Quality Improvement Guidelines for Transhepatic Arterial Chemoembolization, Embolization, and Chemotherapeutic Infusion for Hepatic Malignancy

Daniel B. Brown, MD, John F. Cardella, MD, David Sacks, MD, S. Nahum Goldberg, MD, Debra A. Gervais, MD, Dheeraj Rajan, MD, Suresh Vedantham, MD, Donald L. Miller, MD, Elias N. Brountzos, MD, Clement J. Grassi, MD, and Richard B. Towbin, MD

Abbreviation: HCC = hepatocellular carcinoma

PREAMBLE

THE membership of the Society of Interventional Radiology (SIR) Standards of Practice Committee represents experts in a broad spectrum of interventional procedures from the private and academic sectors of medicine. Generally, Standards of Practice Committee members dedicate the vast majority of their professional time to performing interventional procedures; as such, they represent a valid broad expert constituency of the subject matter under consideration for standards production.

Technical documents specifying the exact consensus and literature review methodologies as well as the institutional affiliations and professional credentials of the authors of this document are available upon request from SIR, 3975 Fair Ridge Dr, Suite 400 North, Fairfax, VA 22033.

METHODOLOGY

SIR produces its Standards of Practice documents with use of the following process. Standards documents of relevance and timeliness are conceptualized by the Standards of Practice Committee members. A recognized expert is identified to serve as the principal author for the standard. Additional authors may be assigned depending on the magnitude of the project.

An in-depth literature search is performed with use of electronic medical literature databases. Then, a critical review of peer-reviewed articles is performed with regard to the study methodology, results, and conclusions. The qualitative weight of these articles is assembled into an evidence table (Appendix 3), which is used to write the document such that it contains evidence-based data with respect to content, rates, and thresholds.

When the evidence of literature is weak, conflicting, or contradictory, consensus for the parameter is reached by a minimum of 12 Standards of Practice Committee members according to a modified Delphi Consensus Method (Appendix 2). For purposes of these documents, consensus is defined as 80% Delphi participant agreement on a value or parameter.

The draft document is critically reviewed by the Standards of Practice Committee members by telephone conference calling or face-to-face meeting. The finalized draft from the Committee is sent to the SIR membership for further input/criticism during a 30-day comment period. These comments are discussed by the Standards of Practice Committee and appropriate revisions made to create the finished standards document. Before its publication, the document is endorsed by the SIR Executive Council.

From the Mallinckrodt Institute of Radiology (D.B.B., S.V.), Siteman Cancer Center, Washington University School of Medicine, 510 South Kingshighway Boulevard, Box 8131, St. Louis, Missouri 63110; Department of Radiology (J.F.C.), University of Colorado Health Sciences Center, Denver, Colorado; Department of Radiology (D.S.), Reading Hospital and Medical Center, West Reading; Department of Radiology (R.B.T.), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Department of Radiology (S.N.G.), Beth Israel Deaconess Medical Center; Department of Radiology, Gastrointestinal/Genitourinary Division (D.A.G.), Massachusetts General Hospital, Boston; Department of Radiology (C.J.G.), Lahey Clinic Medical Center, Burlington, Massachusetts; Division of Interventional Radiology, Department of Medical Imaging (D.R.), University of Toronto, Toronto, Ontario, Canada; Department of Radiology and Radiological Sciences (D.L.M.), F. Edward Hébèrt School of Medicine Uniformed Services University of the Health Sciences, Medical Oncology Clinical Research Unit Center for Cancer Research, National Cancer Institute, Bethesda, Maryland; Department of Radiology (E.N.B.), University of Athens, Athens, Greece. Received September 22, 2005; accepted October 29. **Address correspondence to** D.B.B.; E-mail: brownda@mir.wustl.edu

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INTRODUCTION

Chemoembolization of hepatic malignancy represents an important therapeutic procedure in individuals with liver-dominant neoplasms. These include primary hepatic malignancies and certain other cancers in which the liver is the dominant site of disease. A variety of different cancers are amenable to treatment (1–4). Hepatocellular carcinoma (HCC) has been successfully treated with chemoembolization. Nearly 500,000 patients worldwide are diagnosed with HCC annually and the incidence in the United States is increasing dramatically (5,6). Most patients with HCC are not candidates for surgical treatment at the time of referral to an interventional radiology department. Radiation therapy and systemic chemotherapy are ineffective at prolonging survival (7) and transplantation remains the only curative option. The demand for donated organs far outstrips supply (8). Many patients require some kind of image-guided therapy as a bridge to transplantation or as palliative therapy (9).

The liver is the dominant site of metastatic disease for a number of malignancies, including colorectal cancer, neuroendocrine tumors, and ocular melanoma. Fewer than 20% of patients with metastatic disease are candidates for curative surgical resection (10). Chemotherapy has provided some improvement in survival with colorectal metastases but has limited benefit for the majority of patients with metastatic neuroendocrine tumors (11–13). Patients who are not surgical candidates often have diffuse disease, and chemoembolization can play an important role in the treatment of these patients.

These guidelines are written to be used in quality improvement programs to assess chemoembolization. The most important processes of care are (i) patient selection, (ii) performance of the procedure, and (iii) monitoring of the patient. The outcome measures or indicators for these processes are indications, success rates, and complication rates. Outcome measures are assigned threshold levels.

DEFINITIONS

• *Chemoembolization* is defined as the infusion of a mixture of chemotherapeutic agents with or without ethiodized oil (Ethiodol; Savage Laboratories, Melville, NY) followed by embolization with particles such as polyvinyl alcohol or Gelfoam (Pharmacia & Upjohn, Kalamazoo, MI).

• *Embolization* is defined as blockade of hepatic arterial flow with particles alone (typically polyvinyl alcohol or Gelfoam).

• *Hepatic artery chemotherapeutic infusion* is defined as injection of chemotherapy with or without ethiodized oil in the hepatic artery without embolization.

