Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy

Ron C. Gaba, MD, R. Peter Lokken, MD, MPH, Ryan M. Hickey, MD, Andrew J. Lipnik, MD, Robert J. Lewandowski, MD, Riad Salem, MD, MBA, Daniel B. Brown, MD, T. Gregory Walker, MD, James E. Silberzweig, MD, Mark Otto Baerlocher, MD, Ana Maria Echenique, MD, Mehran Midia, MD, Jason W. Mitchell, MD, MPH, MBA, Siddharth A. Padia, MD, Suvranu Ganguli, MD, Thomas J. Ward, MD, Jeffrey L. Weinstein, MD, Boris Nikolic, MD, MBA, and Sean R. Dariushnia, MD, for the Society of Interventional Radiology Standards of Practice Committee

ABBREVIATIONS

BCLC = Barcelona Clinic Liver Cancer, CLM = colorectal carcinoma liver metastases, CRC = colorectal carcinoma, DEBIRI = drug-eluting beads loaded with irinotecan, DEE = drug-eluting embolic, ECOG = Eastern Cooperative Oncology Group, GM-CSF = granulocyte-macrophage colony-stimulating factor, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, LRT = locoregional therapy, NET = neuroendocrine tumor, OS = overall survival, PFS = progression-free survival, TTP = time to progression, ^{90}Y RE = yttrium-90 radioembolization

PREAMBLE

The mission of the Society of Interventional Radiology (SIR) is to improve patient care through image guided therapy. The Society was founded in 1973 and is recognized today as the primary specialty society for physicians who provide minimally invasive image guided therapies. A Quality Improvement (QI) Guideline attempts to provide clinical guidelines on the application of a specific procedure or treatment of a disease process when a significant body of literature is available.

A QI Guideline is produced by the Standards of Practice Committee. The membership of the SIR Standards of Practice Committee represents experts in a broad spectrum of interventional procedures from both the private and the 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.

From the Division of Interventional Radiology (R.C.G., R.P.L., A.J.L.), Department of Radiology, University of Illinois Hospital & Health Sciences System, 1740 West Taylor Street, MC 931, Chicago, IL 60612; Section of Vascular and Interventional Radiology (R.M.H., R.J.L., R.S.), Department of Radiology, Northwestern Memorial Hospital, Chicago, Illinois; Department of Radiology (D.B.B.), Vanderbilt University Medical Center, Nashville, Tennessee; Division of Interventional Radiology (T.G.W., S.G.) and Center for Image Guided Cancer Therapy (S.G.), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Department of Radiology (J.E.S.), Mount Sinai Beth Israel, New York, New York; Department of Radiology (M.O.B.), Royal Victoria Hospital, Barrie, Ontario, Canada; Department of Interventional Radiology (A.M.E.), University of Miami School of Medicine, Coral Gables, Florida; Interventional Radiology (M.M.), McMaster University, Hamilton, Ontario, Canada; Interventional Radiology and Image Guided Medicine (J.W.M., S.R.D.), Emory University School of Medicine, Atlanta, Georgia; Division of Interventional Radiology (S.A.P.), Department of Radiology, David Geffen School of Medicine at University of California, Los Angeles, California; Vascular and Interventional Radiology (T.J.W.), Florida Hospital, Orlando, Florida; Vascular and Interventional Radiology (J.L.W.), Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and Department of Radiology (B.N.), Stratton Medical Center, Albany, New York. Received April 22, 2017; accepted April 29, 2017. **Address correspondence to** R.C.G., c/o Debbie Katsarelis, SIR, 3975 Fair Ridge Dr., Suite 400 N., Fairfax, VA 22033; E-mail: rgaba@uic.edu

R.M.H. receives personal fees from Bayer (Berlin, Germany). R.J.L. is a paid consultant for BTG International (London, United Kingdom) and Cook, Inc (Bloomington, Indiana), and receives personal fees from Boston Scientific (Marlborough, Massachusetts), Access Medical Ventures (Tel-Aviv, Israel), and ABK Biomedical (Halifax, Nova Scotia, Canada). R.S. receives grants and personal fees from BTG International. D.B.B. receives research support from Sirtex Medical Ltd (North Sydney, Australia), is a paid consultant for BTG International, and is a paid speaker for Boston Scientific. M.O.B. receives personal fees from Boston Scientific. S.A.P. receives personal fees from BTG International. S.G. is a paid consultant for Sirtex, BTG International, and Boston Scientific and receives research grants from Merit Medical Systems, Inc (South Jordan, Utah). None of the other authors have identified a conflict of interest.

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METHODOLOGY

SIR produces its QI Guidelines documents using the following process. Topics of relevance and timeliness are conceptualized by the Standards of Practice Committee members, Service Lines, SIR members, or the Executive Council. A recognized expert or group of experts are identified to serve as the principal author or writing group for the document. Additional authors or societies may be sought to increase the scope, depth, and quality of the document dependent upon the magnitude of the project.

An in-depth literature search is performed using 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, which is used to write the document such that it contains evidence-based data with respect to content, rates, and thresholds. Threshold values are determined by calculating the standard deviation of the weighted mean success and adverse event rates reported in all relevant trials with a sample size of approximately 50 patients or greater. Calculated threshold values represent two standard deviations above or below the mean for adverse event and success rates, respectively.

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 using a Modified Delphi Consensus Method (**Appendix A**). 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 writing group and Standards of Practice Committee members, either by telephone conference calling or face-to-face meeting. The finalized draft from the Committee is sent to the SIR Operations Committee for approval. The document is then posted on the SIR website for the SIR membership to provide further input/criticism during a 30-day comment period. These comments are discussed by the Standards of Practice Committee, and appropriate revisions are made to create the finished standards document prior to its publication.

INTRODUCTION

Transcatheter liver-directed intraarterial therapy represents an important therapeutic approach in individuals with liver-dominant neoplasms. Transarterial chemoembolization and embolization—the archetypical transarterial embolotherapies in interventional oncology locoregional therapy (LRT)—have gained acceptance and application during the past 4 decades for treatment of various primary hepatic malignancies and secondary cancers and are widely employed in current interventional radiology (IR) practice. As such, quality assurance in case selection, procedure performance, and patient outcomes through establishment of threshold levels for therapy indication adherence, procedure success rates, and adverse event incidence is critical in ensuring delivery of high quality, effective, and value-driven care in IR. These updated guidelines—which build on prior versions of this document—have thus been developed for use in QI programs assessing transarterial chemoembolization and embolization outcomes in clinical practice.

