Research Reporting Standards for Radioembolization of Hepatic Malignancies

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ABBREVIATIONS

CR = complete response, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, PD = progressive disease, PFS = progression-free-survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, SPECT = single photon emission computed tomography, TTP = time-to-progression, WHO = World Health Organization

RATIONALE

Radioembolization is a field of interventional oncology that continues to evolve. The number of institutions adopting this approach is increasing; this trend is paralleled by a greater number of research investigations reported in the peer-reviewed literature. Therefore, developing standardization and reporting criteria therefore becomes of para-

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Table 1. Brief Description of Available Radioembolic Devices

Name	TheraSphere	SIR-Spheres	^{131}I-Lipiodol
Radionuclide (symbol)	Yttrium 90 (^{90}Y)	Yttrium 90 (^{90}Y)	Iodine 131 (^{131}I)
Half-life (h)	64.2	64.2	192.5
Carrier	Glass microspheres	Resin microspheres	Iodized oil
Carrier size (μm)	20–30	20–60	NA

Note.—HDD = 4-hexadecyl-1,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol; GMS = glass microspheres.

mount importance in order to facilitate clear communications between investigators. The vehicle of a standards document provides the framework for reporting various aspects of the technique, including classification of methodology, descriptors of toxicities and complications, imaging guidance, and appropriate terminology that require specific attention when reporting clinical studies. It is the standpoint of the group that adherence to the recommendations will facilitate the main objective: improved precision and communication for reporting the various aspects of radioembolization. This approach should translate to more accurate comparison of data across centers and, ultimately, to enhanced research methodology.

INTRODUCTION

Primary Liver Tumors

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver; its incidence is increasing worldwide. It ranks as the sixth most common tumor and third most common cause of cancer-related mortality (1,2). Primary liver tumors include HCC and intrahepatic cholangiocarcinoma. Surgical resection is preferred over transplantation and is considered potentially curative in patients with resectable HCC and normal liver function (3). Transplantation is considered the gold standard for patients with unresectable HCC and whose disease is within the Milan criteria (4). Resection and transplantation have limited roles, given advanced disease (chronic liver disease and/or tumor extent) at presentation and limited organ availability (5–7). Chemoembolization and radiofrequency ablation represent standard therapies in treating patients and serve as a bridge to transplantation in selected patients (8,9). Radioembolization has an emerging role in "bridging" patients within criteria by delaying tumor progression. It has also been shown to downstage disease beyond the Milan, to within, transplant criteria (10–12). A recent study has demonstrated that radioembolization leads to longer time-to-progression and better toxicity profile when compared with chemoembolization (13). Patients with macrovascular tumor involvement have also exhibited evidence of clinical benefit after radioembolization (14).

Secondary (Metastatic) Liver Tumors

Worldwide, secondary liver tumors are more common than primary liver tumors (15). Secondary liver tumors are managed by both surgical and nonsurgical methods. The role of radioembolization for secondary liver tumors is promising and it has been shown to be safe and efficacious in patients with secondary liver tumors from colorectal carcinoma, neuroendocrine tumors, and other primary tumors (16–23).

Requirement for Research Reporting Standards for Radioembolization of Hepatic Malignancies

The International Working Group on Image-guided Tumor Ablation published a document entitled "Image-guided tumor ablation: standardization of terminology and reporting criteria" (24). The main objective was "improved precision and communication in this field that leads to more accurate comparison of technologies and results and ultimately to improved patient outcomes" (24). The publication of this document led to the publication of a document focused on catheter-directed therapies entitled "Transcatheter therapy for hepatic malignancy: standardization of terminology and reporting criteria" (25). A transcatheter therapy that is believed to have potential benefit from standardization of terminology and reporting criteria is radioembolization. This therapy is commonly used for patients diagnosed with primary and secondary liver malignancies. A comprehensive document standardizing the indications, techniques, multimodality treatment approaches, and dosimetry has been presented previously by the Radioembolization Brachytherapy Oncology Consortium (26).

The initial goals of the Working Group's proposal for standardization fall in line with the initiative of the Society of Interventional Radiology (SIR), which promotes interventional oncology. Along these lines, SIR's Technology Assessment Committee has been charged with reviewing and commenting on the standardization of terminology and reporting criteria. Accordingly, the document has been modified in an attempt to align its contents with prior SIR standards and to address additional issues that have been raised by the Technology Assessment Committee. In essence, this independent review and ratification by the SIR Technology Assessment Committee of the previous reports represents a continuation of the collaborative initiative to consolidate and unite all investigators and clinicians practicing interventional oncology by providing a common language to describe therapies and outcomes (24,25). Recognizing that the management of patients with liver tumors requires a multidisciplinary approach, it is recommended to use terms that are in accordance with all disciplines in-

^{188}Re HDD*-Lipiodol	^{32}P-GMS	Milican	^{166}HoMS
Rhenium 188 (^{188}Re)	Phosphorus 32 (^{32}P)	Holmium 166 (^{166}Ho)	Holmium 166 (^{166}Ho)
16.9	342.7	26.8	26.8
Iodized oil	Glass microspheres	Chitosan	Poly (L-lactic acid)
NA	46–76	NA	25–35

volved. The details and definitions reported in the prior documents pertaining to radioembolization have been incorporated into the present document. This document is designed for reporting research and is not intended for clinical procedural notes on individual patients.

