Consensus guidelines for the definition of time-to-event end points in image-guided tumor ablation: results of the SIO and DATECAN initiative

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Angaben zur Veröffentlichung / Publication details:

Puijk, Robbert S., Muneeb Ahmed, Andreas Adam, Yasuaki Arai, Ronald Arellano, Thierry de Baère, Reto Bale, et al. 2021. "Consensus guidelines for the definition of time-to-event end points in image-guided tumor ablation: results of the SIO and DATECAN initiative." *Radiology* 301 (3): 533–40. https://doi.org/10.1148/radiol.2021203715.

Radiology

REVIEWS AND COMMENTARY • STATEMENTS AND GUIDELINES

Consensus Guidelines for the Definition of Time-to-Event End Points in Image-guided Tumor Ablation: Results of the SIO and DATECAN Initiative

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Conflicts of interest are listed at the end of this article.

See also the editorial by Liddell in this issue.

Radiology 2021; 301:533–540 • https://doi.org/10.1148/radiol.2021203715 • Content codes: OI IR

There is currently no consensus regarding preferred clinical outcome measures following image-guided tumor ablation or clear definitions of oncologic end points. This consensus document proposes standardized definitions for a broad range of oncologic outcome measures with recommendations on how to uniformly document, analyze, and report outcomes. The initiative was coordinated by the Society of Interventional Oncology in collaboration with the Definition for the Assessment of Time-to-Event End Points in Cancer Trials, or DATECAN, group. According to predefined criteria, based on experience with clinical trials, an international panel of 62 experts convened. Recommendations were developed using the validated three-step modified Delphi consensus method. Consensus was reached on when to assess outcomes per patient, per session, or per tumor; on starting and ending time and survival time definitions; and on time-to-event end points. Although no consensus was reached on the preferred classification system to report complications, quality of life, and health economics issues, the panel did agree on using the most recent version of a validated patient-reported outcome questionnaire. This article provides a framework of key opinion leader recommendations with the intent to facilitate a clear interpretation of results and standardize worldwide communication. Widespread adoption will improve reproducibility, allow for accurate comparisons, and avoid misinterpretations in the field of interventional oncology research.

Online supplemental material is available for this article.

Interventional oncology is one of the fastest growing disciplines in clinical oncology and health care in general (1). Its success is chiefly based on the minimally invasive nature of the needle-, applicator-, and catheter-based image-guided procedures with lower complication rates, superior toxicity profiles, and often comparable or superior mid- and long-term oncologic outcomes compared with conventional treatment modalities such as surgical resection and systemic therapy (2–7). In clinical oncology, the most objectively defined time-to-event end point to address clinical benefit is overall survival. However, a proliferation of pharmacologic treatments and dosing strategies has led to the use of surrogate end points to measure interim treatment efficacy. Depending on the disease setting, these include disease-free, recurrence-free, and progression-free survival; local tumor progression-free survival; organ-specific progression-free survival and distant progression-free survival; time to progression; time to local (tumor) progression and time to organ-specific progression; primary and assisted technique efficacy rates; local tumor progression rate; and local control (8,9).

Throughout the interventional oncology literature, these survival terms are loosely defined and are often incorrectly used interchangeably. Accurate comparisons between studies are hampered by the heterogeneous and unclear reporting of oncologic outcome parameters, which includes variability in the interpretation and use of time-to-event end point terms and definitions of starting and ending times.

In 2014, Ahmed et al (8) updated their keystone consensus report regarding the standardization of terminology and reporting criteria, improving the precision of communications in this field. Although their article and the supplement to the consensus document concisely mention that *(a)* reporting of overall survival from start of ablation and from time of diagnosis is required for all intermediate- and long-term studies; *(b)* survival at specified time points and median survival times should be reported, as well as time to progression and progression-free survival; and *(c)* local time to progression and local (tumor) progression-free survival should be differentiated from organ-specific time to progression and progression-free survival, clear definitions and recommendations on how to use and interpret these parameters were not provided. Thus, in the field of image-guided tumor ablation, standardization of terms is required to facilitate effective communication.

