Standards of Practice

Transcatheter Therapy for Hepatic Malignancy: Standardization of Terminology and Reporting Criteria

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The field of interventional oncology includes tumor ablation as well as the use of transcatheter therapies such as embolization, chemoembolization, and radioembolization. Terminology and reporting standards for tumor ablation have been developed. The development of standardization of terminology and reporting criteria for transcatheter therapies should provide a similar framework to facilitate the clearest communication among investigators and provide the greatest flexibility in comparing established and emerging technologies. An appropriate vehicle for reporting the various aspects of catheter directed therapy is outlined, including classification of therapies and procedure terms, appropriate descriptors of imaging guidance, and terminology to define imaging and pathologic findings. Methods for standardizing the reporting of outcomes toxicities, complications, and other important aspects that require attention when reporting clinical results are addressed. It is the intention of the group that adherence to the recommendations will facilitate achievement of the group's main objective: improved precision and communication for reporting the various aspects of transcatheter management of hepatic malignancy that will translate to more accurate comparison of technologies and results and, ultimately, to improved patient outcomes.

RECENTLY, the International Working Group on Image-guided Tumor Ablation published a document entitled "Image-guided tumor ablation: standardization of terminology and reporting criteria" (1). 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" (1). Another branch of interventional oncology that was believed could benefit from such standardization of terminology and reporting criteria is catheter-directed treatment of malignancy. This includes chemoembolization, chemotherapeutic infusion, embolization, and radioembolization, which are the most commonly performed procedures by interventional radiologists for patients diagnosed with unresectable hepatic tumors. Accordingly, a panel of experts was convened to develop standard terminology for transcatheter therapy in parallel with the ablation document (1).

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, the Technology Assessment Committee of SIR 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 the

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contents with previous 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 report 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.

CLASSIFICATION OF THERAPIES

Image-guided Transcatheter Tumor Therapy

The term "image-guided transcatheter tumor therapy" is defined as the intravascular delivery of therapeutic agents via selective catheter placement with imaging guidance. Currently, various agents such as chemotherapeutic agents, embolic particles, or radioactive materials are injected via feeding vessels to tumor(s) in an attempt to achieve cytoreduction by enabling more focused delivery or deposition of higher concentrations within the tumor (2–9). Therapeutic material may eventually include drug-eluting microspheres, biologically active agents, chemical mediators of cell function and/or the tumor microenvironment, viral vectors, genetic material, nanoparticles, or other as yet undescribed agents. The term "transcatheter" aims to distinguish these therapies from others that are applied orally or via a systemic, peripheral venous route as well as from direct ablative therapies. We stress the concept of image guidance in the title of this discipline to reflect our radiologic perspective and to highlight that image guidance is critical to the success of these therapies (2–9). Additionally, the term "image guidance" separates these therapies from chemotherapy administered via an implanted hepatic arterial chemotherapy port. Percutaneous placement and management of hepatic arterial infusion ports is beyond the scope of the current work. Currently, transcatheter therapies are performed with the use of fluoroscopy. Given current research into use of complimentary imaging modalities for delivery/monitoring of therapies

(particularly magnetic resonance [MR] imaging), the more general term "image guidance" is preferred to accommodate future technical developments (10,11).

Individual procedures and therapies have often been given multiple different names by various investigators, which may result in confusion. Hence, we propose and recommend a unified approach to the terminology regarding these therapies. The primary aim of this classification is to provide simplicity and clarity, most notably by eliminating extraneous detail and many acronyms. Therefore terms such as "HACE" for hepatic arterial chemoembolization and "TACE" for transhepatic arterial chemoembolization should be avoided. The term "infusion" for the direct delivery of pharmacologic agents is preferred, rather than "instillation," which may refer to administration of an agent for chemical ablation (1).

The methods of image-guided transcatheter tumor therapy most commonly used in current practice are divided into three main categories: (i) chemoembolization, (ii) embolization, and (iii) radioembolization. These categories require further definition and standardization of terminology as outlined later. Chemoembolization, embolization, and radioembolization are performed after catheterization of the common, proper, lobar, or segmental hepatic arteries according to standard angiographic principles as described in the SIR Quality Improvement Guidelines for Transhepatic Arterial Chemoembolization, Embolization, and Chemotherapeutic Infusion for Hepatic Malignancy (12). Other interventional oncologic therapeutic approaches, including the transcatheter and percutaneous delivery of genetic material or growth inhibitors, will likely ultimately require better consensus definition. Yet, they are beyond the scope of this article as they require further maturation of the technique and/or technology before description and standardization of terminology. Nevertheless, many of the issues discussed concerning reporting criteria will likely be equally appropriate for clinical trials of those therapies.