TERMINOLOGY AND DEFINITIONS

Although substantial technical jargon and marketing terminology appear in the peer-reviewed medical literature, these should not be used. Radioembolization is an image-guided transcatheter tumor therapy. Radioactive materials (radionuclide embedded in the carrier, attached to carrier surface, or in suspension with the carrier) are injected via feeding vessel(s) to the tumor(s) in an attempt to achieve cell death by delivering a high dose of focused radiation to the tumor. It is advised to use "radioembolization" instead of terms like "selective internal radiation therapy" or "transarterial radionuclide therapy."

Description of Device

The device manufacturer with the brand name of the device should be reported once in the Methods section. Subsequently treatment should be reference by the agent (eg, yttrium-90 [^{90}Y], iodine-131 [^{131}I], holmium-166 [^{166}Ho]). **Table 1** presents a brief overview of the available radioembolic devices worldwide. The following details also require description.

Radionuclide

Presently, the following radionuclides are available: ^{90}Y (TheraSphere [MDS Nordion, Ottawa, Ontario, Canada] and SIR-Spheres [Sirtex Medical, Lane Cove, Australia]), ^{131}I (Lipiocis; CIS Bio International, Gif sur Yvette, France), rhenium-188 (^{188}Re), phosphorus-32 (^{32}P) (BrachySil; pSividia, Watertown, Massachusetts) and ^{166}Ho. It is recommended to present these radionuclides as the name of the element (not necessarily capitalized) with a dash followed by the mass number or as a symbol with the mass number as a left-hand superscript to the symbol (eg, yttrium-90 or ^{90}Y). The half-life should be presented in standard units of time (hours instead of days).

Carrier

It is also important to appropriately report the carrier of the radionuclide. Iodized oil, chitosan, and microspheres have been used as carriers for the radionuclides. Furthermore, the constituents of the microspheres (ie, resin or glass) should be described. The range of particle size (per the package insert) may be reported. As a result of the development of new radioactive materials, studies comparing different devices may be seen in the future. Thus, when reporting outcomes it is recommended to describe the device early in the manuscript, with emphasis on the radionuclide and the carrier, and define the abbreviations/terms that will be used for the device(s).

Procedure Terms

It is preferred to use the term "procedure" rather than "operation" (24). A "procedure" refers to a single patient encounter for treatment of liver tumor(s). The term "treatment session" is synonymous with "procedure" but it is recommended to choose only one of these terms and use it uniformly throughout the manuscript. Multiple vials may be injected in one treatment session. The term "treatment cycle" consists of all procedures required to complete treatment of the tumor-bearing portion of the liver (not including pretreatment angiography). If a patient has bilobar disease, patients may need two procedures, constituting one treatment cycle. Therefore, a treatment cycle has been completed when all known disease has been treated. It is advised to use the term "progression" to refer to the appearance of new tumor (hepatic or extrahepatic) and for the reappearance of tumor in a previously treated area (local progression). A new treatment cycle may be initiated in case of progression.

POPULATION DESCRIPTION

Demographics

The number of patients in the study, the number of participating institutions, and patient numbers per institution must be provided. Age may be reported as a median and range. A baseline demographics table is of high importance, with appropriate presentation of parameters such as age, sex, and ethnicity.

Risk Factors and Comorbidities

The risk factors for the development of the liver tumors should be reported. In case of HCC, the etiology and incidence of chronic liver disease should be reported (eg, hepatitis B, hepatitis C, alcohol). "Cryptogenic cirrhosis" is a term to describe cirrhosis without a clear etiology. The number/percentage of

Table 2. Eastern Cooperative Oncology Group Performance Status

Status	Description
0	Asymptomatic and fully active
1	Symptomatic; fully ambulatory; restricted in physical strenuous activity
2	Symptomatic; ambulatory; capable of self-care; > 50% of waking hours are spent out of bed
3	Symptomatic; limited self-care; > 50% of time spent in bed, but not bedridden
4	Completely disabled; no self-care; 100% bedridden
5	Deceased

HCCs developing in the absence of cirrhosis should also be reported. In the case of secondary liver tumors, it is recommended to report the primary malignancy. Treatments used for the primary tumor should be reported (eg, history of chemotherapy/radiation therapy/surgery). It is also important to report any relevant comorbidities (eg, performance status > 0, cancer-related symptoms) (27).

Baseline/Pretreatment Evaluation

Physical examination. Physical examination should be performed, and the performance status should preferably be reported according to the Eastern Cooperative Oncology Group score (**Table 2**). Alternatively, the Karnofsky score may be used. Whenever possible, the quality of life should be evaluated using validated instruments (eg, Functional Assessment of Cancer Therapy–General questionnaire or Functional Assessment of Cancer Therapy–Hep questionnaire for patients with HCC) at baseline and during each follow-up encounter.

Baseline laboratory values. These should include complete blood counts, prothrombin time/International Normalized Ratio, liver function tests, and tumor markers (eg, α-fetoprotein for HCC). At minimum, baseline bilirubin values and tumor marker values should be reported in one of two formats: (i) stratified by cutoff values into low or high groups (the rationale behind choosing these cutoff values should be clearly stated in the Methods section) or (i) as medians with 95% CIs.

