STANDARDS OF PRACTICE

Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy

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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.

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

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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 frontline 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.