CLINICAL BACKGROUND ON LIVER TUMORS

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) accounts for 85%–90% of all primary liver cancers and is a significant cause of morbidity and mortality worldwide (1). The incidence of HCC continues to increase both internationally and in the United States, currently spanning > 700,000 new diagnoses and deaths annually (2). Although surgical resection represents a curative treatment, few patients are candidates for hepatectomy owing to advanced multifocal disease, significant extrahepatic tumor burden, poor hepatic reserve, portal hypertension, or reduced functional status (1,3). Use of traditional external-beam radiation therapy is limited by the radiation tolerance of normal liver, and stereotactic radiation remains a nascent therapy, with fewer cumulative data than transarterial chemoembolization (4). Targeted therapies such as sorafenib and regorafenib—although statistically superior to supportive care—have shown only modest effectiveness in the treatment of HCC (5,6). Liver transplantation remains the best curative option for individuals with limited HCC—eg, one tumor < 5 cm in diameter or 3 tumors each < 3 cm in diameter, comprising the Milan criteria (7); however, demand for donated organs surpasses supply. Given these therapeutic limitations, the vast majority of patients with HCC must look to minimally invasive, image-guided IR LRTs such as transarterial chemoembolization, which has shown efficacy in HCC therapy with palliative therapeutic intent (8-11) or as a bridge or downstage to liver transplantation (12); transarterial embolization has shown similar efficacy (13–15). As such, transarterial LRTs have gained endorsement as a vital component of management of patients with HCC by numerous hepatology and oncology societies.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) represents an anatomic subtype of cholangiocarcinoma—the second most common primary hepatic malignancy—defined by tumorigenesis in intrahepatic peripheral bile ducts. The annual US incidence of ICC has been estimated at 0.58–0.85 per 100,000 (16), and this disease is associated with modest survival times approximating 5–13 months after treatment with palliative systemic therapies (17). Patients with this disease may benefit from LRTs such as transarterial chemoembolization for the management of unresectable, metastatic, or postsurgical residual local ICC.

Metastatic Liver Disease

Neuroendocrine tumors (NETs) comprise a broad spectrum of sporadic or inherited tumors arising from the endocrine system, occurring at a frequency of 5.25 cases per 100,000 people (18). Carcinoid tumors represent the most common NET and typically arise in the pulmonary system or gastrointestinal tract. NETs of gastroenteropancreatic origin metastasize to the liver in up to 85% of cases and result in clinical symptoms of flushing and diarrhea in patients with functional, hormone-secreting tumors (19). As systemic therapies have limited benefit for most patients with metastatic NET (20), and because nonsurgical candidates often have multifocal disease, transarterial chemoembolization and embolization can play an important role in treatment.

Colorectal carcinoma (CRC) is the third most common cancer in the United States, and it is the second most frequent cause of cancer-related death (21). Nearly one quarter of patients with CRC will have distant metastases at the time of diagnosis, whereas nearly 60% will later develop distant metastases (22), with the liver as the most common site and most frequent cause of CRC-related death (23). Although surgical resection may offer a chance for cure in patients with limited colorectal carcinoma liver metastases (CLM), only 20% of patients with CLM are eligible for operations (24), and only a small proportion are actually cured (25). Systemic chemotherapy combining 5-fluorouracil with oxaliplatin (FOLFOX) and/or irinotecan (FOLFIRI), in conjunction with biologic agents, remains the standard treatment for CLM (26,27). However, many patients have poor response to or progress despite systemic therapy, and LRT options may be beneficial. Recently, yttrium-90 radioembolization (^{90}Y RE) has shown promise in delaying tumor progression both in the salvage and in the front-line therapy settings. Transarterial chemoembolization has shown potential in this scenario as well.

Uveal melanoma is the most common adult ocular malignancy, occurring in 4.3 cases per 1 million persons (28). Although disease is typically limited to the eye at presentation, 50% of patients will go on to develop metastatic disease within 2–5 years of diagnosis despite effective therapy for the primary tumor (28). A liver-dominant metastatic pattern is present in 70%–90% of patients, with < 10% candidates for surgical resection (29). Response rates to systemic chemotherapy are generally < 10%, and median survival after development of liver metastases ranges from 2 to 9 months (30,31). As such, transarterial chemoembolization, transarterial embolization, and immunoembolization—which is designed to provoke a systemic immune response that can delay extrahepatic metastases while controlling liver metastases—represent potentially beneficial treatment options.

DEFINITIONS/TERMINOLOGY

Although practicing physicians should strive to achieve perfect outcomes (eg, 100% success, 0% adverse events), in practice all physicians will fall short of this ideal to a variable extent. Thus, indicator thresholds may be used to assess the efficacy of ongoing QI programs. For the purposes of these guidelines, a threshold is a specific level of an indicator, which should prompt an internal review. "Procedure thresholds" or "overall thresholds" reference a group of indicators for a procedure, eg, major adverse events. Individual adverse events may also be associated with adverse event–specific thresholds. When measures such as indications or success rates fall below a (minimum) threshold, or when adverse events 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 1 measure of the quality of transarterial chemoembolization quality, then 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 adverse event. 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. *Thus, 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 QI program needs.

Definitions

Relevant tumor and therapy terms—such as index tumor, image guided procedure, image guided transcatheter tumor therapy, and treatment cycle—have been previously defined (32). Other terms and/or procedures germane to this document are defined below.

- *Liver-dominant neoplasm* is defined as a malignancy in which the hepatic component is the only site of disease or is the principal site of disease most likely to lead to patient morbidity and/or mortality.
- *Conventional transarterial chemoembolization* is defined as infusion of single or multiple chemotherapeutic agents with or without ethiodized oil with or without concurrent (as a component of the chemoembolic emulsion) or tandem embolization with particles such as gelatin sponge, polyvinyl alcohol, or calibrated microspheres (32).
- *Drug-eluting embolic (DEE) transarterial chemoembolization* is defined as administration of calibrated microspheres onto which chemotherapeutic medication is loaded or adsorbed with the intention of sustained in vivo drug release (32).
- *Transarterial embolization (TAE)* is defined as blockade of hepatic arterial flow with a vascular occlusive agent, such as gelatin sponge, polyvinyl alcohol, or calibrated microspheres (32).
- *Immunoembolization* is defined as transarterial administration of immunostimulants—including cytokines such as granulocyte-macrophage colony-stimulating factor or interleukin-2—aimed at inciting the immune system to kill tumor cells or immune effector cells aimed at directly killing tumor cells with or without concurrent embolization using agents such as ethiodized oil or gelatin sponge. An example of liver immunoembolization in clinical practice is granulocyte-macrophage colony-stimulating factor/ethiodized oil emulsion followed by gelatin sponge embolization for uveal melanoma liver metastases.