Imaging findings. Imaging modalities including ultrasound, computed tomography (CT), magnetic resonance (MR) imaging, and functional imaging (positron emission tomography with and without CT attenuation correction, and single photon emission CT [SPECT]) are used to help diagnose the liver tumor and help determine whether patients are suitable candidates for this procedure. It is important to report the diagnosis of the liver tumor and to clearly define the diagnostic criteria used (ie, imaging, biopsy, or tumor markers). The distribution (unilobar/bilobar), number (eg, solitary or multifocal, with optional substratification of multifocal tumors), and size of tumors (stratified or median with 95% CI), and the presence of vascular invasion and/or extrahepatic metastases should be reported (28). Caution should be exercised when reporting extrahepatic metastases in the form of lymphadenopathy in HCC; enlarged physiologic lymph nodes may be seen, particularly with hepatitis C–induced cirrhosis. The Bismuth/Couinaud segmentation system should be preferred over other systems when describing the location of tumors (29).

Measurement of Disease Severity

Primary liver tumors. Staging should be performed according to accepted staging systems for the disease. In the case of HCC, in which there is usually coexisting liver cirrhosis, it is also recommended to calculate the Child–Turcotte–Pugh score and report the classes. Some commonly used staging systems for HCC are the Okuda, Barcelona Clinic Liver Cancer, Cancer of the Liver Italian Program, and United Network for Organ Sharing staging systems (30). The Child–Turcotte–Pugh class assesses liver function and should be reported (31). Furthermore, it is recommended to report findings based on a staging system that incorporates tumor characteristics only (eg, United Network for Organ Sharing staging system) or both liver function and tumor characteristics (eg, Barcelona Clinic Liver Cancer staging system) (32). **Table 3** outlines the most commonly used classification systems for HCC. We can not mandate the use of one staging system over another as a result of limited data comparing the various staging systems (33,34).

Secondary liver tumors. Given the numerous types of liver metastases that might be treated, it is impractical to mandate staging based on all tumor types (eg, tumor/node/metastasis staging for colorectal cancer). It is, however, advised to stratify the study population by the presence or absence of extrahepatic disease at time of treatment as well as any exposure to systemic therapy. Stage at initial presentation of colorectal metastases may be reported.

Indications of Treatment

Patients with unresectable/inoperable liver tumors and liver-dominant disease are candidates for radioembolization. The indications and the absolute/relative contraindications may also be reported.

Method of Treatment Assignment

Given the intra- and interinstitutional variability, it is impossible to strictly predefine a patient population that would be offered radioembolization. Thus, a brief description of the reason for choosing radioembolization over other treatments should be included. The intent of the therapy should be stated (eg, downstaging/bridging to curative therapies such as transplantation, palliation, or prolongation of survival).

Inclusion/Exclusion Criteria

The Materials and Methods section should provide detail on the inclusion/exclusion criteria for the study. These details

need to be explicit if the study uses prospective subject accrual. If applicable, a flowchart showing the stepwise selection (ie, exclusion) process starting from the source population to the study population should be presented. Exclusion may be done on the basis of advanced tumor characteristics (eg, extrahepatic metastases) and liver dysfunction (eg, bilirubin level greater than normal, > 2.0 mg/dL). This needs to be appropriately reported.

Other Treatment(s)

All previous systemic and locoregional therapies that the patient has received for the liver tumor need appropriate description; this is important for context. Prior/concomitant therapy is more common in patients with secondary rather than primary liver tumors. When possible, prior/concomitant/subsequent systemic and locoregional therapies should be reported, including (i) nature of additive therapy, (ii) information on whether the additive therapy was performed as a part of a predefined protocol, (iii) rationale and (iv) timing of additive therapy, and (v) information on whether treatment was first-, second-, or third-line in nature. These specifications are required as additive therapies represent a confounding variable that may alter treatment effectiveness and may also have a role in extended survival or, alternatively, the development of complications. The panel recognizes the controversy over the definition of a line of systemic therapy. As a result, investigators are encouraged to define a line of systemic therapy for the purposes of reporting their study. Alternatively, reporting exposure to the cytotoxic chemotherapies (5-fluorouracil, oxaliplatin, irinotecan) and cytostatic biologic agents (eg, bevacizumab, cetuximab, panitumumab) separately is also acceptable.

TREATMENT DESCRIPTION

Preprocedure Angiography

The pretreatment (ie, planning) angiography is an important step in radioembolization; this is discussed in detail in comprehensive manuscripts (35–40). The meticulous mapping of the vascular anatomy helps the interventional radiologist performing the procedure to (i) identify the vascular supply of the tumor and (ii) identify and coil-embolize vessels that may lead to aberrant deposition of the radioembolic material. There is a new concept of flow redistribution (ie, occlusion intrahepatic vessels before radioembolization to cause redistribution of flow) that is being advocated by certain centers; if this technique is used, it should be reported (38,41). Therapy control is defined as the intraprocedural adjustments to increase safety/efficacy of the procedure (25). The embolization of nontarget vessels has been described as "therapy control" by Brown et al. (25). However, as the pretreatment angiography is typically performed before the procedure in case of radioembolization, therapy control is initiated before the procedure.

C-arm CT is now routinely used intraprocedurally in addition to digital subtraction angiography to determine vascular supply to the tumor (42–44). The committee recommends the use of this intraprocedural imaging technique but does not mandate its use as it is not a universally available technique (45).

Imaging with Technetium-99m Macroaggregated Albumin

Technetium-99m (^{99m}Tc) macroaggregated albumin imaging is performed at the time of the pretreatment angiography to quantify lung shunt fraction and identify splanchnic or nontarget flow (46,47). The advent of improved imaging protocols and implementation of SPECT with CT attenuation correction (SPECT/CT), will continue to play a role in evaluating the presence/lack of extrahepatic flow from ^{99m}Tc macroaggregated albumin arterial infusions (48). It is mandatory to describe whether static imaging, SPECT, or SPECT/CT was used for image interpretation.