• *Liver-dominant neoplasm* is defined as a malignancy in which the hepatic component is the only site of disease or is the site of disease most likely to lead to patient morbidity and/or mortality.

• *Image-guided therapy* refers to the use of fluoroscopy, computed tomography (CT), ultrasound (US), or magnetic resonance (MR) imaging to target tumors for therapy. In the liver, this is accomplished by catheter-based means (eg, chemoembolization, embolization, hepatic artery chemotherapeutic infusion) or by percutaneous tumor ablation (14).

• *Tumor ablation* is defined as the direct application of chemical or thermal therapies to a specific focal tumor (or tumors) in an attempt to achieve eradication or substantial tumor destruction. Tumor ablation methods fall into one of two main categories: chemical or thermal (14).

• *Chemical ablation* refers to instillation of a pharmacologic agent to cause tumor necrosis. Examples of chemical agents include absolute ethanol and acetic acid.

• *Thermal ablation* refers to application of energy to cause tumor necrosis. Examples of energy sources include radiofrequency, laser, microwave, US, and cryotherapy.

Chemoembolization, embolization, and chemotherapeutic infusion are performed after catheterization of the proper, lobar, or segmental hepatic arteries with use of standard angiographic principles as described in the SIR quality improvement guidelines for diagnostic angiography (15). Unless otherwise stated, references in this document will specifically refer to chemoembolization, as the majority of the existing literature has reported on the use of this technique.

Although practicing physicians should strive to achieve perfect outcomes (eg, 100% success, no complications), in practice all physicians will fall short of this ideal to a variable extent. Therefore, indicator thresholds may be used to assess the efficacy of ongoing quality improvement programs. For the purposes of these guidelines, a threshold is a specific level of an indicator that should prompt a review. "Procedure thresholds" or "overall thresholds" reference a group of indicators for a procedure, such as major complications. Individual complications may also be associated with complication-specific thresholds. When measures such as indications or success rates fall below a (minimum) threshold, or when complication rates exceed a (maximum) threshold, a review should be performed to determine causes and to implement changes if necessary. For example, if the incidence of abscess formation is one measure of the quality of chemoembolization, values in excess of the defined threshold (in this case, 2%) should trigger a review of policies and procedures within the department to determine the causes and to implement changes to lower the incidence of the complication. Thresholds may vary from those listed here; for example, patient referral patterns and selection factors may dictate a different threshold value for a particular indicator at a particular institution. Therefore, setting universal thresholds is very difficult and each department is urged to alter the thresholds as needed to higher or lower values to meet its own quality improvement program needs.

Complications can be stratified on the basis of outcome. Major complications result in admission to a hospital for therapy (for outpatient procedures), an unplanned increase in the level of care, prolonged hospitalization, permanent adverse sequelae, or death. Minor complications result in no sequelae; they may require nominal therapy or a short hospital stay for observation (generally overnight; Appendix 1). The complication rates and thresholds listed herein refer to major complications.

INDICATIONS

General Indications

Chemoembolization is indicated in patients with liver-dominant hepatic

Table 1
Child-Pugh Scoring System

Variable	1	2	3
Encephalopathy	None	Moderate	Severe
Ascites	None	Moderate	Severe
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	≥3.5	2.8–3.4	<2.8
Prothrombin time (sec)	<14	15–17	≥18

Note.—Child-Pugh Score: A = 5–6; B = 7–9; C = 10–15.

Table 2
Model for End-Stage Liver Disease Scoring System

$R = 0.957 \times \log_e$ (creatinine [mg/dL]) $+ 0.378 \times \log_e$ (bilirubin [mg/dL]) $+ 1.12 \times \log_e$ (INR) $+ 0.643 \times$ (cause of cirrhosis [0 for alcohol-induced cirrhosis and 1 for non–alcohol-induced cirrhosis]).

malignancies who are not candidates for curative resection. All patients should undergo preprocedural contrast material–enhanced CT or MR imaging to ensure that the disease is liver-dominant. The main portal vein should be patent or collateral flow should be present with hepatopetal flow (16,17). If there is a question of adequate portal perfusion on cross-sectional imaging, confirmation can be obtained with catheter angiography immediately preceding chemoembolization. Preprocedural evaluation also includes laboratory evaluation including complete blood count, prothrombin time, and evaluation of liver and kidney function. Exclusion criteria based on laboratory values are not definitively established. However, the constellation of more than 50% liver replacement with tumor, bilirubin level greater than 2 mg/dL, lactate dehydrogenase level greater than 425

mg/dL, and aspartate aminotransferase level greater than 100 IU/L has a strong anecdotal association with increased postprocedural mortality (18). Individual abnormalities of these four parameters have not been shown to predict adverse outcomes of chemoembolization (19). Laboratory values and scoring systems have been used differently by other authors. Commonly used scoring systems are outlined in **Tables 1–3**. A bilirubin cutoff level of 3 mg/dL has been described (20). The Child-Pugh scoring system is superior to the Model for End-Stage Liver Disease system in predicting long-term survival in HCC (19). Patients with Child-Pugh class A disease or class B disease with an albumin level of at least 3.4 g/dL have improved survival. Another group found that Model for End-Stage Liver Disease scores greater than 10 and a Cancer of the Liver Italian Program score greater than 2 constituted a negative predictor of survival (21).

HCC.—As a result of underlying cirrhosis, fewer than 20% of patients with HCC are candidates for surgical resection (7). Transplantation remains the only curative option for patients with HCC, and individuals with limited disease (1 tumor <5 cm or three tumors <3 cm each) should be evaluated for transplantation during workup as part of a multidisciplinary effort.

Initial randomized trials evaluating chemoembolization versus symptomatic treatment had disappointing results (22–25). However, three recent well-constructed randomized trials (1,2,26), two of which were prospectively randomized (1,2), have demonstrated significantly improved survival with chemoembolization. Poor outcomes from the initial trials can be directly linked to treatment of patients with advanced disease and to administration of excessive therapy. These outcomes reinforce the need to treat patients with well-compensated cirrhosis and to repeat therapy only when viable tumor is present on cross-sectional imaging (27). Patients with small tumors may also be considered for percutaneous ablative therapies alone or in combination with chemoembolization (28–30). The choice between therapies should be based on the overall size, number, and location of the tumors. In some situations, chemoembolization and tumor ablation may be appropriate alone or in combination.

