Liver Hepatocellular Carcinoma (HCC)		Original Effective Date:	10/31/2012
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PREFACE

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

FDA INDICATIONS

Transarterial chemoembolization is a procedure not subject to FDA regulation.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does not have a National Coverage Determination for transarterial chemoembolization for primary liver cancer.

INITIAL COVERAGE CRITERIA

1. Transarterial chemoembolization (TACE) is indicated for the treatment of primary hepatocellular liver carcinoma (HCC) when ALL of the following criteria are met [4]:
   - ❑ Localized unresectable or multifocal tumor with all of the following: [ALL]
     - No vascular invasion
     - No extrahepatic spread
     - Tumor burden involving < 50 percent of the liver
     - Tumor size > 5 cm [3 21]
   - ❑ No portal vein thrombus
   - ❑ No encephalopathy

- ❑ No biliary obstruction
- ❑ Serum bilirubin < 2 mg/dL
- ❑ Liver function preserved: [ANY]
  - ♦ Child-Turcote-Pugh (CPT) score A (<7); OR
  - ♦ Child-Turcote-Pugh (CPT) score B (7-9)

***** The Child-Turcote-Pugh (CPT) score determines short-term prognosis among groups of patients awaiting liver transplantation and has been widely adopted for risk-stratifying patients before transplantation.

Child-Turcote-Pugh Score of Severity of Liver Disease[7]

Points	**1**	**2**	**3**
Encephalopathy	None	1 – 2	3 – 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2 – 3	> 3
For PBC/PSC, Bilirubin	< 4	4 – 10	> 10
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
INR*	< 1.7	1.7 – 2.3	> 2.3
PT (seconds prolonged)	< 4	4 - 6	> 6

The individual scores are summed and then grouped as a classification:

< 7 = A
7-9 = B
> 9 = C (forecasts a survival of less than 12 months)

*INR = International Normalized Ratio; PT = prothrombin time.

CONTINUATION OF THERAPY

The TACE procedure may be repeated every 8-12 weeks if there is clear evidence of progressive tumor growth in the treated areas. [2 4]

Note:

- *Multiple courses of TACE, especially if spaced too closely together, can increase deaths from liver failure despite successful tumor shrinkage, and these excess deaths from deterioration of liver function may counterbalance any prolongation of survival that results from enhanced tumor control.*
- *TACE may cause hepatic artery damage, the likelihood of which is higher in patients with impaired liver function.*
- *Hepatic artery interruption by repeated TACE or arterial dissection also leads to the development of extrahepatic collateralization, which may create an alternative blood supply to the tumor, and contribute to treatment failure.* [4]

COVERAGE EXCLUSIONS

TACE is contraindicated when any of the following clinical circumstances occur [3 4 11]:

- Thrombus in the main portal vein and portal vein obstruction
- Encephalopathy
- Biliary obstruction
- Child- Turcote-Pugh C cirrhosis

Relative contraindications include any of the following [3 4 11]:

- Serum bilirubin >2 mg/dL
- Lactate dehydrogenase >425 units/L
- Aspartate aminotransferase >100 units/L
- Tumor burden involving >50 percent of the liver
- Cardiac or renal insufficiency
- Ascites, recent variceal bleed, or significant thrombocytopenia
- Transjugular intrahepatic portosystemic shunt (TIPS)

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Transarterial chemoembolization (TACE) is a procedure used to treat primary liver cancer that involves injection or infusion of a concentrated dose of antitumor or chemotherapeutic drugs into the hepatic artery or its branches followed by arterial embolization to block off or occlude the artery. Intra-arterial injection of antitumor drugs increases their local concentration and reduces systemic side effects, while intra-arterial embolization causes ischemic necrosis of the tumor, depriving it of nutrients and oxygen. The most commonly used chemotherapeutic drugs are doxorubicin, epirubicin, mitomycin, and cisplatin, either alone or in combination. Embolization is performed with gelatin sponge particles, or Gelfoam. Often lipiodol, or iodized poppy-seed oil (Lipiodol, Andre Guerbet, Aulnay-Sous-Bois, France; or Ethiodol, Savage Laboratories, Melville, NY), is added to the chemoembolization regimen, usually as an emulsion with the chemotherapeutic drugs, to enhance the antitumor effect of the drugs by prolonging their contact with tumor cells. The iodized oil, which is selectively deposited within the tumor, functions both as a carrier for the anticancer drugs, releasing the drugs gradually, and as an embolic material. The oil has the unique property of remaining within the tumor for several months after injection, whereas it disappears more rapidly from the nontumorous parenchyma. Chemoembolization is performed by an interventional radiologist and multiple treatments may be required to treat all lesions as well as recurrences. The treatment can be repeated every 8 to 12 weeks; however, the benefit of repetition of TACE needs to be balanced against the progressive liver damage associated with the treatment. [2] The most common adverse effect of TACE, which occurs in 60 to 80 percent of patients, is postembolization syndrome. This consists of varying degrees of right upper quadrant pain, nausea, a moderate degree of ileus, fatigue, fever, and transient elevation of AST, ALT and bilirubin values. Symptoms are usually self-limited, lasting three to four days; full recovery is typical within 7 to 10 days. [4]