The purpose of this modified Delphi consensus project was to provide standardized definitions of patient-, session-, and tumor-related parameters and to offer recommendations on how to uniformly collect, analyze, and report oncologic outcomes for patients treated with image-guided tumor ablation. This project is a collaboration between the Society of Interventional Oncology and the Definition for the Assessment of Time-to-Event

Summary

A panel of experts reached consensus on recommendations on when to assess oncologic outcomes per patient, per session, and per tumor; definitions of starting and ending times; definitions of survival time; and time-to-event end points.

Essentials

- An expert panel reached consensus on *(a)* recommendations on when to assess oncologic outcomes per patient, per session, and per tumor; *(b)* definitions of starting and ending times; *(c)* definitions of survival time; and *(d)* time-to-event end points.
- Clear definitions will ensure an objective and reliable interpretation of results, allow for an accurate comparison of outcomes, avoid misinterpretations, and provide the necessary foundation for scientific reproducibility among studies.
- Adoption of the recommendations will facilitate and improve worldwide communication of scientific advances in the field of interventional oncology.

End Points in Cancer Trials Initiative, or DATECAN, group, whose final intention is to obtain harmonized consensus definitions that advance intersociety communications (9).

Study Methodology

The initial methodology was developed and previously applied in four disease-specific projects, including pancreatic cancer (10), sarcoma and gastrointestinal stromal tumor (11), breast cancer (12), and renal cell cancer (13) initiatives. Institutional review board approval was not required as this study does not involve human participants. This article should be considered a supplement to the standardization of terminology reporting criteria recommended by Ahmed et al (8).

Coordinating Committee

The coordinating committee (Table E1 [online]) was composed of Society of Interventional Oncology research committee members (M.R.M., S.N.G., M.A., M.C.S., J.C., J.P.E., G. Nadolski, I.N.), one representative from the Definition for the Assessment of Time-to-Event End Points in Cancer Trials Initiative (C.B.), one health economist (V.M.H.C.), two epidemiologists (V.M.H.C., B.I.L.W.), one study coordinator (R.S.P.), and one operations manager (T.G.). The coordinating committee was responsible for the methodologic protocol and conduct (M.R.M., R.S.P., S.N.G., M.A., M.C.S., J.C., J.P.E., G. Nadolski, I.N., C.B.), survey and questionnaires (all coordinating committee members), data collection and analysis (M.R.M., R.S.P., S.N.G., M.A., C.B., V.M.H.C., B.I.L.W.), and guideline and manuscript preparation (all coordinating committee members).

Evaluating Committee

The coordinating committee reached out to at least one active board member of the following international scientific groups or organizations: Society of Interventional Oncology, Technology Assessment Committee of the Society of Interventional Radiology, Standard of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe, Interventional Oncology Sans Frontières Expert Panel, and Asian Society of Tumor Ablation. The board members were asked to provide us with a list of key opinion leaders. All potential participants in the evaluating committee (Table E2 [online]) were required to confirm that they had at least 5 years of experience in the field of clinical oncology research, published at least one article for a given cancer site, and participated in at least three clinical oncology trials. After having confirmed these requirements in the online questionnaire, all were asked if they could think of further participants. A total of 62 key opinion leaders from Europe (n = 29), the United States (n = 25), and Asia (n = 8) working in 48 centers eventually joined the evaluating committee. Data on experts' demographics, such as year of birth, current job position, professional membership, country of residence, time (in years) working in the field of interventional oncology, and familiarity with oncologic outcomes metrics, were collected.

Literature Review and Questionnaire Construction

A PubMed literature search resulted in a list of short-, mid-, and long-term oncologic outcome measures and time-to-event end points (Appendix E1 [online]). This list was used by the coordinating committee to generate the first questionnaire. The formal consensus method involved the following steps (Figure): *(a)* definition of problems, literature review, and appointing the experts' committees (by the coordinating committee); *(b)* development of definitions and recommendations (by the coordinating committee); *(c)* a three-round rating process and evaluation of responses (by the coordinating committee plus evaluating committee); *(d)* presentation of results and final attempt to reach consensus during in-person teleconference; and *(e)* creation of a final report with definitions plus recommendations.