Neuroendocrine malignancy.—Initial control of symptoms is usually performed with short- or long-acting somatostatin agents. Most patients with symptomatic disease have diffuse metastases, which are a contraindication to surgery. The frequent presence of diffuse metastases also limits the number of patients who are candidates for percutaneous ablative therapies. Chemoembolization and embolization of patients with hepatic metastases from neuroendocrine tumors can result in durable elimination of hormonal symptoms (3,31). A number of patients with hormonally active liver metastases also have extrahepatic disease at the time of diagnosis. However, because chemoembolization can still reduce or eliminate symptoms, treatment should not be withheld from these patients.

Colorectal carcinoma.—Fewer than 20% of patients with colorectal metastases are candidates for curative resection (10). Survival rates with systemic chemotherapy have improved, with mean survival times approaching 2 years (11). A gold standard chemotherapeutic regimen has not been determined, limiting studies comparing systemic chemotherapy with chemoembolization. Chemoembolization for hepatic me-

Table 3
Cancer of the Liver Italian Program Scoring System

Variable	0 Points	1 Point	2 Points
Child-Pugh stage	A	B	C
Tumor morphology	Uninodular	Multinodular	Massive or >50% of liver
α-Fetoprotein (ng/mL)	<400	>400	NA
Macrovascular invasion	No	Yes	Yes

Note.—NA = not applicable

tastases may be considered as a salvage option when other systemic chemotherapy options have been exhausted. Other treatment methods, such as yttrium Y 90 sphere infusion, are being investigated and may play an increasing role over time (32).

Other metastases.—Other tumors that may present with liver-dominant metastases include ocular melanoma and soft-tissue sarcoma. These tumors have been successfully treated with chemoembolization. Patient survival appears to be improved compared with historical controls, but randomized prospective data are not available (33–36).

Participation by the radiologist in patient follow-up in the hospital and at imaging follow-up is an integral part of chemoembolization and will limit the incidence of postprocedural complications and ensure appropriate scheduling of follow-up therapy. Close follow-up with monitoring and management of the patient by the interventional radiologist is appropriate. Regarding indications for chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy, the threshold is 95% for the presence of liver-dominant malignancy with preserved hepatic function. When fewer than 95% of procedures are for these indications, the department will review the process of patient selection.

Preprocedural Considerations

Premedication before chemoembolization is standard. Hydration is essential with intravenous administration of 150–300 mL/h of normal saline solution. Other premedications include antiemetics and steroids. Many operators administer antibiotic coverage for gram-negative enteric organisms, even though this practice is not universal or prospectively proven to be beneficial for all patients (37,38). In patients without an intact sphincter of Oddi from earlier surgery, sphincterotomy, or biliary drainage, the risk of infection after embolization is significantly increased (39). The risk of postembolization infection appears to be reduced by the performance of bowel preparation the night before treatment (40). In patients with carcinoid tumors, pretreatment with octreotide 150 μg subcutaneously is im-

portant to limit carcinoid crisis caused by hormonal dumping from tumor necrosis after embolization (3).

Procedural Considerations

Given the frequency of variant hepatic arterial anatomy, initial angiography should include study of the superior mesenteric and celiac arteries (41). Imaging should be performed through the portal venous phase to ensure patency of the main portal vein or reconstitution via collateral vessels with hepatopetal flow. Practice patterns for level of catheter selection range from superselective to lobar embolization depending on the type and number of tumors to be treated, as well as the philosophy of the individual performing the procedure. Treatment of the entire liver in one session is associated with an increase in mortality (31). When treatment leads to permanent occlusion of the native hepatic arteries, several collateral pathways have been treated with clinical success, including the inferior phrenic, internal mammary, and intercostal arteries (42–44). If these collateral arteries have potential communication with cutaneous vessels, embolization without chemotherapy should be performed to limit the risk of cutaneous ischemic ulceration (45). Treatment should avoid the cystic artery if possible. If treatment of the tumor is not feasible without including the cystic artery in the infused area, chemoembolization may still be performed. The principal risk of treatment of the cystic artery is pain, which may potentially lengthen the posttreatment hospital stay but does not result in significant risk to the gallbladder itself (46). Intermittent infusion of 1% lidocaine between aliquots of the chemotherapeutic agent/Ethiodol slurry decreases postembolization pain (47,48).

Chemoembolization versus Embolization

Randomized trials for treatment of HCC comparing protocols with and without chemotherapy are limited. A prospective randomized trial with three arms comparing survival with chemoembolization versus embolization versus symptomatic treatment resulted in a significant survival benefit for chemoembolization versus symp-

tomatic treatment, and the trial was halted (2). At the time the trial was terminated, embolization without chemotherapy was associated with similar survival rates as chemoembolization. The trial was not continued to determine whether embolization without chemotherapy would lead to a survival benefit versus symptomatic treatment alone. A separate meta-analysis did not reveal any clear-cut benefit from the addition of chemotherapy to embolization (49). A complicating factor in determining the gold standard arterial infusion therapy is that chemotherapy regimens vary significantly among trials. No ideal chemotherapeutic agent has been identified. A definitive statement regarding treatment with or without chemotherapy can not be made without an adequately powered prospective trial.

Chemoembolization versus Chemotherapeutic Infusion

Few comparisons of chemoembolization versus chemotherapeutic infusion are available. Infusion without embolization appears to result in a lower percentage of tumor necrosis compared with chemoembolization, particularly in HCCs larger than 3 cm in diameter (50). However, toxicity to the surrounding liver may be lower with infusion alone (51). Chemotherapeutic infusion may be considered an option in patients with severe hepatic dysfunction.