DIAGNOSTIC ALGORITHM AND TREATMENT ALGORITHM/DECISION TREE

General Eligibility Criteria

Procedure Indications and Patient Assessment. Transarterial chemoembolization and embolization may be indicated for patients with liver-dominant hepatic malignancies who are not candidates for curative resection or as a bridge or downstage to liver transplantation. Patients should be seen in an IR outpatient consultation before undertaking transarterial chemoembolization or embolization to assess procedure eligibility and for counseling regarding the anticipated procedure outcomes. Patients should undergo imaging evaluation before the procedure (eg, within 30 days of transarterial chemoembolization or embolization procedures), including some combination of contrast-enhanced computed tomography (CT), magnetic resonance (MR) imaging, and/or positron emission tomography (PET)/CT. Tumor size, number, morphology (eg, focal encapsulated vs infiltrative), burden (ie, percent liver replacement), Couinaud hepatic segmental location and unilobar or bilobar nature of disease, presence of extrahepatic disease, and patency of the portal venous system (eg, portal vein thrombosis or vascular invasion by tumor) represent measures to assess to determine prognosis after therapy. Although patients with portal vein thrombosis may be treated safely using selective transcatheter therapy (33), outcomes are optimized in the setting of a patent portal vein or with hepatopetal flow via collateral vessels. Patient performance status should be assessed using standardized scales such as the Eastern Cooperative Oncology Group (ECOG) score (34,35). Evaluation before the procedure should also incorporate laboratory evaluation, including complete blood count, prothrombin time or international normalized ratio, evaluation of liver and kidney function, and measurement of relevant tumor markers (eg, α-fetoprotein, carbohydrate antigen 19-9, 5-hydroxyindoleacetic acid, chromogranin A, or carcinoembryonic antigen).

Procedure Contraindications. Although there are no absolute transarterial chemoembolization or embolization exclusion criteria, recognized relative contraindications include inability to undergo arteriography (owing to uncorrectable thrombocytopenia, coagulopathy, renal insufficiency, or severe allergic reaction to iodinated contrast medium), decompensated liver disease or liver insufficiency (eg, total bilirubin $>$ 3.0 mg/dL), poor performance status (eg, ECOG performance status $\geq$ 3), large tumor burden (eg, $>$ 50% liver replacement by tumor, diffuse infiltrative tumor), biliary abnormality (obstruction, biliary-enteric anastomosis, or indwelling biliary stent), active systemic infection, main portal vein thrombosis, life expectancy $<$ 3 months (eg, related to significant extrahepatic disease burden), contraindication to chemotherapy agent that may be used in transarterial chemoembolization, poor hepatic arterial flow (eg, owing to atretic or damaged vessels), and poor tolerance of prior procedures (36).

Eligibility Criteria in Specific Malignancies

Hepatocellular Carcinoma. Transarterial chemoembolization and embolization inclusion criteria in the setting of HCC usually span therapeutic or palliative intent or a bridge or downstage to liver transplantation (**Table 1**). Treatment allocation is typically determined in a multidisciplinary tumor board, commonly using the Barcelona Clinic Liver Cancer (BCLC) staging scheme (**Table 2**) (37) as a framework for therapy allocation. Although targeted transcatheter therapies are offered to BCLC stage B patients according to published treatment guidelines, BCLC stage 0, A, C, or D disease may not constitute an exclusion criterion, as transarterial chemoembolization or embolization may be offered as definitive therapy in tumors for which thermal ablation is not anatomically (eg, central tumor) or technically (eg, inconspicuous on ultrasound or CT) feasible in BCLC 0/A disease (38), as a bridge to liver transplantation in BCLC A disease (39), or as palliation in BCLC C/D disease (11,40). Recently, the Hong Kong Combined Liver Cancer staging system (**Table 3**) has been proposed as an alternative therapy allocation scheme for HCC (41).

In potential transplant recipients, transarterial chemoembolization—usually prescribed when transplant organ wait time is expected to exceed 6 months (12)—may decrease the drop-off rate from the transplant list (39) and may downstage patients outside of Milan criteria to allow transplant eligibility (42). Transarterial chemoembolization is being investigated for intrahepatic recurrence following transplantation as well (43,44). In limited experience, transarterial chemoembolization has been found to be effective in management of larger tumors and as adjuvant therapy for HCC resection (45,46), but has not demonstrated improved disease-free survival in the neoadjuvant setting (47).

Table 1. Disease-Specific Transarterial Chemoembolization and Embolization Procedure Indications

Disease	Procedure Indications
HCC	Definitive treatment; bridge to liver transplantation; downstage to liver transplantation; palliation
ICC	Surgically unresectable or inoperable, liver-dominant disease; bridge to liver transplantation
Metastatic NET	Surgically unresectable or inoperable liver-dominant disease; clinically symptomatic disease
CLM	Surgically unresectable or inoperable, liver-dominant disease
Metastatic uveal melanoma	Surgically unresectable or inoperable, liver-dominant disease
Other liver metastases	Limited progressive disease not responsive to systemic therapy

CLM = colorectal carcinoma liver metastases; HCC = hepatocellular carcinoma; ICC = intrahepatic cholangiocarcinoma; NET = neuroendocrine tumor.

Table 2. Barcelona Clinic Liver Cancer Staging System (37)

Stage	Tumor	Liver Function	Performance Status
0 (very early)	Single < 2 cm	CP A	ECOG 0
A (early)	Single or 3 nodules ≤ 3 cm	CP A or B	ECOG 0
B (intermediate)	> 3 nodules	CP A or B	ECOG 0
C (advanced)	Macrovascular invasion or extrahepatic spread*	CP A or B	ECOG 1–2*
D (terminal)	Any	CP C†	ECOG 3–4†

CP = Child-Pugh; ECOG = Eastern Cooperative Oncology Group.
*At least 1 criterion: macrovascular invasion or extrahepatic spread or ECOG 1–2.
†At least 1 criterion: CP C or ECOG 3–4.

Both conventional transarterial chemoembolization and DEE transarterial chemoembolization may be effectively employed for HCC therapy (48). Patients with HCC may also be considered for percutaneous ablative therapies or systemic therapy in combination with transarterial chemoembolization. Many patients whose disease is treatable with transarterial chemoembolization may be treated with other transarterial approaches as well, including ^{90}Y RE. At the present time, the choice for adjunctive, concurrent, or alternative therapies should be based on patient-, tumor-, and operator-related considerations, such as liver reserve, performance status, tumor size, number, stage, morphology, distribution, burden, vascularity, presence of portal vein invasion, and operator or institutional experience, expertise, and preference.

Intrahepatic Cholangiocarcinoma. Clinical indications for transarterial chemoembolization or embolization of ICC include surgically unresectable or inoperable liver tumors with liver-dominant disease. An important consideration is the presence of biliary obstruction, which can predispose patients to infectious adverse events and increased risk of biliary abscess (49). Although bile duct reconstructive surgery, biliary stent placement, or sphincterotomy may relieve biliary obstruction, such patients remain at risk for abscess owing to colonization of the biliary system with enteral microbes. Although prior biliary instrumentation does not preclude transarterial chemoembolization or embolization (50), such patients should be treated with periprocedural broad-spectrum intravenous antibiotics to diminish this risk (51,52). As with HCC, patients with ICC may be treated with ^{90}Y RE in lieu of transarterial chemoembolization or embolization.