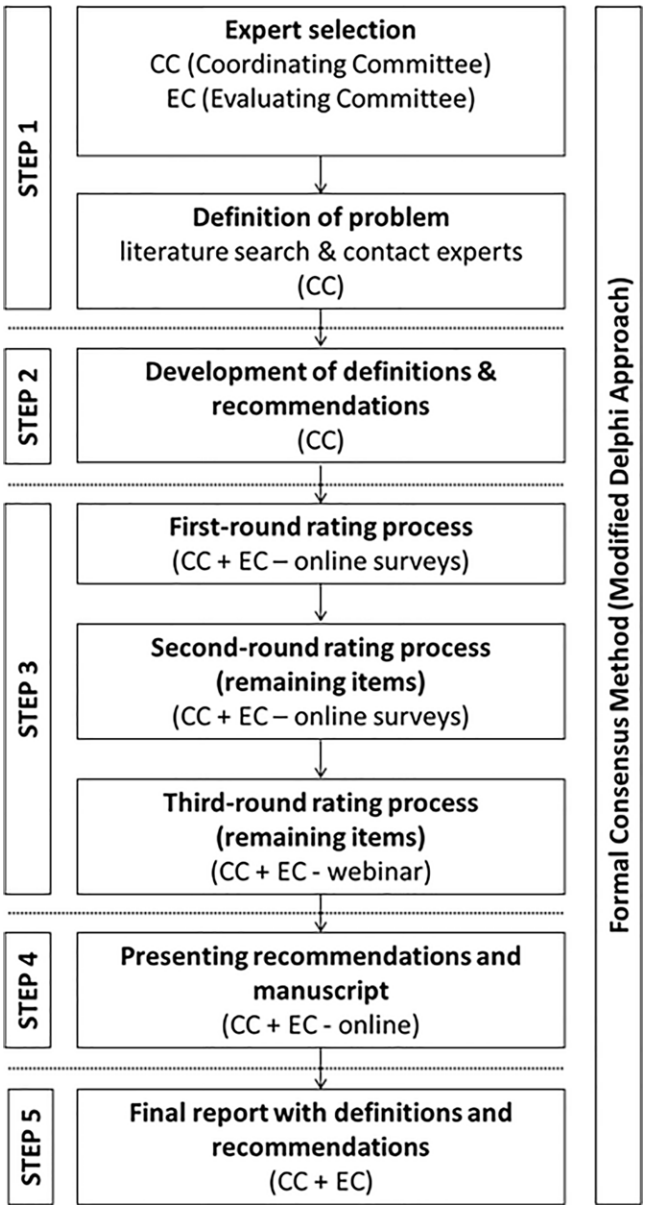
Consensus Process

A modified Delphi consensus is a structured and validated measurement instrument used for evaluation of expert opinion on health and medical topics (14). It has been widely used to establish consensus across a range of subject areas. The Delphi process formalizes the degree of agreement among experts by using a series of surveys that are iterated with feedback until consensus is reached.

The guidelines were developed in four coordinating committee meetings (April 2019, June 2019, October 2019, and January 2020). Two rating rounds and one in-person web-based conference call were scheduled to develop the recommendations. A total of three survey rounds, or fewer if consensus was reached sooner, were prechosen as this enables adequate reflection on group responses and is considered optimal to reach consensus. The questionnaires were internet-based and sent by e-mail. All panelists received a deadline for completing the survey and were sent weekly reminders to encourage participation.

Before the first round, panelists agreed to review three additional documents: *(a)* the standardization of terminology reporting criteria by Ahmed et al (8), *(b)* the list of relevant definitions as suggested by the coordinating committee (Appendix E1 [online]), and *(c)* the key instructions for filling in the consensus document.