Postprocedural Considerations

Many practitioners recommend administration of antibiotics for 3–7 days after chemoembolization to cover gram-negative enteric pathogens. Data regarding the need for routine antibiotic prophylaxis are mixed, without definitive evidence of benefit (38). If a patient has a disrupted sphincter of Oddi, it has been suggested that antibiotics should be administered for 14 days (40). Even with extended administration of antibiotics, data for this group of patients are limited and the operator should proceed with caution in the setting of any biliary abnormality. Antibiotics may be converted to oral administration as soon as patients can tolerate a normal diet to facilitate expedient discharge. Antiemet-

ics should be continued as long as needed. Narcotics should be available. One method preferred by many interventionalists to control pain is to administer narcotics via a patient-controlled analgesia pump.

Postprocedural Imaging

Follow-up imaging should be performed 4–6 weeks after all tumor-bearing areas have been treated. If treatment of both lobes of the liver is planned, imaging between sessions may be performed based on operator preference. Signs of tumor necrosis on CT include Ethiodol uptake and absence of arterial-phase enhancement when it was present before chemoembolization (52,53). Disappearance of arterial enhancement is the principal determinant of tumor necrosis on MR imaging (54). There is a paucity of literature regarding follow-up of lesions after chemoembolization without arterial phase enhancement. Gross enlargement of a lesion or nodular enhancement in portal vein or delayed-phase imaging has been described as evidence of residual or recurrent tumor after radiofrequency ablation of lesions without initial arterial phase enhancement (55). Similar findings may be present in the setting of residual or recurrent tumor after chemoembolization. Patients without active disease at follow-up should undergo follow-up imaging every 3–4 months.

Repeat Treatment

Individuals with HCC or metastases from nonneuroendocrine tumors require further treatment when new or residual disease is detected (27). Patients with liver metastases from neuroendocrine tumors should be treated again if the initial treatment does not result in symptomatic improvement or when symptoms recur. Before additional chemoembolization sessions, liver function tests and complete blood count should be performed again to ensure the patient is still an appropriate candidate.

SUCCESS RATES

Technical Success

Successful chemoembolization is defined as successful catheter place-

Table 4
Thresholds for Median Survival after Chemoembolization of Hepatocellular and Colorectal Carcinomas (3,19,26,56–65)

Disease	Median Survival (months), Reference	Threshold (%)
Hepatocellular carcinoma	20 (19,26,56,57)	50
Colorectal carcinoma	10 (58–63)	50
Neuroendocrine tumors	26 (3,64,65)	50
Ocular melanoma	11 (33)	50
Metastatic sarcoma	19 (34,35)	50

ment and administration of selected agents. The threshold is 95% for technical success of chemoembolization.

Clinical Success

Clinical success is defined as successful tumor necrosis resulting in effective palliation. Effective palliation is tumor-dependent, with survival as the primary outcome for tumors such as HCC and colorectal carcinoma. To reach this success, individual operators should have survival rates comparable to those in the established literature. Thresholds are set at less than 100% because operators will encounter patients in practice who require therapy who have clinical presentations worse than allowed in clinical trials. In patients with symptomatic neuroendocrine malignancy, clinical success is defined as the elimination of hormonal symptoms (**Table 4**) (3,19,26, 56–65).

COMPLICATIONS

Complications occur in approximately 10% of patients. Published complication rates and suggested thresholds include the following:

Postembolization syndrome (fever, pain, increased white blood cell count) by itself is not considered a complication but rather an expected outcome of embolotherapy (46). As noted earlier, a small percentage of patients will have prolonged symptoms that require a greater level of postprocedural care (56). Published rates for individual types of complications are highly dependent on patient selection and are based on series comprising several hundred patients, which is a volume larger than most individual practitioners are likely to treat. Therefore, we recommend that complication-specific

thresholds should usually be set higher than the complication-specific reported rates listed herein. It is also recognized that a single complication can cause a rate to cross above a complication-specific threshold when the complication occurs in a small volume of patients, eg, early in a quality improvement program. In this situation, the overall procedure threshold is more appropriate for use in a quality improvement program.

In **Table 5** (39,56,66–69), all values are supported by the weight of literature evidence and panel consensus except those shown with an asterisk (weak literature evidence, but 80% Delphi consensus), or dagger (weak literature evidence and no Delphi consensus).

OVERALL PROCEDURE THRESHOLD

The threshold is 15% for all major complications resulting from chemoembolization, embolization, or chemotherapeutic infusion.

APPENDIX 1: SIR STANDARDS OF PRACTICE COMMITTEE CLASSIFICATION OF COMPLICATIONS BY OUTCOME

Minor Complications
A. No therapy, no consequence; or
B. Nominal therapy, no conse-

Table 5
Thresholds for Major Complications of Hepatic Arterial Chemoembolization (39,56,66–69)

Specific Major Complication	Reported Rate (%)	Suggested Threshold (%), Reference
Liver failure	2.3	4 (56)
Abscess with functional sphincter of Oddi	<1	2 (39,66)
Post-embolization syndrome requiring extended stay or readmission	4.6	10 (56)
Abscess with biliary–enteric anastomosis/ biliary stent/sphincterotomy	25	25 (39,67)
Surgical cholecystitis	<1	1 (66,68,69)
Biloma requiring percutaneous drainage	<1	2 (68)
Pulmonary arterial oil embolus	<1	1 (69)
Gastrointestinal hemorrhage/ulceration	<1	1 (69)
Iatrogenic dissection preventing treatment	<1	1 (68)
Death within 30 days	1	2 (68,69)

quence; includes overnight admission for observation only.

　Major Complications

　C. Require therapy, minor hospitalization (<48 hours);

　D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours);

　E. Have permanent adverse sequelae;

　F. Result in death.

APPENDIX 2: CONSENSUS METHODOLOGY

　Reported complication-specific rates in some cases reflect the aggregate of major and minor complications. Thresholds are derived from critical evaluation of the literature, evaluation of empirical data from Standards of Practice Committee members' practices, and, when available, the SIR HI-IQ™ System national database.