The American College of Radiology Guidelines and Standards Committee of the Commission on Nuclear Medicine have stated in the American College of Radiology Practice Guidelines and Technical Standards that ^{99m}Tc macroaggregated albumin, in a dosage of 1–5 mCi (37–185 MBq), is introduced into the hepatic arterial perfusion catheter and infused slowly. Because quantifying the percentage of activity that is shunted from the liver to the lungs requires a high density of counts within the images, this committee recommends that the activity infused be at the higher end of the range and that the particle number be at least 500,000. Images of the abdomen are obtained immediately in the anterior (with and without external markers), left anterior oblique, left lateral, and posterior projections (49). The formula used for determining lung shunting should be reported (26,35).

Dosimetry

The details of dosimetry for different formulations have been discussed previously (22,35,38,50–52). The method/formula used to calculate the activity required should be presented in the manuscript, especially if these deviate from the package insert. It is important to understand the difference between dose (in Gy) and activity (in GBq or mCi). Finally, although it is recognized that some authors report dosimetry using the partition model (tumor–to–normal parenchyma hypervascularity ratio), doses to the entire treated tissue assuming uniform microsphere distribution should also be described. For example, investigators would report a median dose of 100 Gy to the overall tissue, assuming uniform distribution. In the same manuscript, investigators would also report 180 Gy to tumor and 40 Gy to normal parenchyma by using partition modeling. If partition modeling was used, the method used to obtain tumor–to–normal parenchyma relative flow should be described.

For dosimetry purposes, the Medical Internal Radiation Dose can be applied, whereas the Monte Carlo–based dosimetry protocols are still under investigation (53,54). The activity actually delivered should be checked, in particular for resin

Table 3. Classification Systems for HCC

Requirements for Calculation	Score	Class/Stage	Characteristics
Child–Pugh Classification System			
Total Bilirubin (mg/dL)			
< 2	1	A	Child–Pugh score 5–6
2–3	2		
> 3	3		
Serum albumin (g/dL)			
> 3.5	1	B	Child–Pugh score 7–9
2.8–3.5	2		
< 2.8	3		
INR			
< 1.7	1	C	Child–Pugh score ≥ 10
1.71–2.20	2		
> 2.20	3		
Ascites			
None	1		
Suppressed with medication	2		
Refractory	3		
Hepatic encephalopathy			
None	1		
Grade I/II (or suppressed with medication)	2		
Grade III/IV (or refractory)	3		
Okuda Staging System			
Tumor size			
≤ 50% of liver	0	I	0 Points
> 50% of liver	1		
Albumin (g/dL)			
≥ 3	0	II	1–2 Points
< 3	1		
Total bilirubin (mg/dL)			
< 3	0	III	3–4 Points
≥ 3	1		
Ascites			
Absent	0		
Present	1		
Cancer of the Liver Italian Program Staging System			
(a) Child–Pugh class			
A	0	0	Sum of a, b, c, and d
B	1		
C	2		
(b) Tumor morphology			
Uninodular and extension ≤ 50%	0	1	Sum of a, b, c, and d
Multinodular and extension ≤ 50%	1		
Massive or extension > 50%	2		
(c) AFP			
< 400	0	2	Sum of a, b, c, and d
≥ 400	1		
(d) PVT			
Absent	0	3	Sum of a, b, c, and d
Present	1		
		4	Sum of a, b, c, and d
		5	Sum of a, b, c, and d
		6	Sum of a, b, c, and d

(continued)

Table 3. Classification Systems for HCC (*Continued*)

Requirements for Calculation	Score	Class/Stage	Characteristics
Barcelona Clinic Liver Cancer Staging System			
Presence/absence of portal hypertension			
Bilirubin level (normal/elevated)			
Tumor characteristics (size, number, vascular invasion, extrahepatic spread)			
ECOG performance status			
Early stage		A1	Solitary tumor, no portal hypertension, normal bilirubin, ECOG PS 0, Child–Pugh A/B
		A2	Solitary tumor, portal hypertension, normal bilirubin, ECOG PS 0, Child–Pugh A/B
		A3	Solitary tumor, portal hypertension, elevated bilirubin, ECOG PS 0, Child–Pugh A/B
		A4	Up to 3 tumors all < 3 cm, ECOG PS 0, Child–Pugh A/B
Intermediate stage		B	Multinodular, ECOG PS 0, Child–Pugh A/B
Advanced stage		C	Vascular invasion or extrahepatic spread, ECOG PS 1/2, Child–Pugh A/B
End-stage		D	Any, ECOG PS 3/4, Child-Pugh C
UNOS Staging System			
Tumor characteristics (size, number, vascular invasion, extrahepatic spread)		T1	Solitary < 2 cm
		T2	Solitary up to 5 cm or ≤ 3 tumors all up to 3 cm
		T3	Solitary > 5 cm or ≤ 3 tumors with at least one > 3 cm
		T4a	≥ 4 Tumors
		T4b	Vascular invasion
		N/M	Extrahepatic metastases (nodal, N; other, M)

Note.—AFP = α-fetoprotein; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; PVT = portal venous thrombosis.

microspheres, as flow stasis sometimes prevents complete delivery of the prescribed activity. If termination of the procedure occurs as a result of flow stasis, the frequency and magnitude of when this occurs should be reported. The Medical Internal Radiation Dose is used for glass microspheres (ie, microembolic) dose calculations. It is important to also report the residual activity that remains in the device and the source vial. To summarize, the methods/formulas used to calculate the activity required and dose delivered should be presented in the manuscript, especially if these deviate from the package insert. Given the ongoing controversy over dosimetry for radioembolization, thorough reporting is important to create reproducibility between investigators.