In round 1, statements were evaluated using a 9-point Likert scale (where 1 = totally disagree and 9 = totally agree)



Flowchart of study design. The formal Delphi consensus method consisted of five steps: step 1, definition of problems, literature review, and appointing the experts' committees (by the coordinating committee [CC]); step 2, development of definitions and recommendations (by the coordinating committee); step 3, three-round rating process and evaluation of responses, including a final third round to reach consensus during a webinar (by the coordinating committee and evaluating committee [EC]); step 4, presentation of recommendations and manuscript to the evaluating committee; and, step 5, creation of the final manuscript.

to produce stable findings in Delphi consensus projects (9). For each statement, panelists were given a free-text response option. Relevant items previously defined by Ahmed et al (8) were presented, and panelists were asked whether the items could use adjustments. Items with strong consensus were locked and archived. Consensus was considered strong if all responses to a certain item were between 7 and 9, allowing up to two outliers. Strong consensus for the remaining single-answer multiple choice questions was defined as having reached at least 80% agreement among panelists. Data were analyzed anonymously.

The first-round answers were gathered and reported back to the panelists in the second round, where panelists rated only those items for which consensus had not been reached. Based on the first-round dispersal of scores (minimum, maximum, and median scores), each panelist was encouraged to reassess his or her initial judgments. Finally, for items remaining without consensus, a third round was organized. This in-person teleconference, led by a representative of the coordinating committee (M.R.M.), involved members of the coordinating committee and evaluating committee. The remaining items were discussed, and a preliminary draft of the recommendations was composed for validation by all panelists.

Results

The coordinating committee drafted a list of 62 key opinion leaders in the field of interventional oncology. Thirty-six of those 62 experts (58%) participated in the first round. All panelists are board-certified interventional radiologists. The panelists had an average of 20.9 years of experience (standard deviation, 7.7 years) in the field of interventional radiology, 11.1 years of experience (standard deviation, 7.7 years) in clinical trials serving as principal investigator, and 17.7 years of experience (standard deviation, 6.7 years) in clinical trials serving as collaborator. All panelists were familiar with oncologic outcome measures in their practice: 78% (28 of 36 panelists) always use them and 22% (eight of 36 panelists) use them occasionally. Additional detailed information regarding the panelists and their affiliated institutions is listed in Tables E1 and E2 (online). The experts rated a total of 62 items. A detailed comprehensive overview of the results, including all items and the level of agreement, is shown in Figure E1 (online).

Response rates were 58% (36 of 62 panelists), 56% (24 of 43 panelists), and 54% (23 of 43 panelists) in rounds 1 (July to October 2019), 2 (November 2019 to January 2020), and 3 (March 30, 2020), respectively. In round 1, consensus was reached on 27 of the 60 items (45%). The remaining 33 items were reiterated in the second round and two additional items, which emerged in the first round, were added. After two rounds, consensus was reached on 56 of the 62 items (90%). The remaining six items were discussed face-to-face in a videoconference (round 3; March 30, 2020). No consensus was reached regarding the recommended validated classification system to register complications, adverse events, quality of life, and health economics–related issues, although the panelists did agree to recommend the following statement: To document complications, adverse events, quality of life, and health economics–related issues, one should use and report the most recent version of a validated patient-reported outcome questionnaire.

In the first round, several panelists requested clarification regarding the use of the terms *to document, to analyze,* and *to report*. Accordingly, for future rounds the steering committee reached consensus regarding the following definitions: *(a)* to document means to collect and store patient-, procedure-, or tumor-related parameters in a centralized (preferably electronic, secure, and anonymized) study or registry database; *(b)* to analyze means to calculate, assess, and interpret congregated data derived from the documented patient-, procedure-, and tumor-related parameters; and *(c)* to report means to disclose the analyzed patient-,

procedure-, and tumor-related parameters in relation to the study outcomes with the intent to publish one's findings.

The consensus items were translated into the following recommendations by the coordinating committee to which the evaluating committee anonymously agreed.