　Consensus on statements in this document was obtained with use of a modified Delphi technique (70,71).

APPENDIX 3: EVIDENCE TABLE

　Appendix 3 is available online at www.jvir.org.

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SIR DISCLAIMER

The clinical practice guidelines of SIR attempt to define practice principles that generally should assist in producing high-quality medical care. These guidelines are voluntary and are not rules. A physician may deviate from these guidelines as necessitated by the individual patient and available resources. These practice guidelines should not be deemed inclusive of all proper methods of care or exclusive of other methods of care that are reasonably directed toward the same result. Other sources of information may be used in conjunction with these principles to produce a process leading to high-quality medical care. The ultimate judgment regarding the conduct of any specific procedure or course of management must be made by the physician, who should consider all circumstances relevant to the individual clinical situation. Adherence to the SIR quality improvement program will not assure a successful outcome in every situation. It is prudent to document the rationale for any deviation from the suggested practice guidelines in the department policies and procedure manual or in the patient's medical record.

APPENDIX 3:
EVIDENCE TABLE

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Lo et al (1)	Single-center, randomized, prospective	79 in two groups	Determine survival with TACE vs observation	Survival at 1, 2, and 3 years with TACE: 57%, 31%, 26% vs 32%, 11%, 3% with observation; univariate analysis significant for improved survival with TACE, asymptomatic at presentation, no branch PV obstruction, tumor < 5 cm, Okuda stage 1; multivariate analysis significant for treatment with TACE and absent PV obstruction	A
Llovet et al (2)	Prospective randomized trial	112; 37 embolization, 40 TACE; 35 symptomatic	Determine survival benefit and prognostic factors for different treatment options; bland embolization done with Gelfoam; TACE done with doxorubicin and Lipiodol; procedures done on calendar basis	TACE significantly better survival than observation ($P = .025$); embolization approached significance but study was stopped ($P = .07$); mean survival with TACE was 28.7 months; mean survival with embolization, 25.3 months; mean survival with observation, 17.9 months	A
Gupta et al (3)	Retrospective review with various treatments for carcinoid tumors	81	Evaluate clinical/radiologic response, duration of response, progression-free survival, overall survival with liver-dominant carcinoid for 9 years	51 patients had extrahepatic disease; 50 with embolization, 31 with HACE; chemotherapy varied from patient to patient; mean time to radiologic progression was 19 months; 64% with carcinoid syndrome had positive response; median survival, 31 months	A
Salman et al (4)	Prospective randomized embolization vs chemoembolization	26 with embolization; 24 with chemoembolization	PVA vs 750 mg/m^2 5-fluorouracil and interferon mixed with PVA	Median survival for all patients was 11 months; survival with extrahepatic disease was 8 months; survival with liver disease only was 15 months; survival similar between groups	B
Velazquez et al (5)	Prospective nonrandomized	463 with cirrhosis	Patients tracked for development of HCC with multiple risk factors evaluated	Hepatitis C positivity and age older than 55 both are significant risk factors. Given the increased incidence of hepatitis C in US, many patients will present with HCC. Older patients are also less likely to be transplant eligible	A

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Caturelli et al (6)	Prospective single-center study in Italy	111 in a single arm	Determine the long-term nontumorous hepatic tissue damage caused by TACE	Mean Child-Pugh score for whole group went from 5.96 to 6.28 after one TACE and 6.51 after second TACE ($P = $ NS); Child-Pugh scores of A did significantly increase from 5.37 to 5.73 after one TACE and 5.89 after two ($P < .05$); no significant change after TACE in Child-Pugh class B disease (7.48 to 7.67 and 7.30)	A
Kanematsu et al (7)	Retrospective review	303	Determine outcomes in large patient population	Majority of procedures were wedge resection (58%); 4.9% mortality rate; >50% morbidity rate, including 13% wound infection, 10% peritonitis, 5% biliary leak, 4% liver failure	A
Wiesner et al (8)	Prospective multicenter	3,437	Applied MELD score to patients on liver transplant waiting list while Child-Pugh scoring was primary determinant of organ reception	12% of patients died on the list; mortality directly correlates with an increase of MELD score; patients dying on transplant list correlated with a need for imaging-guided therapy while waiting	A
Fisher et al (9)	Prospective nonrandomized; single-center	33	Evaluate the effect of an aggressive ablation therapy regimen before liver transplantation on dropout rate and cancer-free survival in HCC	85% received liver transplant; 12.19% dropped off transplant list because of progression; TIII stage or AFP >400 ng/mL predicted dropping off transplant list	B
Nordlinger et al (10)	Retrospective review	130 with 143 resections	Determine risks and benefits of resection for colorectal cancer	25% of patients seen were candidates for resection; 2-/3-year survival rates after initial resection were 57% and 33%; survival decreased after additional resections, surgery with long-term survival	B
Hurwitz et al (11)	Prospective	813	Patients received irinotecan, 5-fluorouracil, and leucovorin with or without bevacizumab	Bevacizumab group had significantly longer survival (20.3 months vs 15.6 months), longer progression-free survival, higher rates of response, and greater duration of response than control group	E