Intraprocedural Imaging (Tumor Targeting)

The term "tumor targeting" is used to describe the step during radioembolization that involves placement of a catheter into the vessel supplying the tumor(s). The decision to use whole-liver, lobar (whole lobe perfused) or selective (≤ 2 hepatic segments perfused) approach is dependent on the patient's baseline characteristics (eg, baseline bilirubin and vascular anatomy) as determined by the pretreatment angiography (55). Targeting is principally accomplished with iodinated contrast agent injection under fluoroscopy and intraprocedural correlation with preprocedural imaging. This allows an appropriate level of vessel selection in any given patient.

Intraprocedural Treatment Monitoring

"Monitoring" is the term that is used to describe the process with which therapeutic effects are viewed during a procedure. Treatment monitoring includes extent of tumor coverage (may be evaluated with C-arm CT) in case of using radioembolic materials that use iodized oil as the carrier. If radioembolic materials that have microspheres as the carriers are used, antegrade flow in the artery of administration should be maintained to avoid nontarget delivery (25).

Technical Parameters to Be Provided for Publication

The authors need to provide sufficient details of the technique employed to permit duplication of the investigator's efforts. For radioembolization, the median dose (with 95% CI) to the treatment site and the lungs (per procedure and cumulative) should be reported. The number of sessions required to achieve technical success should be reported.

ASSESSMENT OF OUTCOMES

Currently, definitions of the appropriate length of follow-up and the time points indicative of technical success are not well established. Hence, specific guidelines need to be adhered to that depend on the type of the disease treated and the intended goal of the study. The following parameters represent treatment study goals: (i) technical success, (ii) technique effectiveness, (iii) tumor progression, and (iv) patient mortality.

Technical Success

The term "technical success" simply addresses whether the tumor was treated according to protocol and was addressed completely. Preliminary angiography can define target vessel(s) for treatment. Additionally, immediate posttreatment CT may show iodized oil retention in the tumor (if the radioembolic material uses iodized oil as the carrier). To confirm hepatic delivery of radioembolic materials, some operators may elect to perform a postradioembolization nuclear medicine scan using Bremsstrahlung imaging (56). As a result of the inherent properties of scatter imaging, the Bremsstrahlung image should not be taken into account for defining whether the procedure was technically successful. However, if performed, acquisition parameters, such as the energy window, and camera specifications, such as the collimator type, SPECT, or SPECT/CT, should be described. Image findings of additive value to information regarding target to nontarget delivery should be reported. The importance of the term "technical success" is to separate those patients in whom the protocol could not be executed completely (because of technical reasons or comorbidities) from those who were treated according to protocol. This is important when considering intent-to-treat analyses.

Failure of procedure. It is possible that the therapy may fail. This may be a result of lack of technical success leading to incomplete targeting of the tumor(s). Thus, identification of all vessels supplying the tumor at the pretreatment angiography is recommended. Technically unsuccessful therapy may also result from vascular spasm, injury, or flow stasis after the use of embolic devices. Failure of the procedure may also be seen during intraprocedural imaging (angiography showing stasis leading to cessation of further radioembolic delivery).

Technique Effectiveness (Clinical Success)

Distinction between "technical success" and "technique effectiveness" must be made. Effectiveness can only be demonstrated with appropriate follow-up. Thus, technique effectiveness may be evident in the following ways: (i) percentage of patients achieving an endpoint after a specified time has elapsed following treatment (eg, tumor response at the 1-month follow-up scan) and (ii) time to response as calculated by the Kaplan-Meier technique in which patients who did not show a response are censored. In cases in which multiple procedures were performed, the median/mean number should be reported. The therapeutic effect of radioembolization may be observed based on (i) imaging findings, (ii) changes in tumor markers, and (iii) pathologic findings (57–60). The committee recognizes that symptomatic response is important and may be reported; the subjective nature of this measure should be recognized as a limitation.

Radiologic findings. Investigators should avoid the use of the term "lesion" as it may be confused with the zone of induced necrosis on imaging (25). Recently, use of the term "primary index tumor" to assess response following locoregional therapy in HCC has been reported (61). It is important to report the imaging modalities (eg, contrast-enhanced CT or MR imaging) and the schedule of imaging (eg, 1 month after treatment and subsequently at every 3 months) used to assess response/progression. Investigators should recognize that, with time-to-progression (TTP) or progression-free-survival (PFS) endpoints, guidelines recommend obtaining scans every 6–8 weeks. The panel recognizes that this is not often feasible clinically but should be recognized as a limitation. There are statistical techniques that may be used to correct for this limitation. One example is backward correction, whereby an endpoint (such as TTP) is reporting as having occurred on scan −1 rather than the one on which the observation (ie, endpoint) is made. This will help minimize (but not eliminate) variable imaging time bias.

The following guidelines are widely accepted for the assessment of response by imaging. World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) guidelines measure the change in size of the index tumor(s) irrespective of the amount of necrosis seen. European Association for the Study of the Liver (EASL) guidelines measure change in the amount of enhancing (ie, viable) tumor only. These guidelines are outlined in **Table 4**.