Hepatocellular Carcinoma General Information

The incidence of hepatocellular carcinoma (HCC), or primary liver cancer is increasing due to the spread of hepatitis virus infection. In the majority of patients, HCC is associated with cirrhosis of the liver, and survival rates for HCC are poor. Patients with primary liver cancer are broadly classified into those with localized resectable, localized unresectable and advanced disease. Surgery is the only potentially curative treatment but only in patients with localized resectable disease, where the tumor is confined to a solitary mass in a portion of the liver that allows its complete surgical removal with a margin of normal liver, and in the absence of cirrhosis and chronic hepatitis. In patients with localized unresectable disease, although the cancer appears to be confined to the liver, surgical resection of the entire tumor is not possible due to its location within the liver or the presence of concomitant medical conditions such as cirrhosis. While some of these patients may be candidates for liver transplantation, limited availability of donor livers remains a problem. In advanced liver cancer, the cancer is present in both lobes of the liver or has metastasized to distant sites. [2]

For patients with localized unresectable HCC or multifocal HCC without extrahepatic metastases, transarterial chemoembolization (TACE) is one of several nonsurgical therapeutic approaches available; other approaches include percutaneous ethanol injection (PEI) and systemic chemotherapy. Chemoembolization involves injection of chemotherapeutic drugs and embolizing agents into the branch of the hepatic artery supplying the tumor. The goal of this procedure is to deliver the chemotherapeutic agents directly to the tumor, and then to block blood flow to the tumor, thereby reducing the size or growth rate of the tumor. [2]

GENERAL INFORMATION

Summary of Medical Evidence

A meta-analysis by Wang and colleagues (2011) [19] to assess the evidence for improved outcomes in hepatocellular carcinoma (HCC) with transarterial chemoembolization (TACE) alone or with percutaneous ethanol injection (PEI) was done. Seven randomized trials were identified that included 623 patients. The results of the meta-analysis are as follows: the 6-month, 1-, 2-, and 3-year survival rates were significantly better in patients with the TACE+PEI group than TACE group; in the decline rates of the AFP level and the reduction rates of tumor size (>50%), the TACE+PEI group has better effects than TACE group; as adverse effects, TACE+PEI group has lower incidence rates than TACE group. In patients with HCC, the efficacy of TACE combined with PEI is significantly better than that of TACE alone. The authors concluded that although there is convincing evidence to confirm the results, large sample, multicenter, randomized, controlled trials need to be done to confirm these findings.

Zhong and colleagues (2010) [17] performed a meta-analysis to evaluate the efficacy of postoperative adjuvant TACE for participants with HCC. Six RCT totaling 659 participants, of whom almost all were of stage IIIA HCC, were included. For the 1-year tumor recurrence rate, hepatectomy plus TACE showed statistically significant less incidence of recurrence, with a pooled risk ratio (RR) of 0.68. For 1-year mortality, the trials were favorable for TACE with a pooled risk ratio of 0.48.For 3-year mortality, the trials also revealed statistically significant less incidence, with a pooled risk ratio of 0.76.However, for 5-year mortality, TACE did not demonstrate statistically significant less incidence. Transient fever and nausea/vomiting were reported as side-effects of TACE but were well tolerated by most participants. The authors concluded that postoperative

adjuvant TACE seems promising for participants with HCC with risk factors (multiple nodules of >5 cm or vascular invasion) but requires further trial.