Recommendations

Addressing Outcomes per Patient, per Procedure, or per Tumor

When assessing time-to-event data in randomized controlled trials, single-arm prospective studies, and/or retrospective comparative and noncomparative series, the following definitions should be analyzed per patient and not on a per-tumor or per-procedure basis: overall survival, disease-specific overall survival, disease-free survival, recurrence-free survival, progression-free survival, and distant progression-free survival (Table E3 [online]). Parameters that address both procedure-related adverse effects and direct costs should be addressed per procedure. This includes short-terms complications, anesthesia techniques, hospital-stay characteristics, and laboratory tests that, for example, assess organ function and the presence or absence of infectious complications. Technical success should be addressed per tumor and per procedure and not per patient. The term *session* can be used as a synonym for procedure. To assess the local efficacy of an ablative intervention, regardless of the oncologic outcome(s), one should address and report the following parameters per patient and per tumor: local tumor progression-free survival, time to local (tumor) progression, freedom from local or organ-specific recurrence, primary and secondary or assisted technique efficacy, residual disease, local progression, recurrence rates, and local control. Multiple index tumors (eg, multiple colorectal metastases or multifocal hepatocellular carcinoma) within one unique patient cannot be regarded as independent as these tumors are potentially correlated and hence study outcomes hypothetically interlinked. When using standard survival estimates (Kaplan-Meier or cumulative incidence functions), in cases with multiple index tumors in one patient, the dependency of partially correlated or clustered data is ignored and this potential limitation should be reported and stated in the discussion.

Starting and Ending Time Definitions

When assessing time-to-event data in randomized controlled trials, patients who did not receive the allocated treatment should be included in the intention-to-treat analysis. According to the intention-to-treat analysis, the starting time should be the date of randomization. In trials where all patients, regardless of the eventual randomization arm, are treated with induction or neoadjuvant therapy, randomization should be performed after completion of the neoadjuvant therapy. In addition, adding a per-protocol analysis should be considered, including only patients who actually received the allocated treatment, especially if a potential bias due to exclusion of patients exists. According to the specific per-protocol analysis, when assessing time-to-event data in randomized controlled trials, the starting time should also be the date of randomization. In addition, it should be considered to add data regarding the time from the intervention, especially when the period between randomization and eventual intervention is long or heterogeneous or if a large number of crossovers and/or patient dropouts exist.

For single-arm prospective studies and for retrospective comparative and noncomparative series, the starting time should be the date of the first intervention even if the therapy may require completion procedures (eg, completion ablation for insufficient margins). In case of sequential procedures (eg, a preplanned two-stage ablation followed by transarterial chemoembolization), the starting time should be the date of the first intervention.

When focusing on single-arm prospective series, where patients receive strict and homogeneous neoadjuvant or induction chemotherapy and/or radiation therapy regimens, one should document the time from *(a)* the date of detection of disease (diagnosis), *(b)* the date of the start of neoadjuvant or induction therapy, and *(c)* the date of the first interventional procedure.

If the risk of including a certain referral bias, lead-time bias, or immortality-time bias is present, then one should report time-to-event data both from the date of diagnosis and from the date of the start of the intervention.

To assess mid- to long-term outcomes following a given interventional procedure, one should document *(a)* the date of unequivocal presence of the event and *(b)* the date of an alternative event that excludes or alters the probability for a future event to occur (competing risk). During follow-up after a given interventional procedure, one should separately document *(a)* the date of the last contact moment (eg, laboratory tests, phone calls, consultations) that reliably confirms or excludes the presence of a given event, *(b)* the date of the last cross-sectional imaging or surrogate test that reliably confirms or excludes the presence of the event, and *(c)* (non)physical contact moments (eg, nontumor-specific laboratory tests, phone calls, consultations) that reliably exclude death, but not the presence or absence of disease.

Survival Time Definitions

If the patient's likelihood of dying from causes other than the disease being studied is substantial (eg, as with elderly patients or those with early-stage disease with a good prognosis), one should document and report both overall survival and disease-specific overall survival. In the statistical analysis, death due to causes other than the disease being studied should be considered a competing risk for the disease-specific survival analysis.

For early disease stages, when the intervention is likely curative (eg, ablation of small renal tumors), one should use recurrence-free survival. For intermediate disease stages, when the intervention is considered potentially curative (eg, ablation of colorectal liver metastases), one should use disease-free survival. For advanced disease stages, when the intervention is considered palliative, one should use progression-free survival.