WHO bidimensional guidelines: the WHO guidelines compare the posttreatment cross-product of the tumor to the baseline cross-product for calculating percent change in size (62,63). Complete response (CR) is defined as 100% decrease in size (complete disappearance of tumor[s]); partial response (PR) is defined as at least 50% decrease in size of the target tumor(s); and progressive disease (PD) is defined as greater than 25% increase in the cross-product from maximum response or appearance of new lesions. All others findings are defined as stable disease (SD) (59,64).

RECIST unidimensional guidelines: the RECIST guidelines use the maximum dimension of the tumor(s) to assess response. CR is defined as 100% decrease in size (ie, complete disappearance of tumor[s]); PR is defined as at least 30% decrease in the size of the target tumor(s); PD is defined as greater than 20% increase in size from maximum response or appearance of new lesions. All other findings are defined as SD (59,64,65). The RECIST 1.1 guidelines have recently been published, which recommend measurement of a fewer number of lesions ($\leq$ 2 per organ, $\leq$ 5 in

Table 4. Imaging Response Guidelines for HCC

Classification	Definition
	WHO Guidelines
CR	100% decrease in cross-product of target tumor(s)
PR	≥ 50% decrease in cross-product of target tumor(s)
SD	< 50% decrease to ≤ 25% increase in cross-product of target tumor(s)
PD	> 25% increase from maximum response of target tumor(s) and/or appearance of new lesions
	RECIST Guidelines
CR	100% decrease in maximum diameter of target tumor(s)
PR	≥ 30% decrease in maximum diameter of target tumor(s)
SD	< 30% decrease to ≤ 20% increase in maximum diameter of target tumor(s)
PD	> 20% increase from maximum response of target tumor(s) and/or appearance of new lesions
	EASL Guidelines
CR	100% decrease in amount of enhancing tissue in target tumor(s)
PR	≥ 50% decrease in amount of enhancing tissue in target tumor(s)
SD	< 50% decrease to ≤ 25% increase in amount of enhancing tissue in target tumor(s)
PD	> 25% increase in amount of enhancing tissue in target tumor(s) and/or new enhancement in previously treated tumor(s) warranting further LRT and/or appearance of new lesions

Note.—LRT = locoregional therapy.

total) compared with the original RECIST guidelines (66).

EASL necrosis guidelines: EASL necrosis guidelines, quantifying the amount of enhancing (and hence viable) tissue in the treated tumor, should also be reported. CR is defined as the absence of any enhancing tissue; PR is defined as the appearance of at least 50% decrease in amount of enhancing tissue from baseline. SD is defined as less than 50% decrease in amount of enhancing tissue (67). PD is recorded per EASL guidelines if new enhancement is identified in a previously treated tumor that may or may not have warranted further locoregional therapy or if new lesions develop. The modified RECIST guidelines have been recently published, which recommend unidimensional measurements of enhancing tissue (68). In a recent study, various combinations of EASL and WHO guidelines were studies for radiologic-pathologic correlation. The study concludes that EASLxWHO scoring system provides a simple and clinically applicable method of response assessment following locoregional therapies for hepatocellular carcinoma (65).

Positron emission tomography. Fluorodeoxyglucose positron emission tomography is a metabolic imaging technique that has a role in response assessment following radioembolization of metastatic hepatic tumors (15,69). Investigators may use this technique as long as their methods are appropriately described.

Changes in tumor markers. The posttreatment changes in tumor markers have been thought to correlate to response to treatment (70). A recent study has consolidated this belief following locoregional therapies (60). The cutoff value for the respective tumor marker used to stratify normal and elevated levels should be described, with appropriate attention to the rationale behind choosing this value. The percent change in serum levels of the tumor marker defined as response should be described. We can not mandate a value for the cutoff or percent change in serum tumor markers as there are currently no accepted values. However, as stated, the rationale behind choosing these investigator-defined values should be described in the Materials and Methods section of the manuscript. When discussing tumor marker response, further stratification by patients with or without extrahepatic disease may be considered.

Pathologic findings. It is not possible to examine all tumors for evidence of pathologic necrosis. The difference between pathologic and imaging findings must be stressed by the appropriate selection of terminology (24,25). However, necrosis on pathologic evaluation should be reported as "coagulation necrosis" or "pathologic necrosis" to minimize confusion (24,25,59). It is necessary to differentiate gross and histologic findings. Gross findings should include (i) evidence and quantification (or approximation and categorization) of coagulation necrosis seen in the treated tumor and (ii) size of the treated tumor(s). Sections of 1 cm or smaller of the treated tumor should be taken and slides should be prepared with routine hematoxylin and eosin stains for histologic examination (59). The details of how the pathologic necrosis was interpreted need to be addressed in the Materials and Methods section.

Tumor Progression

As there are no guidelines that focus on the imaging response/progression assessment following locoregional therapies, progression should be strictly defined in the materials and methods section. As described earlier, RECIST, WHO, and EASL guidelines define progression distinctly. Progression should incorporate development of new tumor, development of vascular invasion, expansion of preexisting vas-

cular invasion (eg, portal vein thrombosis in HCC), and development of extrahepatic metastases. The committee recognizes the difficulty in assessing extrahepatic (untreated) progression. Hence, we do not mandate separating the causes of progression but recommend differentiating progression in treated and untreated tumor, when possible. It is recommended to use the term "local progression" instead of "recurrence" as the latter is a term that is used to define reappearance of tumor following curative therapy (eg, radiofrequency ablation, resection, and transplantation). TTP is a commonly used parameter to assess technique effectiveness (61). The Kaplan-Meier technique should be used to calculate the TTP whereby progression (as defined by the investigator) is the endpoint. PFS may also be reported. The Kaplan-Meier technique is used to calculate PFS whereby progression or death (whichever occurs first) are taken as the endpoints.