APPENDIX 3: Continued					
Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Oberg (12)	Review article	NA	Determine outcomes of different systemic therapies for neuroendocrine tumors	No benefit from chemotherapy noted for carcinoid tumors; 40%–60% of patients with endocrine tumors of the pancreas have temporal benefit from chemotherapy; somatostatin has benefit in 40%-70% of patients with carcinoid tumors	A
Ridolfi et al (13)	Retrospective review	13	Review experience with chemotherapy for a variety of gastrointestinal carcinoid tumors	Two partial remissions, four cases of stable disease; survival benefit not commented on	B
Singh et al (15)	Standards article	NA	Review standards of practice for individuals performing mesenteric angiography	–	A
Pentecost et al (16)	Case series, retrospective	9	Review experience of TACE in patients with PV thrombosis	No patients died as a result of treatment; prolonged responses were obtained; TACE is safe in setting of collateral flow	B
Chung et al (17)	Retrospective review, single-center	110; 33 with <2 segments; 77 with >2 segments	Evaluate safety of TACE with main and primary branch PV thrombosis	Twenty-two of 33 limited tumors had objective response; nine of 77 widespread tumors had significant improvement; median survival in whole group was 6 months; median survival with limited tumor was 22 months; median survival with widespread tumor was 5 months	B
Berger et al (18)	Retrospective review	121 and 314 treatments	Determine morbidity and mortality from embolization and chemoembolization	Morbidity was 5.1%; treatment-related mortality was 4.1%; spectrum of elevated LDH, AST, bilirubin, and extensive tumor infiltration leading to increased mortality	B
Brown et al (19)	Retrospective review	87 with 169 TACE sessions	Evaluate effect of MELD and Child-Pugh scoring on survival	Mean survival of whole group was 17 months; Child-Pugh class not an effective predictor of survival; patients with Child-Pugh A/B disease with albumin level $\geq$ 3.4 g/dL had best survival	A
Stuart et al (20)	Prospective nonrandomized	52	Determination of treatment safety and efficacy	Median survival, 16 months; 17% 30-day mortality rate; note large number of patients with PV thrombosis	B

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Bruix et al (22)	Retrospective review with 50 of 237 evaluated patients treated	50	Gelfoam and coils from "main feeding artery" with multiple bilateral treatments done; survival compared with mathematical model 41/50 patients had mutinodular/ massive tumor occupying most of the liver volume	81% of patients showed objective response at follow-up CT; median survival of group was 20 months and was significantly better than mathematical model	C
Bruix et al (23)	Prospective randomized trial; one hospital	40 in treatment, 40 in symptomatic therapy	Confirm clinical usefulness of arterial embolization in treatment of HCC	No significant difference in survival for whole group; no difference in Child A, Child B, Okuda I or Okuda II; embolization without chemotherapy performed with Gelfoam and coils if lobar embolization done; bilobar embolization done in 16 of embolization group; follow-up embolization criteria not given (quoted that repeat embolization does not work)	C
Pelletier et al (24)	Prospective randomized trial	42	21 patients treated with doxorubicin/Gelfoam powder; 21 patients in control group; chemoembolization given on day 0 and a 2 months, 6 months, and 12 months; exclusion criteria included only encephalopathy and PV thrombosis; some Okuda 3 cases in each group	No significant difference in survival; 33% survival in chemoembolization group at 6 months; no discussion of patient selection	C
Pelletier et al (25)	Prospective randomized trial	73 treated with cisplatin/Gelfoam/ Ethiodol and tamoxifen	Controls received tamoxifen alone; 37 in chemoembolization group, 36 controls; TACE done every 3 months for 4 cycles then every 4 months	Embolization done from proper hepatic artery; no significant difference in survival; significantly greater tumor necrosis in TACE group; questionable technique	C
Barone et al (26)	Retrospective review	110 treated; 83 controls	Survival comparison between groups	Median survival significantly longer with TACE (26 months vs 10 months); multivariate analysis demonstrated longer survival with TACE, Child-Pugh class A, low AFP, and tumor diameter <3 cm	A

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Ernst et al (27)	Retrospective review	80 per group, 160 total	First group, TACE done with 3 sessions at 2-month intervals with follow-up as necessary; second group, embolization with follow-up as dictated by postembolization imaging	Median survival in group 1, 27 months vs 8 months in group 2 ($P < .001$); survival was significantly longer for Okuda I and II cases vs similar Okuda cohorts in group 2; breaking up treatments improves survival	A
Rossi et al (28)	Prospective, nonrandomized	62	RFA performed with Gelfoam embolization or balloon occlusion of feeding hepatic artery; ablation spheres determined	Much larger ablation spheres obtained than typical for radiofrequency ablation alone; tumors as large as 8.5 cm ablated in 1–2 sessions	A
Yamakado et al (29)	Prospective, nonrandomized	64 with 108 tumors	Determine survival and feasibility of tumor ablation of radiofrequency ablation done within 2 weeks of chemoembolization to treat HCC; 32 tumors were >3 cm	Complete necrosis obtained in all tumors; one year survival, 98%; no local recurrences in tumors <5 cm at 1 year	A
Li et al (30)	Retrospective single-center	153	Determine effects of combination TACE/PEI on patients with tumors 2–3 cm ($n = 47$), 3–5 cm ($n = 66$), and 5–13 cm ($n = 40$)	Mean follow-up of 23 months with 1- and 2-year survival rates of 78% and 54%; cirrhosis stage (Child-Pugh B or C vs A) was the only multivariate predictor of cirrhosis	B
Brown et al (31)	Retrospective review	35 with 63 sessions	Determine treatment outcomes after embolization for neuroendocrine malignancy	96% sessions had hormonal response; duration of response was longest for patients with hormonal symptoms (17.5 months) and was shortest when symptoms were pain alone (6.2 months); four deaths occurred after chemoembolization; three of these four patients had whole-liver embolization in one session	A
Gray et al (32)	Prospective randomized phase III trial	74	Determine benefit of addition of SIR-Spheres to regional hepatic artery chemotherapy (12-day infusion of floxuridine)	Partial and complete response rates for SIR Spheres was greater than with chemoembolization alone; longer time to progression with SIR Spheres; improved survival for SIR Sphere group in patients living >15 months	C
Mavligit et al (33)	Retrospective review	30	Determine outcomes after chemoembolization for ocular melanoma	46% complete and partial response rate; median survival for group was 11 months (range, 9–18 months)	A