Table 3. Hong Kong Combined Liver Cancer Staging System (41)

Stage	Tumor	EVM	Liver Function	Performance Status
I	Early	No	CP A	ECOG 0
IIa	Early	No	CP B*	ECOG 1*
IIb	Intermediate	No	CP A	ECOG 0–1
IIIa	Intermediate	No	CP B	ECOG 0–1
IIIb	Locally advanced	No	CP A or B	ECOG 0–1
IVa	Any	Yes	CP A	ECOG 0–1
IVb	Any	Yes	CP B	ECOG 0–1
Va	Early	No	CP C†	ECOG 2–4†
Vb	Intermediate or locally advanced‡	Yes‡	CP C†	ECOG 2–4†

Note–Tumor definitions:
Early tumor: tumor size ≤ 5 cm, ≤ 3 tumor nodules, vascular invasion absent.
Intermediate tumor: (a) tumor size ≤ 5 cm, ≤ 3 tumor nodules, vascular invasion present; (b) tumor size ≤ 5 cm, > 3 tumor nodules, vascular invasion absent; (c) tumor size > 5 cm, ≤ 3 tumor nodules, vascular invasion absent.
Locally advanced tumor: (a) tumor size ≤ 5 cm, > 3 tumor nodules, vascular invasion present; (b) tumor size > 5 cm, ≤ 3 tumor nodules, vascular invasion present; (c) tumor size > 5 cm, > 3 tumor nodules, vascular invasion absent or present; (d) diffuse tumor.
CP = Child-Pugh; ECOG = Eastern Cooperative Oncology Group; EVM = extrahepatic vascular invasion/metastases.
*At least 1 criterion: CP B or ECOG 1.
†At least 1 criterion: CP C or ECOG 2–4.
‡At least 1 criterion: intermediate or locally advanced tumor or EVM.

Metastatic NET. Transarterial chemoembolization and embolization are generally indicated in cases of surgically unresectable, clinically symptomatic metastatic NETs. Most patients with symptomatic disease secondary to hormone production or bulk have multifocal metastases, which precludes surgery and percutaneous ablative therapies. Although initial control of symptoms is usually performed with somatostatin agents, treatment of NET hepatic metastases with transarterial chemoembolization can result in durable elimination of hormonal symptoms (53,54). A number of patients with hormonally active liver metastases also have extrahepatic disease. However, because embolotherapy can still reduce or eliminate symptoms, treatment should not be withheld from these patients if reduction in symptoms is thought to be feasible as a result. Notably, transarterial chemoembolization or embolization may also be used in cases exhibiting a large burden of metastatic liver disease in the absence of clinical symptoms. Similar to transarterial chemoembolization and embolization, ^{90}Y RE may be used to treat metastatic NET.

CRC Liver Metastases. Although there are no formal guidelines for selection of patients for transarterial chemoembolization treatment of

CLM, several published studies have limited therapy to patients with metastases deemed surgically unresectable, not amenable to thermal ablation, involving < 50%–60% of the liver volume, and having > 80% of tumor burden located in the liver (55–57). Liver function and performance status should be preserved (55–57).

Metastatic Uveal Melanoma. Patient selection criteria for transarterial chemoembolization, transarterial embolization, and immunoembolization for metastatic uveal melanoma parallel that for other malignancies and include liver-dominant disease, preserved hepatic function, and retained performance status (31).

Other Liver Metastases. Other tumors that may manifest with liver-dominant metastases include soft tissue sarcomas such as gastrointestinal stromal tumor, breast carcinoma, and gynecologic malignancies. Treatment of these tumors may be undertaken in cases of limited progressive disease not responsive to systemic therapy.

Preprocedure Considerations

Risk Stratification. Scoring systems commonly used for risk stratification include the Child-Pugh scheme (**Table 4**) (58), the Cancer of the Liver Italian Program score (59), and the Model for End-stage Liver Disease score (60). The Child-Pugh scoring system is superior to the Model for End-stage Liver Disease system at predicting long-term survival in HCC (61). Patients with Child-Pugh class A or B disease with an albumin level of at least 3.4 g/dL have improved survival (61). Model for End-stage Liver Disease scores > 10 and Cancer of the Liver Italian Program scores > 2 are negative predictors of survival (62). Regarding abnormalities of individual parameters, a bilirubin cutoff value of 3 mg/dL has been described (63). Recently, albumin-bilirubin grade has been shown to outperform Child-Pugh class at discriminating survival in patients receiving transarterial chemoembolization (64). The optimal scoring system to predict survival following therapy remains undefined, and investigation of novel predictors of outcome continues (10,65,66). As a final note, although it is important to consider patient-specific risk for procedure induced adverse events, it should be recognized that transarterial chemoembolization or embolization could be performed safely despite relative contraindications (67).

Preprocedure Preparation

Care before the procedure may include hydration, antiemetic agents, antihistamine drugs, and steroids. Many operators administer antibiotic coverage for gram-negative enteric organisms, although this practice is not universal or prospectively proven to be beneficial for all patients; a recent series confirmed that transarterial chemoembolization may be performed safely without prophylactic antibiotics in cases of HCC and an intact sphincter of Oddi (68). In patients with an incompetent sphincter of Oddi from previous surgery, sphincterotomy, or biliary drainage, the risk of infection following embolization is significantly increased (49). The risk of postembolization infection appears to be reduced by prolonged antibiotic therapy before and after embolization (51,52). The need for bowel preparation before treatment is not definitive (51). In patients with carcinoid tumors (symptomatic or asymptomatic), treatment with octreotide before embolization is important to limit carcinoid crisis caused by hormonal dumping from tumor necrosis after embolization (54,69). Bevacizumab should be discontinued for 4–6 weeks prior to treatment, as its concomitant use with transarterial chemoembolization has been associated with severe septic and vascular adverse events without improved clinical outcomes (70).

Table 4. Child-Pugh Scoring System (58)

Variable	1	2	3
Encephalopathy	Absent	Mild-moderate	Severe-refractory
Ascites	Absent	Mild	Severe
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3

Note–A score of 5–6 represents Child-Pugh class A disease, 7–9 represents class B disease, and 10–15 represents class C disease.
INR = international normalized ratio.

Treatment Technique

Transarterial chemoembolization and embolization are performed after catheterization of the hepatic arteries according to standard angiographic principles previously described (32). Technical aspects of treatment planning, tumor targeting, treatment monitoring, therapy control, and assessment of treatment response have been previously described (32).

Procedural Considerations

Given the frequency of variant hepatic arterial anatomy, arteriography may include study of the superior mesenteric artery in addition to the celiac artery. However, arterial anatomy—including aberrant supply—is usually well depicted on contrast-enhanced cross-sectional imaging obtained before the procedure. Angiography should be performed through the portal venous phase to ensure no change in the patency of portal venous structures from imaging obtained before the procedure, although short-term correlation between cross-sectional imaging and angiographic findings is high (71). Practice patterns for level of catheter selection range from subsegmental to lobar embolization, depending on the type and number of tumors, underlying liver disease, institutional protocols, operator preference, and tool availability. Treatment guidelines based on expert consensus panels suggest that segmental or subsegmental therapy is favored over lobar treatment (72,73). Treatment of the entire liver in 1 session is associated with greater deterioration of liver function (74). Lobar treatment is thus more acceptable in cases of multifocal disease, assuming adequate liver function (73). As intraprocedural cone-beam CT has proven useful for visualization of tumors and tumor-feeding arteries as well as assurance of therapy completeness (75), this technology may be used to enhance tumor targeting during transarterial chemoembolization and embolization. When treatment has led to permanent occlusion of the native hepatic arteries, several collateral pathways have been treated with clinical success, including the inferior phrenic (76), internal mammary (77), intercostal (78), and renal capsular (79) arteries. If these collateral arteries have communication with cutaneous vessels, embolic protection with metallic coils may limit the risk of cutaneous ischemic ulceration (80). Treatment should avoid the cystic artery if possible. If tumor treatment is not feasible without including the cystic artery in the infused area, transarterial chemoembolization or embolization may still be performed, as the principal risk of treatment of the cystic artery is pain, which may potentially lengthen hospital stay but does not result in significant risk to the gallbladder itself (81). Intermittent infusion of aqueous lidocaine between aliquots of chemotherapy emulsion decreases pain after embolization (82).