Patient Mortality

Substantial patient mortality that is unrelated to the intervention is expected as a result of (i) cancer, (ii) underlying liver disease, and (iii) comorbidities. Mortality rates should not be confused with survival. Mortality rates are represented by the percentage of patients who have died at a specific time. "Overall survival" (in which the endpoint is death of any cause) and "disease-specific survival" (in which the endpoint is death from a specific cause, eg, tumor progression or liver failure) are calculated using the Kaplan-Meier technique. A brief overview of how to calculate these parameters is outlined in the subsequent section on statistical analyses. However, when reporting outcomes in HCC, it may be difficult to specifically identify the cause of death (eg, liver dysfunction, tumor progression). For tumor-related death, further subclassification (eg, differentiating death from hepatic or extrahepatic tumor progression) may be reported.

COMPLICATIONS

Complications following radioembolization may occur as a result of (i) toxic dose to normal hepatic parenchyma, (ii) toxic dose to extrahepatic tissue, (iii) complications of wire/catheter placement (eg, groin complications) and manipulation (eg, vessel dissection) during the planning or treatment angiogram, and (iv) side effects (71). The standard SIR grading system for complications of image-guided transcatheter tumor therapies is recommended (72). **Table 5** presents the SIR definitions and grading system of complications. Complications reported in accordance with the SIR standard table allow consistent categorization by complication severity. Adverse events secondary to treatment delivery should be defined by using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (or most recent version) (73). Specifically, it is recommended to specify liver-related biochemical toxicities (eg, bilirubin, ascites). Common Terminology Criteria for Adverse Events, version 3.0, is designed to be applied to all treatment modalities. It is recommended to report severe toxicities (ie, grade ≥ 3) separately.

Table 5. SIR Definition and Grading System of Procedural Complications

Grade	Description
Minor	
A	Necessitates no therapy, causes no consequence
B	Necessitates nominal therapy, causes no consequence; includes overnight admission for observation only
Major	
C	Requires therapy, minor hospitalization
D	Requires major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 h)
E	Results in permanent adverse sequelae
F	Results in death

As it is difficult to differentiate between adverse events that result from worsening of liver disease, progression of tumor, and treatment toxicity, complications should be distinguished based on the time elapsed between the procedure and their occurrence. SIR recommends grouping them into the following: (i) immediate ($\geq$ 24 h after the procedure), (ii) early (ie, 1–30 d after the procedure), and (iii) delayed (ie, $>$ 30 d after the procedure). All complications that are judged to have a high likelihood of being attributable to the procedure should be reported. Complications may be reported on a per-procedure, per–treatment cycle, or per-patient basis. Details of the procedure resulting in the complications, including but not limited to agents used and vessel(s) treated, should be provided. Thirty-day mortality must be reported. The temporal relationship of reported toxicity from the treatment should be defined in the Materials and Methods section.

A major complication is defined as an event that leads to substantial morbidity and disability, increasing the level of care or resulting in hospital admission or substantially lengthened hospital stay (SIR classifications C–E; **Table 5**). This includes any case in which a blood transfusion or interventional drainage procedure is required (24,25). All other complications are considered minor.

Hepatic Complications

Hepatic complications include liver failure, portal hypertension (resulting from hepatic fibrosis), liver abscess, intrahepatic biloma, and liver infarction (74–76). Liver dysfunction (or failure) seen after radiation is termed radiation-induced liver disease. It may be necessary to stratify the occurrence of radiation-induced liver disease based on the pretreatment liver functional status (as

Table 6. Summary of Reporting Standards

Parameter	Required	Recommended
Details of study		
Study design (flow diagram preferred)	X	
Inclusion/exclusion criteria	X	
Method of treatment assignment	X	
Sponsorship/funding/role of sponsor/medical writing support	X	
Participating centers	X	
Institutional review board approval	X	
HIPAA compliance	X	
Description of statistical methods	X	
Population description		
Population demographics (table preferred)	X	
Baseline evaluation (clinical/imaging/laboratory)	X	
Primary neoplasm (eg, HCC, colorectal cancer, neuroendocrine)	X	
Method of diagnosis	X	
Performance status	X	
Tumor staging	X	
Prior therapy for liver tumor	X	
Concomitant therapy for liver tumor	X	
Treatment description		
Description of device (radionuclide and carrier)	X	
Details of dosimetry	X	
Median number of treatment sessions	X	
Tumor targeting (lobar/segmental)		X
Median dose delivered	X	
Outcomes assessment		
Technical success	X	
Clinical success/failure (survival, TTP, PFS, response rate)	X	
Complications (according to SIR reporting and/or NCI CTCAE version ≥ 3.0)	X	
Description of adverse events	X	
Quality of life assessment		X
Other		
Costs/cost effectiveness		X
Limitations	X	
Conclusions	X	

Note.—CTCAE = Common Terminology Criteria for Adverse Events; HIPAA = Health Insurance Accountability and Portability Act; NCI = National Cancer Institute.

shown by the Child–Turcotte–Pugh class) (77). Radiation-induced liver disease is defined as the development of or worsening of liver functions compared with baseline. Clinical signs and symptoms (eg, worsening ascites, jaundice) and laboratory tests (eg, elevation in total bilirubin level) may indicate postprocedural liver dysfunction. The committee recommends the use of the term "radioembolization-induced liver disease" to define hepatic toxicity following radioembolization. Several investigators are currently attempting to better differentiate the clinical characteristics of radiation-induced liver disease and radioembolization-induced liver disease.