A systematic review of 18 studies including 3 randomized trials and 15 observational studies was completed by Chua et al. (2010) to identify published studies of TACE administered preoperatively as a neoadjuvant treatment for resectable HCC. This comprised of 3927 patients, of which, 1293 underwent neoadjuvant TACE. The median disease-free survival (DFS) in the TACE and non-TACE group ranged from 10 to 46 and 8 to 52 months, respectively, with 67% of studies reporting similar DFS between groups despite higher extent of tumor necrosis from the resected specimens indicating a higher rate of pathological response (partial TACE 27-72% vs. non-TACE 23-52%; complete TACE 0-28% vs. non-TACE zero), with no difference in surgical morbidity and mortality outcome. No conclusion could be drawn with respect to overall survival (OS). Overall survival (OS), rate of pathological response, impact on surgical morbidity and mortality and pattern of recurrences were secondary endpoints of this review. Both randomized and non-randomized trials suggest the use of TACE preoperatively as a neoadjuvant treatment in resectable HCC is a safe and efficacious procedure with high rates of pathological responses. However, it does not appear to improve disease-free survival (DFS). [8]

A systematic review by Llovet and colleagues (2003) [14] was done to assess the evidence of the impact of medical treatments for HCC on survival. Randomized controlled trials (RCTs) that were published as full papers assessing survival for primary treatments of HCC were included. The primary end point was survival, and the secondary end point was response to treatment. Estimates of effect were calculated according to the random effects model. Sensitivity analysis included methodological quality. 61 randomized trials were identified but only 14 met the criteria to perform a meta-analysis assessing arterial embolization (7 trials, 545 patients) or tamoxifen (7 trials, 898 patients). Arterial embolization improved 2-year survival compared with control (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.32-0.89; P =.017). Sensitivity analysis showed a significant benefit of chemoembolization with cisplatin or doxorubicin (OR, 0.42; 95% CI, 0.20-0.88) but none with embolization alone (OR, 0.59; 95% CI, 0.29-1.20). Overall, treatment induced objective responses in 35% of patients (range, 16%-61%). Tamoxifen showed no antitumoral effect and no survival benefits (OR, 0.64; 95% CI, 0.36-1.13; P =.13), and only low-quality scale trials suggested 1-year improvement in survival. The authors concluded that chemoembolization improves survival of patients with unresectable HCC and may become the standard treatment. Treatment with tamoxifen does not modify the survival of patients with advanced disease.

Marelli and colleagues (2007) [18] performed a systematic review of published cohort and randomized studies to evaluate whether specific patient characteristics and/or radiological transarterial techniques result in better outcomes. 175 articles were reviewed. Anticancer drugs were used as sole agent in 75% of cases (double 15% and triple 6%): doxorubicin (36%), cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin (8%), and SMANCS (5%). Embolizing agents used were: gelatin sponge particles (71%), polyvinyl alcohol (PVA) particles (8%), degradable starch microspheres (DSM) (4%), and embospheres (4%). Sessions per patient were 2.5 +/- 1.5 (interval: 2 months). Objective response was 40 +/- 20%; survival rates at 1, 2, 3, and 5 years were: 62 +/- 20%, 42 +/- 17%, 30 +/- 15%, and 19 +/- 16%, respectively, and survival time was 18 +/- 9.5 months.

The post-TACE complications were: acute liver failure, 7.5% (range 0-49%); acute renal failure, 1.8% (0-13%); encephalopathy, 1.8% (0-16%); ascites, 8.3% (0-52%); upper gastrointestinal bleeding; 3% (0-22%); and hepatic or splenic abscess, 1.3% (0-2.5%). Treatment-related mortality was 2.4% (0-9.5%), mainly due to acute liver failure. Our meta-analysis of nine randomized controlled trials (RCTs) confirmed that TACE improves survival; but a meta-analysis of TACE versus TAE alone (3 RCTs, 412 patients) demonstrated no survival difference. The authors concluded that no chemotherapeutic agent appears better than any other. There is no evidence for benefit with lipiodol. Gelatin sponge is the most used embolic agent, but PVA particles may be better. TAE appears as effective as TACE. New strategies to reduce the risk of post-TACE complications are required.