Postprocedure Considerations

Postprocedure Care. Although patients may remain hospitalized for overnight observation following transarterial chemoembolization, same-day hospital discharge may be safe as well (83,84). Narcotic agents should be available for pain control (eg, via a patient-controlled analgesia pump). Antiemetic medications may be continued as long as needed. Many practitioners recommend antibiotic treatment for 3–7 days following transarterial chemoembolization or embolization to cover gram-negative enteric pathogens. Data regarding the need for routine antibiotic prophylaxis are mixed, without evidence of benefit (85). If a patient has a disrupted sphincter of Oddi, antibiotic treatment should be continued for approximately 2 weeks (51). Even with extended administration of antibiotics, data for this group of patients are limited, and operators should proceed with caution in the setting of any biliary abnormality.

Antibiotics may be administered orally as soon as patients can tolerate a normal diet.

Postprocedure Imaging. IR participation in patient follow-up, both in the hospital and at imaging surveillance, is an integral part of transarterial therapy. Follow-up CT or MR imaging examination should be performed approximately 4 weeks after all tumor-bearing areas have been treated, with response assessment using validated radiologic response criteria (86–89); PET is not routinely recommended by current cancer treatment guidelines. If treatment of both liver lobes is planned, imaging between treatment sessions may be performed based on operator preference and relative biologic behavior of the tumor. Signs of tumor necrosis include ethiodized oil uptake on CT (90) and disappearance of arterial-phase contrast enhancement that was present prior to treatment on CT or MR imaging (91). There is a paucity of literature regarding follow-up after transarterial chemoembolization or embolization of hypovascular tumors lacking arterial phase contrast enhancement. In this circumstance, use of necrosis response assessment strategies, such as the European Association for the Study of the Liver (88) and modified Response Evaluation Criteria for Solid Tumors (89) schemes, may not be appropriate. Gross enlargement of a lesion or nodular enhancement on portal vein or delayed-phase imaging has been described as evidence of residual or recurrent tumor following thermal ablation of tumors without initial arterial-phase contrast enhancement (92). Similar findings may be present in the setting of residual or recurrent disease following transarterial chemoembolization or embolization. Patients without viable disease at initial follow-up should undergo follow-up surveillance imaging every 3–6 months.

Repeat LRT. Liver tumors require further treatment when residual or new disease is detected. Treatment is typically repeated on an "on demand" basis in the setting of viable tumor on follow-up cross-sectional imaging (93) rather than at scheduled intervals, as administration of excessive therapy has been associated with poor outcomes (94). Cases of high disease burden—as occurs in infiltrative disease—may warrant scheduled or programmed therapy given the inability for complete tumor treatment in a single transcatheter therapy session. Scoring systems—such as the Assessment for Retreatment with TACE score—have been developed to help guide retreatment decisions (95). Patients with symptomatic NET liver metastases should be retreated if the initial treatment does not result in symptomatic improvement or when symptoms recur. Before additional transarterial chemoembolization or embolization sessions, patients should be clinically evaluated to ensure that they continue to meet eligibility criteria. Laboratory parameters and functional status should be rechecked.

Clinical Outcomes in Different Tumors

Hepatocellular Carcinoma. Although initial randomized trials evaluating transarterial chemoembolization versus symptomatic treatment had disappointing results, 3 well-constructed randomized trials published in 2002–2003 demonstrated significantly improved survival with transarterial chemoembolization and embolization (96–98). After these seminal studies established this LRT as the standard of care treatment for BCLC stage B disease, additional clinical investigations and meta-analyses have continued to support the favorable outcomes of conventional transarterial chemoembolization in HCC treatment in contemporary clinical practice (8–11,99). A 2016 systematic review of conventional transarterial chemoembolization for treatment of HCC included 10,108 patients spanning 101 studies and reported an objective tumor response rate of 52.5%, median time to progression (TTP) of 3.1–13.5 months, and median overall survival (OS) of 19.4 months (70.3%, 40.4%, and 32.4% 1-, 3-, and 5-year survival) (100).

DEE transarterial chemoembolization provides sustained release of chemotherapy associated with favorable pharmacokinetics and reduced systemic drug and may improve drug delivery compared with conventional transarterial chemoembolization. The efficacy of DEE transarterial chemoembolization for HCC treatment was validated in a 2010 prospective multicenter randomized controlled trial that found no statistical difference in tumor response at 6 months after treatment between DEE transarterial chemoembolization and standard of care conventional transarterial chemoembolization (101). Subsequent clinical studies have further substantiated DEE transarterial chemoembolization safety and efficacy (102-105), collectively confirming this LRT to be an accredited HCC treatment option.

Intrahepatic Cholangiocarcinoma. Although most ICC studies are retrospective, nonrandomized, heterogeneous in procedural methodology, and small in sample size, transarterial chemoembolization has shown promise in the treatment of ICC. A 2013 meta-analysis reviewed the outcomes of 542 patients with surgically unresectable ICC who underwent chemotherapy-based transarterial LRT across 16 studies (106). This study showed a median survival of 15.7 months compared with the reported survival following palliative therapy of 5–13 months, representing a likely survival benefit of 2–10 months (17,106); 1-year OS was 58% (106). Nearly 77% of subjects demonstrated disease control (partial response plus stable disease) at follow-up imaging using Response Evaluation Criteria for Solid Tumors criteria (106). Although 30-day mortality rate was very low (0.7%) (106), the adverse event rate was high (18.9%), with major toxicities spanning hepatic insufficiency, liver abscess, and sepsis (106).

Metastatic NET. Clinical outcomes of transarterial chemoembolization and embolization for treatment of metastatic NET support the benefit of LRTs for this disease process. Median survival time ranges from 39.6 to 80 months, and hormonal symptoms resolve in 60%–90% of cases (107). Although early reports of DEE transarterial chemoembolization for metastatic NET suggest efficacy (108–110), initial safety results suggest that application in a research protocol may be most sound until more robust data are obtained (111).