Extrahepatic Complications

Extrahepatic complications can generally be separated into complications resulting from systemic effects resulting from the procedure (eg, lymphopenia) or the extrahepatic deposition (ie, nontarget embolization) of injected material. The latter includes radiation pneumonitis, radiation cholecystitis, and gastrointestinal ulcers (46,78,79). In case of their occurrence, relevant details of the vascular anatomy on angiography and findings on imaging with ^{99m}Tc macroaggregated albumin that may have been missed should be briefly discussed.

Vascular Complications

It is recommended to report the incidence of vascular complications (eg, groin hematoma and dissection). Given that systemic chemotherapeutic agents may render the vessels fragile, these complications potentially occur more often after systemic chemotherapy for secondary liver tumors.

Side Effects

Side effects are expected, undesired, and frequent consequences of the procedure that rarely result in substantial morbidity. The most common side effect of radioembolization is a postradioembolization syndrome that consists of the following clinical symptoms: fatigue, nausea, vomiting, anorexia, fever, and abdominal discomfort. Hospitalization is usually not required. Postradioembolization syndrome is less severe than that observed after other embolic therapies where fatigue and constitutional symptoms predominate (11,80–82). Mild abdominal pain may be experienced following radioembolization (56,81). All toxicities should be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (or most recent version) (73).

STUDY DESIGN AND STATISTICAL EVALUATION

Given that most reports of radioembolization have been case series, a major benefit of uniform reporting standards is the ability to perform metaanalyses of outcomes to compare therapies (83). Prospective randomized studies are considered the standard for pivotal studies and should be performed whenever possible (84). However, the committee recognizes the obstacles that limit the ability to perform such studies in interventional oncology and the benefit of reporting less robust forms of data such as prospective investigations, retrospective analyses, and case series and reports (85). The study design needs to be defined with focus on the primary and secondary endpoints that are under consideration. Study flowcharts are recommended. It is necessary to describe the statistical methods employed for the analysis. It is also recommended to present substratification analyses wherever possible. A brief description of some commonly used tests is presented later.

Comparison of Categoric Variables

It is recommended to use the Fisher exact test or χ^2 test when comparing independent categoric variables. The McNemar test may be used for comparing dependent categoric variables.

Comparison of Continuous Variables

It is recommended to use the Mann-Whitney *U* test if comparing independent continuous variables (eg, age comparison between two treatment arms). The Kruskal–Wallis test may be used if there are more than two categories of the variable (eg, age comparison among three treatment arms). It is recommended to use the Wilcoxon test if comparing dependent continuous variables (eg, pre- and postradioembolization tumor size). The Friedman test may be used for more complex comparisons.

Univariate Time-to-endpoint Analyses

Time-to-endpoint (eg, TTP, PFS, and overall survival) analyses should be calculated using the Kaplan–Meier technique and should be reported as a median and 95% CI where possible (86). It may also be reported as 1-year, 2-year, and 3-year rates. The log-rank test may be used to calculate the hazard ratios of the difference between the reference category (which should be specified) and the category of interest. It is recommended to illustrate the Kaplan–Meier curves wherever possible. *P* value adjustments for multiple comparisons should be considered.

Multivariate Time-to-endpoint Analyses

It is also recommended to perform multivariate analyses if possible by using the Cox proportional-hazards model. This allows correction for and identification of the covariates that have independent effect on survival (or any other parameter, eg, TTP). It is necessary to specify (i) the variables entered into the model, (ii) the rationale for entering the variables into the multivariate model (ie, clinical and statistical reasoning), and (iii) the method used for entry (simultaneous entry, stepwise, backward, or forward). Only one variable should be chosen (either the composite variable or its constituents) if there is overlapping of factors of the variables (eg, ascites, bilirubin, albumin; are all included in calculating Child–Pugh score). In cases in which composite variables such as Child–Pugh score are included in the model, it is inappropriate to also enter covariates that are constituents of the composite variable in the same model (87). The results of the Cox proportional-hazards model are reported as hazard ratios with 95% CIs (88). In specific cases in which there are covariates that are time-dependent (such as changes in tumor size at various time points following therapy), specific methods used to correct for the time dependence should be appropriately described.

CONCLUSIONS

Radioembolization is establishing its role in the management of liver tumors. The intent of this proposal for standardization of terminology is to provide an appropriate vehicle for reporting the various aspects of radioembolization. Our intent is to provide such a framework to facilitate the clearest communication between investigators and the greatest flexibility in comparison among the many emerging technologies. Clearly this is an ongoing process that will require modifications as our understanding of these technologies improves, new treatment paradigms emerge, and greater consensus is achieved on standardizing the reporting of currently unresolved issues. Constructive feedback from the medical community at large is welcomed in an attempt to further refine this proposal. Nevertheless, we encourage all our colleagues to adopt the terminology and reporting strategies outlined in this

proposal. A summary of the reporting standards described here is presented in **Table 6**.

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