Chemoembolization

Chemoembolization is defined as the infusion of a mixture of chemo-

therapeutic agents with or without iodized oil followed by embolization with particles such as polyvinyl alcohol, calibrated microspheres, or Gelfoam (Pharmacia & Upjohn, Kalamazoo, Mich) (12). When results with chemoembolization are reported, the dose and method of reconstitution of chemotherapy (empiric or weight-based), the use of iodized oil, the method of mixing the chemoembolic solution or emulsion, the timing of addition of the embolic agents to the chemotherapeutic mixture, and the type, size, and volume of embolic particles used should be included in the Materials and Methods section.

Embolization

Embolization is defined as blockade of hepatic arterial flow with a vascular occlusion agent. Most commonly, particulate agents such as Gelfoam, polyvinyl alcohol, or calibrated microspheres have been used, although use of other agents including glue and herbal agents such as bletilla striata have been described (12). When results with embolization are reported, the type, size(s), and volume of particles used should be specified. Additionally, arteriographic criteria used to determine the selection of particle size(s) and the embolization endpoints should be described

Radioembolization

Radioembolization is defined as the infusion of radioactive substances including. microspheres containing yttrium Y 90, iodine I 131 iodized oil, and similar agents (12). Outcomes from preprocedural hepatic artery/pulmonary shunt studies should be reported. Pretreatment embolization of nontarget vessels (eg, gastroduodenal and right gastric arteries) should be documented. The method used to calculate activity for the individual patient population should be consistent and reported in the Materials and Methods section. Activity of the agent should be reported in gigabecquerels (GBq) and dose should be reported in Grays (Gy). The disparity between the prescribed and the delivered activity (if any) should be documented.

Procedure Terms

A procedure refers to a single patient encounter for treatment of liver tumor. The term "procedure" is preferred to "operation" as the latter implies open surgery rather than a percutaneous approach. The term "session" is synonymous with "procedure" for the purposes of this document. The term "treatment cycle" consists of the procedures required to complete treatment of the tumor-bearing portion of the liver. If a patient has bilobar liver metastases, typically two or more procedures will be needed to complete one treatment cycle. Similarly, if a patient undergoes two segmental sessions to treat a tumor in the right lobe, this would constitute one treatment cycle. Therefore, a treatment cycle is completed when all known disease has been treated. If a patient has progression of disease after a successful treatment cycle that requires additional therapy, a new treatment cycle is begun. Each manuscript should state clearly how many procedures/sessions and treatment cycles were needed and why. Given the variability in practices, the extent of liver being treated in a single session—be it subsegmental, segmental, lobar, or whole-liver—should be clearly specified for a given protocol.

IMAGE GUIDANCE

All procedures mentioned in this article refer to transcatheter tumor therapy guided by imaging. "Guidance" refers to procedures in which use of imaging (eg, fluoroscopy, ultrasound [US], computed tomography [CT], and MR) is required before, during, and after the procedure. Imaging is used in five separate and distinct components: treatment planning, tumor targeting, treatment monitoring, therapy control, and assessing treatment response (13). Treatments are planned before each procedure in a treatment cycle, and the assessment of treatment response occurs after the completion of a treatment cycle. Targeting, monitoring, and controlling are all performed during the procedure.

Treatment Planning

Treatment planning incorporates findings on physical examination, se-

rologic values (including liver function and tumor markers when appropriate), and imaging findings. Imaging techniques, including US, CT, MR imaging, and position emission tomography with and without CT fusion, are used to help determine whether patients are suitable candidates for these procedures. Imaging aspects that are particularly important include size, number (operators may wish to focus on as many as 10 index masses as used by Response Evaluation Criteria in Solid Tumors [RECIST]), Couinaud segmental location, presence of extrahepatic disease, and patency of the portal venous structures (14–16). Additionally, assessment for variant arterial anatomy is performed. Tumor location at the dome of the diaphragm, anterior border of the liver, or posterior lateral margin can be associated with extrahepatic collateral flow from the inferior phrenic, internal mammary, or intercostal arteries, respectively (17,18).

Tumor Targeting

The term "tumor targeting" is used to describe the step during a transcatheter procedure that involves placement of a catheter into the vessel supplying the tumor(s). Targeting is principally accomplished with iodinated contrast agent injection under fluoroscopy and intraprocedural correlation with preprocedural imaging. In addition to determining the pathway to the target vessel, this portion of treatment should confirm the presence/absence of portal vein patency and direction of flow. Correlation of this information with preprocedural imaging and laboratory values allows an appropriate level of vessel selection in any given patient.