CRC Liver Metastases. Early studies investigating use of conventional transarterial chemoembolization in the salvage treatment of CLM reported median OS rates ranging from 9 to 14 months from the time of LRT, but they lacked control groups and employed chemotherapeutic agents that do not reflect standard regimens for CRC (112–114). In a 2011 multicenter, multinational single-arm study, Martin et al (115) described the outcomes of 55 patients who failed systemic chemotherapy and were then treated with 99 sessions of drug-eluting beads loaded with irinotecan (DEBIRI) transarterial chemoembolization, resulting in a response rate of 75% at 12 months, progression-free survival (PFS) of 11 months, and OS of 19 months. In a 2012 randomized controlled trial comparing DEBIRI with FOLFIRI, Fiorentini et al (55) showed improved median OS for the DEBIRI group (22 months vs 15 months, $P = .031$). Subsequent small, single-arm studies have reported use of DEBIRI in conjunction with oral 5-fluorouracil and capecitabine (56) or the biologic agent cetuximab (116). In a 2015 multicenter randomized controlled trial, Martin et al (57) reported on the addition of DEBIRI to systemic FOLFOX and bevacizumab as a first-line treatment of CLM in 70 patients (first 10 patients comprised the pilot group followed by 60 patients randomly assigned to FOLFOX and bevacizumab with or without DEBIRI). The addition of DEBIRI to FOLFOX/bevacizumab improved overall and target-disease response rates, median hepatic PFS (17 months vs 12 months, $P = .05$), and rates of downsize to resection (35% vs 6%, $P = .05$).

Metastatic Uveal Melanoma. Tumor response after cisplatin, fotemustine, or bis-chloroethyl-nitrosourea conventional transarterial chemoembolization ranges from 6% to 39% (29,117,118), and median OS after transarterial chemoembolization rarely exceeds 10 months (31,117–120). However, transarterial chemoembolization responders typically have longer reported OS than nonresponders (15–22 months vs 5–9 months) (117,119,120). Additionally, the extent of liver replacement is associated with median OS in multiple studies, with $< 25\%$, 25%–50%, 50%–75%, and $> 75\%$ tumor liver volume having median OS rates

reported at 14–17 months, 5–6 months, 5–7.3 months, and 2.1–5.6 months (28,29,117,118,120). In a retrospective review of 53 consecutive patients treated with immunoembolization (34 patients) or bis-chloroethyl-nitrosourea transarterial chemoembolization (19 patients), both median OS (20.4 months vs 9.8 months) and systemic PFS (12.4 months vs 4.8 months) were significantly longer with immunoembolization (31). A 52-patient randomized, double-blind phase 2 trial comparing immunoembolization with ethiodized oil and gelatin sponge embolization demonstrated an increased systemic immune response that correlated to increased PFS as well as median OS of 21.5 months (121).

Other Liver Metastases. Soft tissue sarcomas such as gastrointestinal stromal tumor, breast carcinoma, and gynecologic malignancies have been successfully treated with transarterial chemoembolization, and patient survival appears to be improved compared with historical controls (122–125). Randomized prospective data are not available, however.

Clinical Outcomes in Different Procedures

Conventional Transarterial Chemoembolization versus Transarterial Embolization for HCC. Randomized trials for treatment of HCC comparing protocols with and without chemotherapy are limited. A 289-patient, prospective randomized controlled trial of ethiodized oil transarterial embolization with or without concomitant doxorubicin demonstrated no difference in 3-year survival rate (33.6% vs 34.9%, $P > .05$) but revealed a significantly greater reduction in α-fetoprotein in the doxorubicin group (126). A 46-patient, prospective randomized controlled trial comparing ethiodized oil, gelatin sponge, and cisplatin conventional transarterial chemoembolization with ethiodized oil and gelatin sponge transarterial embolization showed no survival differences (52.5% and 26.2% vs 72.5% and 39.5% 1- and 2-year survival rates, $P > .05$) (127). A prospective randomized trial with 3 arms comparing survival with transarterial chemoembolization versus embolization versus symptomatic treatment (96) showed a significant survival benefit for transarterial chemoembolization versus symptomatic treatment, and the trial was halted. At the time of trial termination, transarterial embolization had shown similar survival to conventional transarterial chemoembolization. The trial was not continued to determine whether transarterial embolization 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 (128). A complicating factor in determining the gold standard transarterial therapy is that chemotherapy regimens vary from trial to trial. No ideal chemotherapeutic agent has been identified. A definitive statement regarding treatment with or without chemotherapy cannot be made without an adequately powered prospective trial.

DEE Transarterial Chemoembolization versus Transarterial Embolization for HCC. Although trials of DEEs loaded with doxorubicin and other agents are emerging (102), transarterial embolization has established effectiveness in the treatment of HCC (13,14). To date, there are few comparative studies of DEE transarterial chemoembolization and embolization for HCC treatment. A 2010 single-center, 84-patient, prospective randomized trial revealed that treatment with doxorubicin-loaded DEEs resulted in a longer TTP than transarterial embolization (42.4 weeks vs 36.2 weeks, $P = .008$) (129). A 2010 single-center, 16-patient, retrospective study showed a higher rate of complete histologic necrosis on liver explant among 8 patients treated with epirubicin-loaded DEE transarterial chemoembolization versus transarterial embolization (77% vs 27%, $P = .043$) (130). A 2016 single-center, 101-patient, prospective randomized trial demonstrated no difference in median PFS (2.8 months vs 6.2 months, $P = .11$) and OS (20.8 months vs 19.6 months, $P = .64$) between doxorubicin-loaded DEE transarterial chemoembolization and embolization (131).

Conventional Transarterial Chemoembolization versus DEE Transarterial Chemoembolization for HCC. Chemotherapy-eluting DEEs afford potential advantages of prolonged drug delivery, increased intratumoral chemotherapy concentrations, and decreased peak systemic concentrations of chemotherapy compared with conventional transarterial chemoembolization. Prospective clinical trials suggest that DEE transarterial chemoembolization results in fewer adverse events than conventional transarterial chemoembolization. A phase II trial that randomly assigned patients to conventional transarterial chemoembolization or doxorubicin-loaded DEE transarterial chemoembolization with 300–500 μm microspheres demonstrated improved objective tumor response at 6 months after treatment and lower toxicity in the DEE transarterial chemoembolization arm for a subset of patients with more advanced disease (101). A randomized trial comparing conventional transarterial chemoembolization with doxorubicin-eluting 50–100 μm superabsorbent polymer microspheres reported fewer grade 3 or 4 adverse events in the DEE transarterial chemoembolization arm (104).

It is unclear how DEE transarterial chemoembolization impacts longer-term outcomes such as TTP or OS. A prospective randomized study of 177 patients with BCLC stage A–C disease treated with conventional transarterial chemoembolization or doxorubicin DEE transarterial chemoembolization using 100–300 μm microspheres showed no difference in tumor response, TTP, or 1- or 2-year survival between the 2 arms, although pain after chemoembolization was less frequent and less severe in the DEE transarterial chemoembolization arm (103).