Takasu (2012) [10] reviewed the survival benefits of two randomized controlled trials for transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. Chemoembolization accounted for initial treatment of 32% of patients and 58% for recurrent foci. The indications of chemoembolization are various: they are multinodular tumors in the Barcelona Clinic Liver Cancer staging system and two or three tumors >3 cm or four or more tumors in the Japanese guidelines, and both indications fulfill the Child-Pugh Class A/B or liver damage A/B and exclusion of vascular invasion or extrahepatic spread. Recently, both guidelines were identified to have almost similar content. The 4966 patients stratified to chemoembolization recommended by the Japanese guidelines showed that 3-year survival of patients with two or three tumors >3 cm or four or more tumors was 55 and 46% in Child-Pugh A, respectively, and 30 and 22% in Class B, respectively. Chemoembolization with drug-eluting beads and radioembolization with yttrium-90 microspheres have been introduced, and each of them showed similar tumor response and median survival compared with conventional chemoembolization.

Morimoto and colleagues (2010) [16] randomly compared the efficacy of radiofrequency ablation (RFA) combined with transcatheter arterial chemoembolization (TACE) to RFA alone, for the treatment of intermediate-sized hepatocellular carcinomas (HCCs). The authors randomly assigned 37 patients with solitary HCCs (diameter, 3.1-5.0 cm in the greatest dimension) to 2 groups: the TACE-RFA group, in which the patients received TACE followed by RFA on the same day, and the RFA group, in which the patients received only RFA. Technical success was achieved after 1.4±0.5 RFA sessions in the RFA group and after 1.1±0.2 RFA sessions in the TACE-RFA group (P<.01). The mean diameters of the longer and shorter axes of the RFA-induced ablated areas were 50±8.0 mm and 41±7.1 mm, respectively, in the RFA group and 58±13.2 mm and 50±11.3 mm, respectively, in the TACE-RFA group; the mean diameters of the shorter axes were significantly different (P=.012). The rates of local tumor progression at the end of the third year in the RFA and TACE-RFA groups were 39% and 6%, respectively (P=.012). The 3-year survival rates of the patients in the RFA and TACE-RFA groups were 80% and 93%, respectively (P=.369). The authors concluded that in patients with intermediate-sized HCCs, RFA combined with TACE is more effective than RFA alone for extending the ablated area in fewer treatment sessions and for decreasing the local tumor progression rate.

Hayes, Cochrane, UpToDate, MD Consult etc.

A Cochrane review (2011) [9] was published to assess the beneficial and harmful effects of transarterial chemoembolization (TACE) or transarterial embolization (TAE). Nine trials with 645 participants were included. Six trials assessed TACE versus control and three trials assessed TAE versus control. Seven trials had low risk of selection bias based on adequate generation of allocation sequence and concealment - but all these trials had other risks of bias. Three trials were stopped early due to interim inspections and one due to slow accrual. For all-cause mortality, statistical heterogeneity between trials was low to moderate (I2= 30%). Meta-analysis of trials with low risk of selection bias showed that TACE or TAE versus control does not significantly increase survival. Two trials with low risk of selection bias, no early stopping, and no co-intervention did not establish any significant effect of TACE or TAE on overall survival. Trial sequential analysis confirmed the absence of evidence for a beneficial effect of TACE or TAE on survival indicating the need for future randomization of up to 383 additional participants. Substantial differences in criteria for assessing tumor response did not allow quantitative analyses. One trial investigated quality of life but did not detect any significant differences between the intervention groups. A range of adverse events including post-embolization syndrome and serious complications were reported. The conclusions were that firm evidence to support or refute TACE or TAE for patients with unresectable HCC cannot be made until additional bias protected trials are completed.

UpToDate:

Curley and colleagues [4] summarize that arterial embolization is a reasonable option for patients with an unresectable HCC that is either too large or multifocal for percutaneous ablation techniques such as RFA, with relatively preserved liver function (Child-Pugh A/B, and no extrahepatic tumor spread, vascular invasion, or main portal vein thrombus). TACE rather than bland embolization alone is recommended in guidelines from the American Association for the Study of Liver Disease (AASLD), and from an expert consensus group of the American Hepato-Pancreato-Biliary Association (weak evidence). Guidelines from the National Comprehensive Cancer Network (NCCN) recommend chemoembolization, bland embolization, or radioembolization in this setting. Doxorubicin as a single agent at a fixed dose is recommended for the procedure, although other centers add mitomycin and/or cisplatin; there is no evidence that either approach is better. Where available, DEBs may be preferred, although long-term outcomes using this technique are not available. Patient selection is critical to the success and safety of TACE. The best candidates for TACE are patients with unresectable lesions without vascular invasion or extrahepatic spread, and preserved liver function (i.e., Child-Pugh A or B cirrhosis). TACE is not recommended prior to a planned HCC resection. While it is commonly used as a bridging maneuver in patients awaiting liver transplantation, data proving benefit in this setting are lacking.