Time to progression is defined as the time between the starting time and any disease recurrence (local, regional, or distant). Distant progression-free survival is defined as the time between the starting time and distant tumor progression, but not local or regional progression. Local tumor progression-free survival is defined as the time between the starting time and local tumor progression per tumor treated (per-tumor analysis) or per patient treated (per-patient analysis). Time-to-local (tumor)

progression is defined as the time between the starting time and local tumor progression per tumor treated, resulting in a horizontally flipped survival curve (1 − local tumor progression-free survival).

Death due to any cause without documented signs of local, regional, or distant disease progression should be considered a competing risk.

Time-to-Event Outcome Definitions and Data Censoring

To calculate the survival probability, one should use the Kaplan-Meier survival estimate method, including the number of events and the numbers at risk at each evaluation time point. Cumulative incidence function curves are preferred or should be added to the Kaplan-Meier estimates if the number of competing risks in a certain (sub)group is substantial, showing the cumulative failure rates over time due to a particular cause. With respect to data censoring, one should report the type of data censoring (right-, left-, or interval-censored observations). The date of cross-sectional imaging or any other technique that unequivocally demonstrates a certain event should be considered the date of the event (left-censored data). Both for interim and final analyses, the date of assessment should be predefined either at a fixed point in time after inclusion of a certain number of individuals or after reaching a certain number of events. Any individuals remaining event-free and at risk should be right censored. Interval-censored observations, where a virtual halftime date between two cross-sectional imaging examinations is considered as the actuarial date of the event, should be avoided.

Eligibility

In prospective randomized and nonrandomized studies, the number of eligible patients (who fulfill the inclusion criteria and who do not meet the criteria for exclusion) should be documented and reported, as well as the number of eligible patients who eventually do not participate. If possible, the reason for nonparticipation (eg, refusal or failure to meet the inclusion and exclusion criteria during work-up and/or during neoadjuvant or induction therapy) before formal recruitment (inclusion) should be documented and reported.

Recruited (included) patients who signed informed consent are considered active study participants during the predefined time they are "within the study." Active study participants who, for any reason (patient's wish to end study participation or loss to follow-up), fail to continue participation in the period predefined as "within the study" should be considered study dropouts, regardless of whether they dropped out before or after randomization.

If active study participants refuse to undergo the allocated treatment arm, then the patient undoes their trial enrollment. To eliminate any undesired impact on study-related outcomes, the investigators should formally end patients' active participation before they receive any alternative therapy. Patients who cross over from their allocated treatment arm to another study treatment arm, but who remain "within the study," should be regarded as crossover patients. The number of patients who cross over to another treatment arm should always be minimized.

Technical Success, Technique Efficacy, Local Control, and Ablation Confirmation

Technical success addresses whether the tumor was treated according to protocol and covered completely by the ablation zone, if possible by using ablation confirmation techniques (see explanation below). One should document and report the technical success rates. Technique efficacy refers to a prospectively defined point in time when complete ablation of macroscopic tumor was achieved, as evidenced by imaging follow-up or any alternative technique (ie, biopsy or serologic criteria). If a patient died due to any cause before that point in time, then the event should be analyzed and reported as a competing risk. Primary efficacy rate refers to the percentage of target tumors successfully eradicated following the initial ablation, whereas secondary or assisted technique efficacy rate refers to the percentage of target tumors eventually eradicated, including with repeat ablations, using the ablative method being studied. Local control is equivalent to assisted technique efficacy, with the exception that repeat treatments using alternative methods (other ablative methods, radiation therapy, or surgical excision) are allowed. Residual unablated tumor refers to the presence of residual viable tumor at the ablative margin at initial follow-up imaging, whereas local tumor progression refers to reappearing viable tumor provided that at least one contrast-enhanced follow-up study did not reveal residual viable tumor at the ablative margin.

Ablation confirmation refers to postprocedural imaging, or any alternative technique, that is implemented with the intent to allow for additional overlapping (completion) procedures either within the same procedure or in a complementary completion session in the days or weeks hereafter. For percutaneous ablations, one should attempt to document and report the minimum tumor-free margin. For CT-guided ablations, rigid or nonrigid image fusion and registration should be performed to confirm complete ablations, including circumferential safety margins of treated peri-ablational tissue (8,15,16). One should attempt to report the method of assessment of complete tumor coverage and safety margins (eg, image fusion software) as close to the time of ablation as possible, ideally immediately, or at least within 24 hours after ablation.