Treatment Monitoring

"Monitoring" is the term that is used to describe the process with which therapeutic effects are viewed during a procedure. Changes in imaging that occur during a procedure can and should be used to determine treatment efficacy and determine the endpoint of a procedure. Examples of monitoring include the extent of tumor coverage (ie, included and/or encompassed) by the iodized oil/chemotherapy mixture during chemoembolization or evaluation

for persistent forward flow in the artery chosen for delivery to avoid nontarget treatment during radioembolization. The term "monitoring" should not be used to describe response to treatment; for this, "treatment assessment" or "follow-up" is used.

Therapy Control

The term "therapy control" is used to describe the intraprocedural adjustments used for therapeutic optimization and to avoid damage to noncancerous tissue. For a catheter-directed procedure, this aspect is currently performed via fluoroscopic monitoring. This may simply be repositioning of a catheter on the basis of physician experience or imaging findings, or it could eventually include integration of corollary techniques such as optical imaging (19). This term would also include embolization of nontarget vessels such as the gastroduodenal or right gastric arteries during radioembolization and particle embolization to decrease arterial–portal shunting during chemoembolization of a hepatocellular carcinoma (HCC).

Assessment of Treatment Response

Patient performance status and quality of life should be compared to baseline values with standardized scales such as the Karnofsky scale or Eastern Cooperative Oncology Group score (20). Imaging used to assess treatment outcomes after a single treatment or treatment cycle is discussed in a subsequent section as "postprocedural imaging" (9,21,22). Assessment of change in tumor markers and/or hormonal symptoms is also used to determine outcomes.

PATHOLOGIC AND IMAGING FINDINGS

The difference between pathologic findings and imaging findings must be stressed by the appropriate selection of terminology. Early investigation of chemoembolization demonstrated reasonable, albeit incomplete, overlap in findings between CT and pathologic examination (23–25). Similar research has not been performed with more current imaging techniques such as triphasic helical CT and dynamic enhanced MR imaging, although

some limited information is available on these newer imaging techniques (26). Investigations to study the findings after radiofrequency (RF) ablation of small HCC have demonstrated over- and underreporting of the extent of residual disease with newer imaging techniques, with a range of 75%–98% of tumor cells within a zone of presumed death having been eradicated (27). A similar pattern is virtually certain with transcatheter-directed tumor therapy. Hence, careful differentiation between imaging and pathologic findings must be made, with pathologic findings (when available) acting as the ultimate arbiter of treatment success. This distinction is critical, given that the accuracy of assessment of the extent of tumor destruction by means of imaging findings is limited by the resolution of images and the uncertainty about the viability of cells.

Zone of Cell Death at Pathologic Examination

Tumor(s) treated by transcatheter therapies undergo necrosis (23–26). The mechanism of tumor cell death with current methods (ie, chemoembolization/embolization/radioembolization) is coagulation necrosis. Although many tumors may undergo central necrosis without treatment, the appropriate term "coagulation necrosis" is preferred over the use of "necrosis" alone because it denotes that the treatment is actively leading to tumor destruction. For simplicity, the remainder of this document will refer to cell death as coagulation necrosis.

Tumor Destruction on Postprocedural Imaging

The majority of patients treated with transcatheter techniques will not undergo resection and/or pathologic examination. The term "lesion" is to be avoided, given the potential confusion about the intended meaning, as the term "lesion" has been used to refer to the area of successfully treated tumor and the underlying tumor to be treated.

Appropriate terminology must reflect the fact that, although imaging is used to define the gross extent of induced coagulation necrosis, its accuracy is limited by spatial and contrast resolution to approximately 2–3 mm

(depending on the imaging modality) (23–26). Hence, postprocedural imaging findings are only a rough guide to the success of transcatheter therapy, as microscopic foci of residual disease, by definition, cannot be expected to be identified. Although the term "tumor destruction" is applicable to ablation, it can not be equally applied to transcatheter therapies given the different mechanism of treatment effect and the limited outcomes data comparing imaging findings to pathologic findings for transcatheter techniques (24,25). It should be recognized that imaging findings after transcatheter therapy are not equivalent to pathologic findings.

One validated finding after chemoembolization is the uptake of Ethiodol (Savage Labs, Melville, NY) in HCC. Increasing uptake of Ethiodol correlates to increased survival (28,29). Conversely, increasing uptake of Ethiodol has been correlated directly to coagulation necrosis of tumor after chemoembolization for HCC (24,30–32). Absence of arterial-phase enhancement on cross-sectional imaging or characteristic findings on diffusion-weighted MR imaging may also be useful to estimate tumor necrosis after transcatheter therapy (4,22,33,34). Outside of these assessment tools for HCC, validation of imaging techniques for induction of necrosis with transcatheter techniques is limited and further study is required. For this reason, investigators should use validated measures such as the World Health Organization (WHO) or RECIST criteria with the following points listed later (12,35).