Transarterial Chemoembolization Combined with Percutaneous Thermal Ablation for HCC. Percutaneous radiofrequency (RF) ablation is a standard therapy for HCCs measuring ≤ 3 cm in diameter. Nonetheless, local tumor recurrence may occur and is more common for tumors > 2 cm. Occluding vasculature within and adjacent to HCC by performing transarterial chemoembolization prior to RF ablation is a proposed strategy to reduce convective heat loss via heat-sink effects and increase the effectiveness of RF ablation for intermediate sized (3.1–5.0 cm) or larger HCCs. This strategy has been evaluated in several prospective clinical trials. A meta-analysis of 8 randomized controlled trials suggests that combined transarterial chemoembolization and RF ablation confers a recurrence-free and OS benefit compared with RF ablation monotherapy for intermediate and large HCCs (132). No benefit was observed for combination therapy in the treatment of small HCCs (132).

Combination therapy of percutaneous microwave ablation and transarterial chemoembolization has been evaluated in small retrospective observational studies (133,134). Xu et al (135) compared outcomes of 139 patients with HCCs > 5 cm treated with transarterial chemoembolization monotherapy versus combination therapy consisting of transarterial chemoembolization followed by percutaneous microwave ablation approximately 1 week later. Although improved OS was observed in the combination therapy group, patients in the monotherapy group had greater baseline tumor burden and likely more advanced stage disease. Although results of combined transarterial chemoembolization and thermal ablation have been promising, further research is needed to determine whether transarterial chemoembolization combined with RF ablation or microwave ablation improves outcomes compared with transarterial chemoembolization alone for intermediate and large HCCs.

Transarterial Chemoembolization Combined with Systemic Therapy for HCC. Sorafenib is an oral multikinase inhibitor with effects against vascular endothelial growth factor receptors and other angiogenic and proliferative pathways. Two large randomized placebo-controlled trials demonstrated a survival benefit for a patient population that had predominantly Child-Pugh class A and BCLC stage C disease, though treatment-related adverse events occurred in $> 80\%$ (5,6). Transarterial chemoembolization–induced tumor ischemia is associated with upregulation of vascular endothelial growth factor expression; therefore, it has been proposed that concomitant sorafenib

may reduce tumor angiogenesis and recurrence after transarterial chemoembolization. A randomized placebo-controlled trial of DEE transarterial chemoembolization with or without concomitant sorafenib for patients with intermediate stage HCC and preserved liver function showed no unexpected adverse events from combination therapy but did not demonstrate clinical efficacy in the primary endpoint of TTP (136). A phase II single-arm study of concomitant DEE transarterial chemoembolization and sorafenib for advanced stage HCC found combination therapy to be adequately tolerated and associated with a 94% disease control rate at 6 months; the results suggest a benefit for combination therapy in patients with advanced stage HCC who have preserved performance status and liver function that must be validated with further investigation (137). Further research is needed to establish the appropriate role of combined systemic antiangiogenic and transarterial chemoembolization therapy in clinical practice.

ADVERSE EVENTS

Published rates for individual types of adverse events (**Appendix B**) are highly dependent on patient selection and may be based on series comprising several hundred patients, which is a volume larger than most individual practitioners are likely to treat. Generally, the adverse event–specific thresholds should therefore be set higher than the adverse event–specific reported rates listed in **Table 5**. It is also recognized that a single adverse event can cause a rate to cross above an adverse event–specific threshold when the adverse event occurs within a small patient volume, (eg, early in a QI program). In this situation, the overall procedure threshold is more appropriate for use in a QI program.

Transarterial chemoembolization and embolization related adverse events occur in approximately 10% of patients (32), and adverse events should be defined using a standardized scheme, such as the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 published by the US Department of Health and Human Services (138) or the SIR Adverse Event classification (**Appendix B**). Use of DEEs is relatively new, and understanding of toxicities related to this technique is evolving (105), especially with clinical implementation of smaller particle sizes. Published rates of specific adverse events are presented **Table 5**. Postembolization syndrome (fever, pain, and leukocytosis) by itself is not considered an adverse event, but rather an expected outcome of embolotherapy. Transarterial chemoembolization–induced hepatic arterial damage is also an unavoidable side effect of treatment, the principal repercussion of which is elimination of arterial access to tumor and limitation of LRT.

PROCEDURE TYPES OR SUBSETS

QI Definitions

- *Technical success* is defined as successful advancement of a catheter into a tumor vascular supply and transarterial therapy (selected chemotherapeutic and embolic agents) administration according to an investigator-designated plan (32).
- *Clinical success* is defined as technique effectiveness resulting in the desired clinical outcome (eg, effective palliation, bridging to transplantation, or tumor downstaging).
- *Technique effectiveness* is defined by response to treatment assessed at imaging follow-up at a prospectively defined time point (eg, 1–3 months after a treatment cycle) using standardized, validated radiologic response criteria (86–89).
- *Effective palliation* is defined by control or elimination of cancer-related symptoms (as in patients with symptomatic, hormone-secreting NETs) or by clinical outcome improvement quantified using standard oncologic measures such as OS, PFS, or TTP (as in tumors such as HCC and CLM).
- *Adverse events* are defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (32).

Table 5. Transarterial Chemoembolization and Embolization Adverse Events

Complication	Reported Rate (%)	Representative References	Suggested Threshold (%)
Technical adverse events			
Iatrogenic vessel dissection precluding treatment	< 1	(139)	1
Hepatic adverse events			
Liver failure	3–5	(140)	4
Liver infarction	< 1	(141)	1
Abscess, functional sphincter of Oddi	1–2	(142,143)	2
Abscess, biliary-enteric anastomosis, biliary stent, or sphincterotomy with premedication	0–15	(51,52)	10
Biloma requiring percutaneous drainage	< 1	(139)	2
Extrahepatic adverse events			
Surgical cholecystitis	< 1	(139,140)	1
Hematologic suppression (eg, anemia, thrombocytopenia, leukopenia)	7–23	(144)	15
Pulmonary arterial oil embolus	< 1	(140)	1
Gastrointestinal ulceration/hemorrhage	< 1	(140)	1
Contrast induced nephropathy or acute renal failure	3–10	(145–148)	7
Death within 30 days	0–4	(100,139,140)	4
Procedure side effects			
PES requiring extended hospital stay or readmission	6–31	(11,149)	10
Hepatic artery occlusion (owing to chemotherapy damage)	1–63	(150–152)	30
Radiation related adverse events			
Skin injury	< 1	(153,154)	1

PES = postembolization syndrome.

QI Considerations and Thresholds

Procedure Indication. The standard indication for transarterial treatment of hepatic malignancy is the presence of liver-dominant malignancy with adequately preserved hepatic function and patient performance status. The threshold for adherence to standard transarterial chemoembolization and embolization indications is 95%. When < 95% of procedures are performed for this indication, operators should consider reviewing the process of patient selection.

Technical Success. Technical success should be attainable in the vast majority of cases. The threshold for transarterial chemoembolization and embolization technical success is 95%. When technical success rates fall below this threshold, operators should consider reviewing institutional procedural methodology.