Complications, Adverse Events, Quality of Life, and Health Economics–related Outcomes

Complications, defined as any unexpected departure from a (post)procedural course, and adverse events, defined as any actual or potential injury related to a procedure, should be documented and reported, citing the most recent version of the used validated classification system so that they can be categorized consistently according to severity, time of occurrence (eg, intraprocedural, postprocedural, or late), and likelihood of the event being related to the procedure. Although not meant to represent an exclusive list, the following classification systems are used to report complications and adverse events: *(a)* Common Terminology Criteria for Adverse Events standards, *(b)* Clavien-Dindo classification, *(c)* Society of Interventional Radiology classification, and *(d)* Cardiovascular and Interventional Radiological Society of Europe Quality Assurance Document and Standards for Classification of Complications (17–20). In accor-

dance with the previous standardization of terminology consensus document by Ahmed et al (8), pain should be reported using the most recent version of the Common Terminology Criteria for Adverse Events of the National Cancer Institute.

Quality of life should be stratified according to disease stage and patient's functional status. One should document and specifically cite the most recent version of the validated classification system used. Quality of life should be assessed both before (baseline) and after treatment, regardless of disease progression. Although not meant to represent an exclusive list, the following standardized questionnaires have been issued for assessing the quality of life: *(a)* European Organization for Research and Treatment of Cancer, *(b)* Functional Assessment of Chronic Illness Therapy or Cancer Therapy, *(c)* World Health Organization Quality of Life scale (WHOQOL-BREF), *(d)* Health Utilities Index, *(e)* Short Form Health Surveys (SF-36, SF-12), *(f)* Nottingham Health Profile, *(g)* Quality of Well-Being Scale, and *(h)* Consumer Assessment of Healthcare Providers and Systems. Irrespective of the chosen method, one should always attempt to use general measures; cancer-, treatment-, and symptom-specific questionnaires; and non–cancer-specific (satisfaction) questionnaires.

For health economics–related outcomes, both a cost-effectiveness analysis and a comparative-effectiveness analysis are essential for defining the position of tumor ablation in relation to its alternatives. Health economics–related outcomes should be documented and reported, specifically citing the most recent version of a validated classification system used. Although not meant to represent an exclusive list, standardized questionnaires that can be used include the generic EuroQoL Group (Rotterdam, the Netherlands) forms for the assessment of quality-adjusted life years (EQ-5D; EuroQol Group) and the Productivity and Disease Questionnaire, or PRODISQ, for the assessment of cost-effectiveness.

Discussion

Over the past 2 decades, image-guided thermal and nonthermal tumor ablation techniques have become indispensable therapeutic options for a variety of cancer types. For certain smaller-size malignant tumors (eg, hepatocellular carcinoma, colorectal and other liver and lung metastases, renal cell carcinoma, prostate cancer, and neuroendocrine tumors), international guidelines have already adopted thermal ablation as a first-line treatment option (21–23). The continuing emergence of novel treatment options and growing demand for minimally invasive image-guided tumor ablation techniques have raised the need for evidence-based interventional oncology, and with that comes the need for clear documentation of oncologic outcome parameters.

The response rates in our study were 58%, 56%, and 54% in rounds 1, 2, and 3, respectively. After three rounds, consensus was reached for all items but three (95%; 59 of 62 items). Consensus was not reached for the preferred validated classification system to document, analyze, and report complications and adverse events, quality of life, and health economics–related issues. Nonetheless, the panelists unanimously agreed on the statement that "complications and adverse events, quality of life, and health economics–related issues should be documented and reported specifically citing the most recent version of the validated classification system used." Review of the literature and discussions within the committees made it clear that outcome assessment in interventional oncology can be challenging. To date, neither a specific outcome nor a specific outcome measure is a widely accepted standard tool in interventional oncology. The disproportionate interest in the local effectiveness of a certain ablative technique and the complexity of correctly analyzing treatment methods that can be repeated and that can be used to treat multiple index tumors in a single individual can explain this. However, it does not relieve treating physicians of their duty to provide hard and unequivocal evidence that our treatments prolong survival, improve quality of life, or reduce costs.