Complete Radiologic Response.—In the absence of pathologic assessment, the best method to evaluate tumor destruction is via imaging findings. As noted earlier, there are likely to be small pockets of residual disease beyond the resolution capabilities of current imaging techniques (21,23–25). Patients who do not have evidence of active tumor on imaging typically go into serial follow-up as the intervention has been technically successful as can be best determined. Complete radiologic response therefore represents the imaging definition of technical success as the treatment has reached a globally accepted endpoint. It should be clearly understood that complete radiologic response differs from the standard definition of complete re-

sponse in trials of systemic therapies, which requires complete disappearance of the tumor. The definition of response method used must be explicitly stated in any report of therapy. It is important to recognize that changes in tumor enhancement or metabolic activity are not validated outcome measures, and an appropriate level of skepticism must be maintained when reporting such findings as surrogates for treatment efficacy. In addition, they are somewhat qualitative and subjective. Use of subtraction imaging and signal quantification with MR imaging should ideally be employed rather than subjective image interpretation.

Residual Disease.—A single treatment cycle may result in areas that have not undergone complete coagulation necrosis. In contrast to absence of active disease on postprocedure imaging representing a complete radiologic response, active disease remaining after treatment is termed "residual disease." Residual disease may be represented by incomplete replacement of a HCC with Ethiodol or persistent arterial-phase enhancement on CT or MR identified before and after treatment (21,23–25). Unlike thermal ablation, in which there are relatively few measurable zones of treatment, estimation of the residual volume of viable tumor for metastases may be quite difficult, as many tumors have clearly identifiable areas of coagulation necrosis before transcatheter therapy. If, when compared with a previous imaging study, there is stable disease based on tumor size and there is a limited amount of active disease, an operator may decide the best course of action is short-term follow-up rather than initiation of another treatment cycle. A key component in reporting outcomes aside from contrast enhancement is to be sure that growth of the treated tumors has not occurred, which would represent progressive disease. Time to treatment failure and/or progression should be reported in transcatheter studies.

Partial Response.—Partial response is defined by greater than 50% reduction in the total tumor load of all measurable masses determined by two studies at least 4 weeks apart (according to WHO criteria) or at least a 30% decrease in the sum of the longest diameters of a maximum of five index tumors using the sum of the baseline longest diameters as a denominator (according to RECIST) (35,36).

Stable Disease.—Stable disease is categorized as the presence of more residual tumor than for partial response but less than for progressive disease. According to WHO criteria, stable disease is defined as less than 50% reduction in tumor load of all measurable masses determined by two studies at least 4 weeks apart (36). With the RECIST, stable disease is defined as less than a 30% decrease in the sum of the longest diameters of a maximum of five index tumors using the sum of the baseline longest diameters as a denominator (35).

Progressive Disease.—Progressive disease is defined as greater than 25% increase in size of one or more measurable tumors or the development of new tumors (according to WHO criteria) or greater than 20% increase in the sum of the longest diameters of the target tumors from baseline (according to RECIST) (35,36). Given that the response to transcatheter therapy can be nonuniform, change in diameter rather than contrast enhancement is considered to be the hallmark of progression (eg, a 10-cm tumor may initially decrease to 6 cm in maximum diameter and then develop a 2-cm area of growth at the margin). In the setting of progressive disease, and depending on the primary tumor, investigators should report whether progression was of the index/treated tumor(s) (such progression should be reported as local progression rather than local recurrence), elsewhere in the liver, or extrahepatic. Time to progression and time to treatment failure (if applicable) should be reported in all studies as well.

Regression.—Unlike thermal ablation, in which involution describes resorption of coagulated tissue in the ablated margin and tumor, regression refers to resorption of tumor alone after transcatheter therapy (1). The term "shrinkage" should be avoided as imprecise. It is important to note that no or minimal regression does not imply treatment failure.

Reporting of Tumor Sizes and Posttherapeutic Outcomes

Appropriate uniform guidelines and standards are needed to report the extent of induced coagulation necrosis and disease status. This terminology should be in keeping with existing validated oncologic criteria and would ideally be applicable to all cross-sectional imaging modalities. Description of findings should be consistent among modalities to clarify disease status and determine treatment outcomes. Hence, uniform standards of comparison are essential and must be adopted.

Index Tumor.—"Index tumor" is the preferred term to describe as many as five tumors before treatment (35). Use of the term "index tumor" will most commonly be in reference to patients with HCC or limited metastatic disease. Investigators should avoid use of the term "lesion" because this term could be confused with the zone of induced coagulation on imaging.