Hayes

There is a Directory report called Chemoembolization for Primary Liver Cancer that was last updated in 2007 and archived in 2008.

Professional Organizations

American College of Radiology (ACR) [21]**:** The 2011 Appropriateness Criteria®: radiologic management of hepatic malignancy recommends that transarterial chemoembolization is usually appropriate for patients who have:

- hepatocellular solitary tumors that are > 5cm
- more than one tumor with at least one > 5cm

American Society for the Study of Liver Disease (AASLD): The AASLD Practice Guideline Management of Hepatocellular Carcinoma: An Update indicates that TACE is recommended as first line non-curative therapy for non-surgical patients with large/ multifocal HCC who do not have vascular invasion or extrahepatic spread. The AASLD notes that the development of polyvinyl chloride spheres that release chemotherapy after being injected (DEBs) have allowed a reduction of the side effects of the passage of chemotherapy into systemic circulation. [6]

Cardiovascular and Interventional Radiological Society of Europe [11] **(CIRSE) 2012:** The CIRSE guidelines for hepatic transarterial chemoembolization indicate that for unresectable intermediate-stage HCC (BCLC stage B or Child-Pugh class A/B with large or multifocal HCC, no vascular invasion, or extrahepatic spread), the current standard treatment is TACE. General exclusion criteria for TACE based on laboratory assays have not been definitively established even though a bilirubin level >2 mg/dL, a lactate dehydrogenase level >425 mg/dL, and an aspartate aminotransferase (AST) level >100 IU/L have been reported to be strongly associated with increased post procedural mortality. In general, Child-Pugh class C is considered a contraindication for TACE. Indications for TACE in patients with HCC include all of the following:
Tumor status:

- No extrahepatic localizations
- No main PV thrombosis
- Tumor involvement >50 % of the liver parenchyma
- Patients with HCC not suitable for curative treatments such as resection, liver transplantation, or percutaneous ablation according to BCLC staging classification and treatment schedule

Patient performance status:

- Eastern Cooperative Oncology Group performance status < 3 or Karnofsky score > 70

Patient metabolic status

- Patients with well-preserved liver function (Child-Pugh class A/B) without encephalopathy and mild or severe ascites
- Serum creatinine <2 mg/dL (177 lmol/L)
- Platelet count >50,000/mm3
- Prothrombin activity > 50 %

National Comprehensive Cancer Network (NCCN) 2012 [3]**:**
The 2012 NCCN guidelines for hepatocellular carcinoma indicate that all tumors may be amendable to embolization (chemo, bland or radio) provided that the arterial blood supply may be isolated without non-target embolization. Chemoembolization is contraindicated in patients with bilirubin > 3mg/dL and in cases of main portal vein thrombosis and Child-Pugh Class C. Unresectable or inoperable tumors > 5cm should be considered for treatment using embolic approaches or systemic therapy.

Society of Interventional Radiology [20]**:** The 2009 position statement on chemoembolization of hepatic malignancies suggests that hepatic arterial chemoembolization is a safe, proven, and effective technique for the treatment of a number of malignancies, including hepatocellular carcinoma (HCC), neuroendocrine tumors, ocular melanoma, cholangiocarcinoma, and sarcoma. Furthermore, it has a palliative role for patients with colon carcinoma and may be useful with patients who have hepatic-dominant metastatic disease from other primary malignancies. However, the benefit of chemoembolization for these individuals should be evaluated on a case-by-case basis.