These guidelines for the definition of time-to-event end points have been developed as an in-depth supplement to the more concise standardization of terminology and reporting criteria in image-guided tumor ablation published by Ahmed and colleagues (8). The participation of independent epidemiologists and members of the Definition for the Assessment of Time-to-Event End Points in Cancer Trials initiative study group and the large number of international key opinion leaders from various institutions in the expert panel, as well as the relatively high response rates for all survey rounds, strengthen our methodology and indicate its importance. As stated by the Centre for Evidence-based Medicine, Delphi consensus studies are considered level 5 evidence (24). As an anonymous technique, it prevents expert participants from conforming to the opinion of others (25). Depending on the participant selection tools, the number of rounds and what to do in which round, the specific cutoff values applied, and whether to discuss with the experts has led to several variants of the original Delphi method. The coordinating committee chose to use the well-documented three-step modified Delphi consensus method as proposed by Jones and Hunter (14), which is also used in the development of various national clinical guidelines.

One potential drawback of our study was the relative homogeneity of the academic and professional background of the panelists (all interventional radiologists). This may impair the generalizability and validity of the recommendations made herein. Nonetheless, image-guided tumor ablation is most often performed by interventional radiologists, and the responsibility to attend multidisciplinary tumor boards, to have a thorough understanding of the guidelines and available evidence, to establish periprocedural care, and to provide robust evidence for new oncologic interventions has previously been emphasized by many, thus minimizing this limitation. General limitations of the Delphi consensus method are the lack of guidance and agreed standards on how to select participants and the fact that it is time-consuming and laborious for participants, which explains why it is vulnerable to dropouts. Participants might also drop out due to the long temporal commitment, distraction between rounds, or disappointment with the process.

This study provides a framework of key opinion leader recommendations regarding patient-, procedure-, and tumor-related definitions, starting and ending time definitions, survival time definitions, time-to-event end points, and patient-reported outcome measures. Clear definitions will provide the necessary foundation for scientific reproducibility between studies as they will ensure an objective and reliable interpretation of results, allow for accurate comparison of outcomes, and

avoid misinterpretations. We encourage all of our colleagues to adopt the recommendations outlined in this proposal to facilitate worldwide communication of scientific advances in the field of interventional oncology.

Author contributions: Guarantors of integrity of entire study, R.S.P., Y.A., G.C., A.K., F.O., M.R.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, R.S.P., M.A., A.A., C.B., C.L.B., D.J.B., E.B., G.C., J.C., A.D., A.G., B.G., T.H., A.K., M.W.L., P.L., D.S.L., D.C.M., G.M., M.F.M., R.M., G. Nadolski, F.O., J.R., W.R., R.S., H.J.S., C.T.S., L.A.S., D.S., B.J.W., S.N.G., M.R.M.; clinical studies, R.S.P., R.A., C.L.B., E.B., G.C., F.d.C., D.E.D., A.G., R.I., P.L., M.F.M., G. Nadolski, G. Narayanan, F.O., H.R., W.R., R.S., L.A.S., T.J.V., M.R.M.; experimental studies, A.G., R.I., G. Nadolski, F.O., H.R., L.A.S.; statistical analysis, R.S.P., C.B., A.G., B.I.L.W., F.O., L.A.S., T.J.V., M.R.M.; and manuscript editing, R.S.P., M.A., Y.A., R.A., T.d.B., R.B., C.B., C.A.B., C.L.B., D.J.B., E.B., M.R.C., J.C., V.M.H.C., L.C., A.D., J.P.E., D.F., A.G., B.G., T.H., T.W.K., H.S.K., T.K., F.T.L., E.W.L., D.S.L., D.C.M., G.M., M.F.M., R.M., G. Nadolski, G. Narayanan, B.N., F.O., P.L.P., U.P., J.R., W.R., H.J.S., C.T.S., L.A.S., S.B.S., M.C.S., D.S., R.U., T.J.V., D.S.W., B.J.W., S.N.G., M.R.M.

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