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Rajan et al (34)	Retrospective review	16	Determine outcomes after chemoembolization of sarcomas from gastrointestinal tract, spleen, and other locations	Thirteen of 16 patients had radiographic response; seven patients developed intrahepatic progression at mean of 10 months; four patients had stable disease with no progression; median survival for whole group was 20 months	B
Mavligit et al (35)	Retrospective review	14	Determine outcomes after chemoembolization of liver-dominant sarcomas using PVA/cisplatin and intraarterial vinblastine infusion	Ten major imaging responses; 70% of responses were durable for 8–31 months (median, 12 months)	B
Bedikian et al (36)	Retrospective review	201	Determine survival with a variety of methods to treat liver-dominant uveal melanoma including chemoembolization, intraarterial infusion, and systemic chemotherapy	Chemoembolization was the best therapy at inducing tumor response; only chemoembolization produced a meaningful response rate and should be the primary treatment for ocular melanoma	B
Reed et al (37)	Retrospective review	236	Compare outcomes with and without antibiotic prophylaxis	11% rate of infection/sepsis without antibiotics; 2.6% rate of infection with antibiotics	A
Kim et al (39)	Retrospective single-center trial	397 TACE in 157 patients; 136 of 157 with metastases	Studied clinical radiologic findings, organisms, and outcomes	2% rate of abscess per procedure; one abscess without bilioenteric anastomosis; remainder of infections in patients with bilioenteric anastomosis (RR 894)	A
Geschwind et al (40)	Retrospective review	8; 4 treated with bowel preparation; 4 treated with standard premedication	Evaluate new preparation with (bowel preparation and piperacillin) vs skin-coverage antibiotics to limit abscess formation in patients with biliary enteric anastomosis	All 4 patients without bowel prep/piperacillin developed abscesses whereas none of the 4 patients with new preparation developed infection	B
Covey et al (41)	Retrospective review	600	DSA of 600 patients reviewed to evaluate variant anatomy encountered during TACE	Replaced LHA in 19.8%, replaced RHA in 14.8%; 4.7% had replaced LHA and RHA; 4% had hepatic artery arising directly from the aorta; 61.3% had "standard" hepatic anatomy	A
Chung et al (42)	Retrospective review	50	Evaluate outcomes from chemoembolization of inferior phrenic artery branches with doxorubicin/Ethiodol/PVA	Complete or partial response in 31 patients; 78% survival at 1 year, 46% at 2 years; one complication of livery abscess/empyema in one patient	A

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Kim et al (43)	Case series	2	Determine outcomes of chemoembolization via the internal mammary artery	Treatment was safe and effective with significant reductions in AFP in both patients	B
Tajima et al (44)	Retrospective single-center trial	44	Evaluate outcomes; thoracic complications graded as follows: 1, no intrathoracic abnormalities; 2, consolidation/pleural reaction without Ethiodol; 3, Ethiodol on pleura; 4, Lipiodol scattered in lung; 5, Lipiodol everywhere	Thirty-one of 44 patients had abnormal CT after procedure; 52% had Lipiodol in lungs; consolidation seen in 68%; pleural effusion in 41%; only 32% had normal CT; no clinical description given of outcomes; increasing chemotherapeutic agent and Ethiodol dose increased complications; arteriovenous shunting did not increase complications	A
Arora et al (45)	Case series	5	Report adverse outcomes after chemoembolization via multiple extrahepatic collateral vessels	Four patients had ischemic ulceration of the skin resulting from chemoembolization; one patient developed radiation burn from multiple sessions of chemoembolization, which degenerated into squamous cell carcinoma	B
Leung et al (46)	Retrospective review	29 with 70 TACE sessions	>1 day length of stay for gallbladder embolization, liver volume embolized, embolized volume occupied by tumor, previous embolization in same territory, dose administered	PES more common with first embolization (although not significant); gallbladder embolization and >80% of chemoembolization dose led to greater PES	A
Hartnell et al (47)	Retrospective comparison	27 with no lidocaine; 29 with lidocaine	Determine effect of intraarterial lidocaine on pain resulting from chemoembolization	As much as 56 mg of 1% lidocaine infused without complication; significantly less intraprocedural and postprocedural narcotics were required; less postprocedural prochlorperazine was required in treatment group; treatment group was significantly more likely to tolerate solid food within 24 hours and be discharged earlier	A
Lee et al (48)	Prospective single center	113	Determine effect of intraarterial lidocaine immediately before TACE ($n = 30$), immediately after TACE ($n = 46$), and no lidocaine ($n = 37$)	Lidocaine before TACE significantly reduced pain and postprocedural analgesic requirements	A

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Camma et al (49)	Meta-analysis	2,466 in 18 trials	Determine survival benefit of chemoembolization from randomized controlled trials; also determine benefit if any of chemotherapy in embolization slurry	Chemoembolization significantly reduced the 2-year mortality rate compared with symptomatic therapy; no evidence that arterial chemoembolization is more effective than embolization alone	B
Maeda et al (50)	Single center, nonrandomized, retrospective	356; 189 with TACE, 167 with chemotherapeutic infusion of Ethiodol only	Determine factors regarding survival with each treatment as well as local recurrence	Survival overall similar; for patients with small tumors, TACE superior to Ethiodol infusion; local recurrence significantly more common in TACE group at all time points; great potential for selection bias	A
Ikeda et al (51)	Retrospective review single center Japan	168 in two groups	Determine efficacy of embolization vs infusion chemotherapy mixed with Lipiodol (TAI); 94 patients treated with TAI (cisplatin/Lipiodol) or TAE (same with Gelfoam)	No difference in survival; 73% complete plus partial response rate for embolization vs 51% for infusion chemotherapy ($P < .01$); toxicity similar except for nausea and liver function (both worse with TAE)	A
Higuchi et al (52)	Retrospective review, single center	84 with HCC treated/resected; 22 with HCC not treated (controls)	Determine necrosis rates after TACE and areas of cellular activity	50 tumors <3 cm (19/100% necrotic,16/95-99%, 10/50-94%, 5/<50%); 34 tumors > 3 cm (10/100% necrotic, 5/95-99%, 12/50-94%, 7/<50%); significantly worse necrosis with > 3 cm; small HCC most often had residuals in extracapsular zone whereas large HCC had residual cells interiorly	A
Takayasu et al (53)	Retrospective review; multicenter, Japanese	41 surgical specimens	Compared Ethiodol uptake and change in size to tumor necrosis as WHO criteria do not fit HCC well	Mean necrosis at CT was 78% vs 67% at pathologic examination ($r = .83$); mean tumor reduced 21.2% in size; reduction rate of tumor and necrosis rate did not correlate ($r = .38$); no relationship between size reduction and necrosis	A
Kubota et al (54)	Retrospective review	84 tumors in 54 patients	Evaluate role of power Doppler and MR vs Lipiodol CT	Postprocedural power Doppler sonography/MR were excellent predictors of treatment success/failure of chemoembolization	B