Size Classification and Number of Tumors.—Given that the selected treatment modality (ie, direct ablation, transcatheter therapy, or a combination of both) may be determined by size, the maximum diameter of the tumor(s) in three dimensions must be specified to optimize care on a treatment-by-treatment basis. Tumor number should be reported as well.

Transcatheter Therapy Alone.—Changes in tumor diameter should be reported according to RECIST or WHO criteria (35,36). Given that preexisting intratumoral necrosis may be present, determining the extent of coagulation necrosis may be a difficult, if not impossible, point of differentiation from findings after percutaneous ablation. For studies following chemoembolization outcomes for HCC with CT, classifying uptake of Ethiodol is useful and correlates to survival. A recommended scale consists of a five-grade system (no uptake, <10% uptake, 10%–50% uptake, >50%–99% uptake, complete uptake) (31). The focus of reporting outcomes after transcatheter therapy alone should be on the arrest of tumor progression with appropriate notation of time to tumor progression and/or time to treatment failure.

Transcatheter Therapy Combined with Direct Ablative Therapy.—The aforementioned recommendations for reporting regarding transcatheter therapy should be included plus those stipulated for ablative therapy (1). When combined therapy is performed, four additional pieces of information are required. The first is the timing of the ablative component of therapy with respect to transcatheter treatment. This reporting should include a description of which component was performed first as well as the time interval between the two modalities (ie, during the same treatment session, the following day, within 1 week, within 1 month). If the timing between application of modalities varies, a median and range of values should be provided. The second is that the definition of the treatment cycle should be expanded to include the number of transcatheter and ablation sessions to treat the target tumor(s). Third, the rationale for the sequence used (transcatheter therapy before ablation or vice versa) should be described. Finally, whether the treatments were used in a planned cycle of treatment or for salvage should be specified. More specifically, a planned cycle of treatment would infer that both therapies were used based on well defined circumstances (ie, tumor size or distribution). Salvage therapy would infer that one treatment followed failure of another modality (ie, thermal ablation of a small residual component after arterially directed therapy).

Transcatheter Therapy Combined with Systemic Therapy.—The aforementioned recommendations for reporting regarding transcatheter therapy should be included. Additional required information includes the temporal relationship of transcatheter therapy to systemic therapy. This reporting should include which component was performed first as well as the timing of transcatheter therapy within the systemic treatment cycle. If the timing within a given systemic treatment cycle varies, a median and range of values should be provided. Second, the rationale for the sequence used (transcatheter therapy before to systemic therapy or vice versa) should also be described. Finally, the rationale for the systemic agent(s) selected should be specified.

STANDARDIZATION OF FOLLOW-UP

Currently, definitions of the appropriate length of follow-up and the time points to technical success are not well established. One investigator's long-term follow-up is often another's short-term follow-up. Hence, specific guidelines need to be adhered to that depend on the type of disease treated and the intended goal of the study. Treatment study goals are generally related to one or more of the following

four categories, which usually need to be distinguished from each other:

1. Technical success, or was the tumor treated according to the protocol?
2. Technique effectiveness, or was the tumor effectively treated?
3. Morbidity, or what was the treatment toxicity and were complications avoided? and
4. Outcomes, or was there some improvement in survival, quality of life, or palliation?

Technical Success

The term "technical success" simply addresses whether the tumor was treated according to protocol and was addressed completely. Tumor coverage can be assessed during or after the procedure. During the procedure, preliminary angiography can define the targeted vessel(s) for treatment. Additionally, accumulation of embolic material and/or Ethiodol may be identified in the tumor(s). Some operators may elect to perform CT the day after chemoembolization to evaluate Ethiodol uptake or a nuclear medicine study (ie, Bremsstrahlung scan) immediately after radioembolization to evaluate delivery of ^{90}Y microspheres (37). Technical success will often be principally determined by angiographic mapping. A tumor treatment that is performed according to protocol and completely addresses the tumor as determined at the time of the procedure is "technically successful." The importance of this term is to help investigators separate those patients in whom the protocol could not be executed completely for technical reasons or reasons related to comorbid disease from those who were treated according to protocol.

Technique Effectiveness

Distinction between "technical success" and "technique effectiveness" must be made. Effectiveness can only be demonstrated with appropriate clinical follow-up. "Technique effectiveness" should therefore refer to a prospectively defined time point (ie, 1–3 months after a treatment cycle), at which point response is assessed at imaging follow-up using standardized, validated follow-up criteria. The number of treatments (ie, the number of interventional procedures) to achieve the

specified endpoint should likewise be defined.