Clinical Success. To reach a clinical success threshold, individual operators should have tumor response rates and clinical outcomes (OS, PFS, TTP) comparable to those in the published literature in at least 50% of cases (Table 6), allowing for the fact that operators in clinical practice will encounter and treat patients with clinical presentations that are worse than allowed in clinical trials.

Adverse Events. The overall procedure threshold is 15% for the aggregate of serious adverse events, life-threatening or disabling adverse events, and patient deaths resulting from transarterial chemoembolization or embolization. Published rates for individual types of adverse events 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, it is recommended that adverse event–specific thresholds should usually be set higher than the particular reported rates listed in Table 5. It is also recognized that a single adverse event can cause a rate to exceed an adverse event–specific threshold when the adverse event occurs in a small patient cohort (eg, early in a QI program). In this situation, the overall procedure threshold is more appropriate for use in a QI program.

CONCLUSIONS

Transarterial chemoembolization and embolization are fundamental pillars of interventional oncology and have proven roles in the treatment of hepatic malignancies. Although transarterial chemoembolization and embolization methodology may vary by practice, diligent periprocedure care, attentive interventional technique, and thorough clinical follow-up will optimize success rates and diminish adverse event incidence to ensure high quality oncologic care. Additional relevant citations used to support the factual statements and numerical data presented in this work are listed in Appendix C (available online at *www.jvir.org*).

Table 6. Thresholds for Median Survival for Various Tumor Pathologies from Time of Transarterial Chemoembolization or Embolization

Tumor	Median Survival (months)	Representative References	Suggested Threshold (%)*
HCC	20	(8–11,13–15, 96–98,100)	50
ICC	15	(106),†	50
Metastatic NET	26	(107),*	50
CLM	10	(55–57,112–114,116)	50
Metastatic uveal melanoma‡	10	(31,117–120)	50
Metastatic sarcoma	19	(122,123)	50

CLM = colorectal carcinoma liver metastases; HCC = hepatocellular carcinoma; ICC = intrahepatic cholangiocarcinoma; NET = neuroendocrine tumor.
*Percent of cases that should achieve indicated median survival time.
†Including references therein.
‡Treatment with immunoembolization.

APPENDIX A. CONSENSUS METHODOLOGY

Reported adverse event–specific rates in some cases reflect the aggregate of adverse events of varying severities. Thresholds are derived from critical evaluation of the literature, evaluation of empirical data from Standards of Practice Committee members, and, when available, the National Benchmarks from the National Quality Registry for IR. Modified Delphi technique may be utilized to enhance effective decision making (155,156).

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APPENDIX B. SIR ADVERSE EVENT CLASSIFICATION

Adverse event description

A. Description narrative of adverse event (including sedation and anesthesia)

B. Adverse event severity assessment*: escalation of level of care

1. Mild adverse event: No therapy or nominal (nonsubstantial) therapy (postprocedural imaging performed and fails to show manifestation of adverse event); near miss (eg, wrong site of patient prepared, recognized and corrected prior to procedure, wrong patient information entered for procedure);
2. Moderate adverse event: moderate escalation of care, requiring substantial treatment eg, intervention (description of intervention and result of intervention) under conscious sedation, blood product administration, extremely prolonged outpatient observation or overnight admission after outpatient procedure not typical for the procedure (excludes admission or hospital days unrelated to adverse event);
3. Severe adverse event: marked escalation of care, ie, hospital admission or prolongation of existing hospital admission for > 24 h hospital admission that is atypical for the procedure, inpatient transfer from regular floor/telemetry to ICU or complex intervention performed requiring general anesthesia in previously nonintubated patient (generally excludes pediatrics or in circumstances where general anesthesia would primarily be used in lieu of conscious sedation, eg, in mentally challenged or severely uncooperative patients);
4. Life-threatening or disabling event, eg, cardiopulmonary arrest, shock, organ failure, unanticipated dialysis, paralysis, loss of limb or organ;
5. Patient death or unexpected pregnancy abortion

**The SIR Adverse Event Severity Scale is intended to approximate the surgical Clavien-Dindo scale and the National Cancer Institute CTCAE scale. The SIR scale is tailored towards the procedures and adverse events encountered in IR practices. The grading of interventional oncology adverse events can selectively incorporate relevant adverse event grading definitions published in the current CTCAE for oncologic interventions, which may be particularly relevant in the context of research publications. All adverse events occurring within 30 days of a procedure should be included in the adverse event description and analysis, regardless of causality, in the interest of objectivity. The adverse event scale itself does not assess operator performance.*

Modifier: M = multiple adverse events, each of which is counted and evaluated separately if possible. The preceding part refers to adverse event description and severity characterization. It is suitable for scientific use (eg, presentations, publications) as well as for adverse event reviews within a practice, practice group, facility, or specialty.

The following part pertains to adverse event analysis. It is designed to enable a confidential and constructive review of any adverse event within an IR practice or practice group. Applicability for scientific publications is limited and there is none for other public use. The following content is meant to provide a strictly confidential, legally nondiscoverable, nonpunitive, objective, consistent, and clinically constructive analytic guide that may result in QI measures to advance the quality of patient care in IR.

Adverse Event Analysis

A. Causality
   - Category 1. Adverse event not caused by the procedure
   - Category 2. Unknown whether adverse event was caused by the procedure
   - Category 3. Adverse event caused by the procedure

B. Patient and procedural risk modifier

Risk modifier:
   - Category 1. High risk patient AND technically challenging procedure
   - Category 2. High risk patient (eg, American Society of Anesthesiologists 4, uncorrectable coagulopathy, poor functional status [ECOG 3 and 4], polypharmacy/polyintravenous therapy and transfusion, septicemia, hemodynamic instability, recent catastrophic event/ICU admission/major surgery or interventions) OR low risk patient and technically challenging procedure (eg, transjugular intrahepatic portosystemic shunt with occluded portal vein, percutaneous biliary drain placement in nondilated biliary system)
   - Category 3. No modifier

C. Adverse event preventability
   - Category 1: Rarely preventable, ie, well described and "typical" for the procedure and occurring despite adequate precautionary and preventive measures
   - Category 2: Potentially preventable
   - Category 3: Consistently preventable, eg, inappropriateness of procedural indication (may use checklist, see Appendix*)

D. Adverse event management
   - Category 1: Most operators would have handled the adverse event similarly;
   - Category 2: Some operators would have handled the adverse event differently;
   - Category 3: Most operators would have handled the adverse event differently;

Appendix*

Consistently Preventable Event:
Wrong patient
Absolute contraindication for procedure
Wrong side for procedure
Wrong procedure
Wrong medication/contrast agent/blood product (dose/administration route)
Exposure to known allergens
Intraarterial placement of catheter meant to be intravenous or nonvenous placement of inferior vena cava filter
Ferromagnetic devices contraindicating performance of MR imaging
Failure to follow up or communicate laboratory, pathology, or radiology results
Use of known malfunctioning equipment or patient monitor system
Lack or inappropriate use of monitoring equipment during sedation

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SIR DISCLAIMER

APPENDIX C

The following references represent additional relevant citations used to support the factual statements and numerical data presented in this work (1–119).

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