APPENDIX 3: Continued					
Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Chopra et al (55)	Retrospective review	25	Determine recurrence patterns of hepatic malignancies after radiofrequency ablation	Recurrences can be at the initial ablation site, elsewhere in the liver or extrahepatic; locally recurrent disease usually has a nodular, halo, or gross enlargement of a previously ablated site	C
Brown et al (56)	Retrospective review	46 treated with bland embolization	Determine survival with embolization alone; procedure done from left or right hepatic artery and not from proper hepatic artery	86 embolizations in 46 patients; median survival was 11.7 months; significantly worse survival for Okuda stage II than Okuda stage I (16 months vs 6 months); mean stay after embolization was 3.8 days; 81% of patients had PES	B
Solomon et al (57)	Single arm prospective	38	Describe morphologic and biologic responses in a Western population with HCC to TACE	Median/mean survival of 17/17.4 months; time to progression (median/ mean), 13.5/11.6 months; no complete responses, numerous partial responses	A
Leichman et al (58)	Prospective	33	Estimate 1-year survival and time to progression via treatment with HACE at weeks 1 and 6 followed by 5-fluorouracil/ leucovorin starting at week 12; chemoembolization mix was collagen, cisplatin, mitomycin-c, doxorubicin	Thirteen of 24 patients with high CEA had >50% reduction with HACE alone; median time to progression was 8 months; median survival of cohort was 14 months	D
Martinelli et al (59)	Prospective randomized	24	12 randomized to PVA 150-250 μm; 12 randomized to 5-fluorouracil, interferon-α, and PVA	No difference between groups in response or survival; median survival was 9.3 months from time of embolization with a mean of 12 months follow-up; survival increase with longer follow-up?	D
Sanz-Altamira et al (60)	Prospective	40	1000 mg 5-fluorouracil, 10 mg mitomycin-c, 10 mL ethiodized oil followed by Gelfoam	Median survival with ECOG performance status of 0/1 was 24 months, median survival of 3 months with status of $\geq$ 2; patients with metastatic disease confined to liver survived a median of 14 months vs 3 months with disease outside the liver	B
Tellez et al (61)	Prospective	30	Bovine collagen, cisplatin, doxorubicin, mitomycin-c	Median survival, 8.6 months after initial TACE	D

APPENDIX 3:
Continued

Study	Study Type	No. of Pts.	Objective	Results and Comments	Strength*
Popov et al (62)	Prospective	11	Patients received mitomycin-c (no dose given) mixed with Ethiodol from common hepatic artery every 3-4 months	No radiologic or CEA responses noted; median survival was 9 months	D
Hunt et al (63)	Prospective randomized	61	22 patients treated with Gelfoam; 19 treated with 500 mg 5-fluorouracil and starch microspheres; 20 received no treatment	Median survival in treated groups of 13 months; median survival in groups who received no treatment of 9.6 months; difference not significant, although study groups were small	D
Kim et al (64)	Prospective	30: 14 islet cell, 16 carcinoid	Evaluate effects of chemotherapy added to particle embolization; carcinoid tumors treated with 150 mg cisplatin and 50 mg doxorubicin; islet-cell tumors treated with 350 mg 5-fluorouracil and 1,000 mg streptozotocin	Biochemical response in 75% of carcinoid tumors and 90% of islet-cell tumors in patients with symptoms; median duration of survival was 15 months	B
Clouse et al (65)	Retrospective review	20 with various histologies	Evaluate the effect of adding chemotherapy to particles (doxorubicin 40–80 mg)	Patients with hormonally active tumors had mean of 90% decrease in levels 1–2 weeks after treatment; median survival of group was 24 months	A
Gates et al (66)	Review article	251	Review complications resulting from chemoembolization at a single institution	Complications listed and added to complication table in manuscript	A
Sakamoto et al (68)	Retrospective review	2,300 chemoembolization procedures	Review complications resulting from chemoembolization in a large institutional experience	Overall complication rate of 4.4%; details added to table in manuscript	A
Chung et al (69)	Retrospective review	351 with 942 procedures	Elucidate major complications and their predisposing factors	Significant predisposing factors included biliary obstruction or previous biliary intervention, poor liver function and nonselective embolization	A

*Literature support for guidelines is as follows: A, good study; supports guideline, threshold, or recommendation; B, Fair study; supports guideline, threshold, or recommendation; C, poor study; study evidence does not support or refute guideline, threshold, or recommendation; D, fair study; evidence is in opposition of guideline, threshold, or recommendation; E, good study; evidence is in opposition of guideline, threshold, or recommendation.

Note.—AFP = α-fetoprotein; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen; DSA = digital subtraction angiography; ECOG = Eastern Cooperative Oncology Group; HACE = hepatic arterial chemoembolization; HCC = hepatocellular carcinoma; LDH = lactate dehydrogenase; LHA = left hepatic artery; MELD = Model for End-Stage Liver Disease; NA = not applicable; PEI = percutaneous ethanol injection; PES = postembolization syndrome; PV = portal vein; PVA = polyvinyl alcohol; RHA = right hepatic artery; TACE = transhepatic arterial chemoembolization; WHO = World Health Organization.