Comparison of technical success and technique effectiveness among various protocols has been challenging because many authors have adopted different terminology or guidelines. This problem is further compounded by the clinical need to treat a tumor over multiple sessions and the possibility of treating growing foci of local tumor progression months after the initial course of therapy. A window for an initial treatment cycle for each catheter-based technique should be defined (eg, 1–3 months) depending on the size, type, and number of the tumor(s), as well as the rationale for therapy. The broad latitude given to this definition was purposeful, given the evolving consensus on defining more specific parameters because each disease process may vary. If complete treatment cannot be achieved within these specified parameters, the tumor(s) should be classified as "unsuccessfully treated."

Primary and Secondary Technique Effectiveness Rates

Given that multiple treatments with image-guided transcatheter tumor therapy are often given over the course of the disease, primary and secondary technique effectiveness rates should be reported. The primary effectiveness rate is defined as the tumor volume that was successfully treated following the initial treatment cycle. The secondary or assisted effectiveness rate includes tumors that have undergone successful repeat treatment following identification of local tumor progression or when residual disease is treated. The term "repeat treatment" or "re-treatment" should be reserved for describing treatment of locally progressive tumor in cases in which complete necrosis was initially thought to have been achieved on the basis of imaging findings that demonstrated "adequate tumor destruction." De novo treatment of intrahepatic progression away from the index tumor(s) should be discussed as a new treatment session as a separate treatment plan will be made regarding the method of therapy and the number of sessions over a prescribed time.

The technical success and technique effectiveness rates are very important as we define the limitations of our technologies, ideally in a manner sim-

ilar to that used in other disciplines (eg, articles about surgical resection typically report a positive margin rate). Nevertheless, for some protocols, the concepts of local technical success and local tumor progression may have limited impact on the most important outcome parameter: patient survival. For example, use of three to four procedures over a period of 3 months as the window of technique effectiveness may be of secondary importance if the patient lives for several years with a high quality of life because of the treatment or if the tumor is completely eradicated over multiple courses of treatment over many years.

Failure of Therapy

Causes of Treatment Failure.—The distinction among lack of technical success (ie, tumor progression), new foci of disease in the target organ (ie, distant intrahepatic progression), and extrahepatic progression should be distinguished whenever possible and reported. Discrimination between "local tumor progression" and new tumor separate from the treated area is important for determining the potential utility (ie, technical success) of a given method in the setting of many potentially confounding causes of the death of a given patient. Additionally, for patients with cirrhosis, the causes of mortality should be differentiated among tumor progression, worsening of underlying cirrhosis, and others.

Local Tumor Progression.—Many authors have used the term "local recurrence" to describe the appearance during follow-up of foci of untreated disease in tumors that were previously considered to be completely treated. This is often a misnomer, given the fact that the tumor in essence did not recur but instead was incompletely treated. Hence, the process often described is actually "residual untreated tumor." However, in many cases, it is virtually impossible to determine whether there was incompletely treated viable tumor that continued to grow or if a new tumor (or in the case of HCC, "daughter" or "satellite" tumors) grew at the original site. Given this reality, local tumor progression is the preferred term over "local recurrence" if the initial treatment encompassed the area of newly developed disease.

Patient Mortality

Given that the population of patients that is treated most often is that with cancer, substantial patient mortality that is unrelated to the intervention is anticipated, particularly in clinical studies with long-term follow-up. Therefore, the cause of death should be specified as "disease-specific survival" or "overall survival," with separate survival curves reported for each measure. For tumor-related death, further subclassification (eg, differentiating death of hepatic or diffuse metastatic burden), if possible, will often be useful because it can potentially shed further light on the effectiveness of therapy.

COMPLICATIONS

Complications from transcatheter procedures can occur from accessing the appropriate vessel to deliver therapy or as a result of treatment effect on cancerous or noncancerous tissues. The standard SIR grading system for complications or image-guided transcatheter tumor therapy should be used as outlined later for catheter-based complications (12,38,39). Complications reported according to the SIR standard table allow consistent categorization by complication severity. Adverse events secondary to treatment delivery should be defined using the Common Terminology Criteria for Adverse Events, version 3.0 (40). These criteria are universally accepted in the medical, radiologic, and surgical oncology communities and their use provides interventional oncologists an opportunity to communicate in a common manner with these other specialties. This system is designed to be applied to all treatment modalities; therefore, interventional oncologists should use this system.