CODING INFORMATION

CPT	Description
37243	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
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation

HCPCS	Description
	N/A

ICD-9	Description
155.0	Malignant neoplasm of liver, primary
155.2	Malignant neoplasm of liver, not specified as primary or secondary
197.7	Secondary malignant neoplasm of respiratory and digestive systems; liver, specified as secondary

ICD-10	Description
C22.0	Carcinoma malignant, hepatocellular
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

RESOURCE REFERENCES

1. Centers for Medicaid & Medicare Services (CMS). Search for National Coverage Determination (NCD) Accessed at: http://www.cms.gov/medicare-coverage-database/
2. Hayes Medical Technology Directory. Chemoembolization for Primary Liver Cancer. Winifred Hayes, Inc. Lansdale PA. July 2002, last updated April 2007. Archived Jan 2008.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Guidelines in Oncology. Clinical practice guidelines in oncology. Hepatobiliary Cancers. Version V2. 2012. http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
4. UpToDate. Curley SA, Stuart KE, Schwartz JM. Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization. Aug 30, 2012.
5. DynaMed. [Internet]. Ipswich (MA): EBSCO Publishing. 1995. Hepatacellular Carcinoma. Updated June 27, 2012.
6. Bruix J, Sherman M. American Association for the Study of Liver Diseases (AASLD) guideline on management of hepatocellular carcinoma: an update. HEPATOLOGY, Vol. 53, No. 3, 2011. Accessed at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf
7. American Association for the Study of Liver Disease (AASLD) Clinical Practice Guidelines. Evaluation of the patient for liver transplantation. Hepatology. 2005, June. Re-reviewed 2008. Accessed at: http://www.aasld.org/practiceguidelines/documents/bookmarked%20practice%20guidelines/liver%20transplant.pdf
8. Chua TC, Liauw W, Saxena A, Chu F, Glenn D, Chai A, Morris DL. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. Liver International 2010; 30(2): 166-174. Accessed at: http://onlinelibrary.wiley.com/doi/10.1111/j.1478-3231.2009.02166.x/full
9. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD004787. DOI: 10.1002/14651858.CD004787.pub2
10. Takayasu K. Transarterial chemoembolization for hepatocellular carcinoma over three decades: current progress and perspective. Jpn J Clin Oncol. 2012 Apr;42(4):247-55. Epub 2012 Mar 9. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/22407946
11. Basile A, Carrafiello G et al. Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Standards of Practice Guidelines 2012. Quality Improvement Guidelines for Hepatic Transarterial Chemoembolization. Cardiovasc Intervent Radiol. 8 May 2012. Accessed at: http://www.cirse.org/files/files/SOP/2012/SOP_CIRSE_2012_Quality-Improvement%20Guidelines%20for%20Hepatic%20Transarterial%20Chemoembolization.pdf
12. MD Consult [website]: Hepatocellular Carcinoma. April 15, 2010
13. Llovet J, Real M, Montanya X, et al: Arterial embolization, chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomized controlled trial. Lancet 2002; 359:1734-1739. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)08649-X/fulltext
14. Llovet J, Bruix J: Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37:429-442.
15. Lo CM, Ngan H, Tso WK, et al: Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35:1164-1171. http://onlinelibrary.wiley.com/doi/10.1053/jhep.2002.33156/abstract
16. Morimoto M, Numata K, Kondou M, et al. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency

ablation combined with transcatheter arterial chemoembolization. Cancer. 2010 Dec 1;116(23):5452-60. doi: 10.1002/cncr.25314. Epub 2010 Jul 29.
17. Zhong JH, Li LQ. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: A meta-analysis. Hepatol Res. 2010;40(10):943-953.
18. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol. 2007;30(1):6-25. Accessed at: http://polysalov.vipvrach.ru/download/Transarterial_Therapy_for_Hepatocellular_Carcinoma.pdf
19. Wang N, Guan Q et al. TACE combined with PEI versus TACE alone in the treatment of HCC: a meta-analysis. Med Oncol. 2011 Dec;28(4):1038-43. Epub 2010 Jul 15.
20. Brown DB, Geschwind JF, Soulen MC, Millward SF, Sacks D. Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. J Vasc Interv Radiol 2009 Jul;20(7 Suppl):S317-23. Accessed at: http://www.guidelines.gov/search/search.aspx?term=hepatocellular+liver+carcinoma
21. Kouri BE, Funaki BS, Ray CE Jr, Abou-Alfa G, Burke CT et al. Expert Panel on Interventional Radiology. ACR Appropriateness Criteria® radiologic management of hepatic malignancy. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. Acessed at: http://www.guidelines.gov/content.aspx?id=35140&search=hepatocellular+liver+carcinoma
22. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Internal Medicine, Oncology, Hematology. October 15, 2012