Complications should be divided into immediate (within 6–24 hours of the procedure), early (≤30 days after the procedure), and late (>30 days after the procedure). This classification will increase understanding of the timing of specific complications or side effects and enhance recognition and knowledge of when and how to treat these sequelae. Reported complications should include any problems noted within the early or periprocedural time period that can be related to

the procedure and any problems identified in the late or delayed time period (eg, at follow-up imaging) judged to have a high likelihood of resulting from the procedure. All complications and side effects should be reported according to the number of procedures or sessions on a per-procedure or per-session basis. Details should be provided about the procedure performed including which category of procedure was performed, the agents used, and the vessel(s) treated for all complications.

A major complication is any event that results in additional therapy including an increased level of care, hospital stay beyond observation status (including readmission after initial discharge), permanent adverse sequelae including substantial morbidity and disability, and death (SIR classifications C–E). Included in the category of major complications is transfusion of blood products or additional interventions such as percutaneous drainage procedures or surgery. All other complications are classified as minor (SIR classifications A and B). It is important to recognize that many complications, such as liver failure, cholecystitis, organ damage caused by to nontarget embolization, pulmonary embolism caused by arteriovenous shunting, or iatrogenic dissection of the celiac artery or one of its branches can be major or minor complications depending on the severity and ultimate outcome (41–43).

Patient death within 30 days of transcatheter tumor therapy should be reported on a per-patient basis. The cause of death should be reported, with the potential and degree of causality to the endovascular procedure.

Complications can be divided into hepatic complications, extrahepatic complications, and complications of catheter/guide wire manipulation. The last of these three subtypes is self-explanatory. Death can be related to one or a combination of these. All hepatic and extrahepatic complications should be reported based on the procedure performed and agents administered as defined earlier in this document, as some complications are more or less closely associated with one of the agents.

Hepatic Complications

Hepatic complications, which include liver failure, liver abscess, intrahe-

patic biloma formation, and liver infarction, should be described in association with the pretreatment Child-Pugh classification or comparable description of baseline hepatic function, as well as the presence, level, and degree of portal vein thrombus if applicable (15,34). Patients with greater degrees of baseline hepatic compromise or dysfunction and patients with portal venous thrombus or hepatofugal flow may require modification of the treatment plan to minimize complication risk (44).

A minor persistent elevation of the Child-Pugh score after chemoembolization has been described (45). Liver dysfunction or failure resulting from the procedure is defined as the development of or worsening of liver function compared with baseline. Signs indicative of severe acute liver dysfunction include the new development of ascites, encephalopathy, or jaundice. Development of liver abscesses has been linked to previous intervention in the biliary system, and authors must provide information relative to known previous sphincterotomy or biliary drainage as well as the use of pre- and postprocedural antibiotic prophylaxis when abscess complications are reported (46,47).

Extrahepatic Complications

Extrahepatic complications can generally be separated into complications resulting from systemic effects resulting from the procedure (eg, bone marrow suppression or alopecia) or its therapeutic effects (eg, carcinoid crisis) and the extrahepatic deposition of injected material (41,48). Extrahepatic deposition of injected material is not uncommon. The results largely relate to the tolerance of the affected organ, vascular compromise, and nature of the agent deposited.

Chemoembolization and radioembolization have been associated with gastrointestinal toxic effects caused by the presence of extrahepatic perfusion (49,50). Details of the gastrointestinal effects, their location (gallbladder vs duodenum), and relevant angiographic findings should be reported when possible to increase the understanding of this troubling and potentially serious complication. In the case of radioembolization, details of the preprocedural arteriography, extrahepatic branches embolized, and results of technetium Tc 99m macroaggregated albumin infusion should also be supplied (51).

Cholecystitis can occur as a result of ischemia or local toxicity of the injected agent. Most cases are observed radiographically or pathologically and are asymptomatic ([42]). Therefore, this complication is likely largely minor in degree and probably underappreciated. Rarely, patients require intervention with percutaneous drainage or cholecystectomy. Cases resulting in the need for percutaneous or surgical intervention require descriptors regarding the agents used and the need for and type of intervention undertaken.

Nontarget embolization to the lungs can occur with any of the procedures described as a result of to the presence of arteriovenous shunts, which have been described on intrahepatic injection of [99mTc] macroaggregated albumin ([52]). Given the small size of the particles and potential for severe pulmonary toxicity, this complication has received more attention with the evolution of radioembolization. Potential pulmonary toxicity should be avoided in patients undergoing radioembolization by adjusting the activity based on findings on the screening arteriogram with maintenance of pulmonary exposure to less than 30 Gy ([53]). When pulmonary toxicity occurs after radioembolization, the results of [99mTc] macroaggregated albumin infusion with calculation of the hepatopulmonary shunt fraction and administered [90Y] activity should be reported. Pulmonary embolization of Ethiodol can be identified on CT after chemoembolization ([54]). With the use of Ethiodol, the administered volume should be reported, as severe lung injury has been noted with administration of greater than 20 mL ([55]).

Side Effects

Side effects are expected undesired consequences of the procedure that, although they occur frequently, rarely if ever result in substantial morbidity. The most common side effect of embolization and chemoembolization is postembolization syndrome, whereas suppression of appetite and fatigue are common after radioembolization. Postembolization syndrome (eg, fever, pain, increased white blood cell count) by itself is not considered a complication but rather an expected outcome of embolotherapy ([12,48]). A small percentage of patients will have prolonged

symptoms that require a greater level of postprocedural care ([4]). Although [90Y] microspheres have an embolization effect, the principal goal of treatment is not embolization (ie, occlusion of the entire feeding artery). The appetite suppression and fatigue after radioembolization are clinically different than typical postembolization syndrome. All toxicities should be reported according to Common Terminology Criteria for Adverse Events, version 3.0 ([40]).

OTHER IMPORTANT ASPECTS REQUIRING ATTENTION WHEN REPORTING CLINICAL RESULTS

Other Study Population Data to Be Reported

Demographics.—Patient age should be provided as a range and median. Mean age may also be provided. The number of male and female patients in a given study should be provided when appropriate. Ethnicity should be reported as appropriate. Inclusion/exclusion criteria should be reported.

Functional Status.—Patient performance status and comorbidities that may affect survival should be reported. Studies focusing on HCC should report on the clinical status of the patient population using established criteria such as Child-Pugh, Okuda, or Cancer of the Liver Italian Program.

Previous/Concurrent Therapy.—Administration of other traditional oncologic therapies (chemotherapy or radiation alone or in combination) to patients enrolled in a clinical trial should be specified. This should be further classified according to whether patients received the conventional oncologic therapies previously, around the time of treatment (within 1 month), or during the follow-up period. The specific therapy sequence should also be provided. Transcatheter therapy may be used as an adjunct therapy with conventional treatments or as a salvage procedure after failed systemic chemotherapy, and at a minimum, the principal systemic therapy should be noted.

Tumor Status.—Tumor type and size of the index tumor should be reported. The presence or absence of the primary tumor should be discussed. The degree of proof of disease re-

quired to enter into the study (ie, biopsy, imaging, serologic criteria, or a combination) should be clearly specified. Pretreatment evaluation (ie, tumor size, location, and number) also needs to be reported.

Outcomes.—Acceptable surrogates for survival such as time to progression and time to treatment failure should be defined and reported.

Comparison with Other Treatments

Given that most reports of image-guided therapy have been relatively small case series, a major benefit of uniform reporting standards is the ability to perform metaanalyses of outcomes to compare therapies ([56]). Clinical research studies should be reported in such a manner that the results can be directly compared with various cancer therapies, including other forms of image-guided tumor management, surgery, radiation therapy, and chemotherapy. The goal of interventional oncology therapies is maximum survival, disease-free survival, and quality of life stratified according to disease stage and patient functional status ([57,58]). Nevertheless, scant data addressing these issues for most diseases treated with image-guided tumor management exists ([27]). Randomized, controlled, and blinded studies are considered the standard for pivotal studies and should be performed when possible ([59–61]). By the same token, the committee acknowledges the very real obstacles to performing such studies (eg, patient recruitment, long periods of data collection, expense, multimember organization) and the benefit of reporting less robust forms of data, including retrospective studies, case series, and case reports ([59,62]).

Study Design and Statistical Evaluation

Regardless of the study type, rigorous statistical evaluation appropriate for the data collected should be presented ([60,61]). The primary and secondary study endpoints should be clearly stated. Survival outcomes should be reported with use of life-table (ie, Kaplan-Meier) analysis. Reports of Kaplan-Meier analyses should include error ranges or 95% CIs and numbers of patients at risk at each interval. Patients

should be randomized if possible. Results should be reported based on: (i) intent to treat, (ii) whether patients were treated as randomized, and (iii) whether they were treated per protocol (ie, excluding protocol violations). It should be noted that in small randomized studies, intent to treat may have limited value as one or two outliers will significantly affect the result. Outcomes may further need to be stratified according to multiple factors (eg, tumor type, grade, and stage; functional status; comorbidities). Appropriate methods for assessment of quality of life should likewise be selected (63).

CONCLUSIONS

The intent of this proposal for standardization of terminology is to provide an appropriate vehicle for reporting the various aspect of image-guided transcatheter tumor therapy. Our intent is to provide such a framework to facilitate the clearest communication between investigators and the greatest flexibility in comparison among the many new, exciting, and 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.

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