

Research Reporting Standards for Percutaneous Thermal Ablation of Lung Neoplasms

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Abbreviations: FGD = [¹⁸F]fluorodeoxyglucose, NSCLC = non-small-cell lung cancer, PET = positron emission tomography, RF = radiofrequency, SIRTAC/IWGIGTA = Society of Interventional Radiology Technology Assessment Committee and International Working Group on Image-Guided Tumor Ablation

CANCER is the leading cause of death in the United States for persons between the ages of 1 and 85 years (1). Non-

small-cell lung cancer (NSCLC) is the leading cause of cancer mortality in American men and women, accounting for approximately 29% of all cancer deaths (1–3). In addition, the lungs are the second most common organ for metastases from solid tumors (4,5).

Dupuy and colleagues (6) first reported the use of radiofrequency (RF) ablation for treatment of lung cancer in 2000. Since that report, at least 30 peer-reviewed manuscripts involving more than 1,000 patients have been published on the topic of RF and other thermal ablation techniques to treat lung cancers (7–38). These works suggest therapeutic efficacy for thermal ablation of lung and other thoracic malignancies in selected patients. Unfortunately, these investigators have used a wide range of study designs and reporting lexicons, which limits the ability to translate the experience of individual reporting institutions to that of the overall community of thermal ablation operators. This nonuniformity of reporting limits the ability to meaningfully compare outcome data for optimization of patient selection, ablation technique, and clarification of direction of future research. Particularly lacking are large prospective randomized controlled trials comparing thermal focal ablative therapy to competitive surgical and nonsurgical standard therapies for treatment of specific cell types and stages of lung malignancies. The purpose of this article is to improve the quality and translatability of research on the use of thermal ab-

lation to treat primary and secondary lung malignancies by presenting universal guidelines from the Society of Interventional Radiology (SIR) on research reporting standards on this topic. This document is designed for reporting research, not reporting clinical procedural notes on individual patients.

With respect to NSCLC, prognosis and treatment options are highly dependent on the clinical stage of the tumor as well as comorbid conditions. Familiarity with the tumor/node/metastasis (TNM) staging system of NSCLC is crucial for thermal ablation operators and investigators in the field of lung cancer. An outline of the TNM staging system is presented in **Tables 1 and 2**. In general, when technically feasible in a patient who can withstand surgery, surgical resection affords a patient with NSCLC the highest probability of long-term survival (39). For patients with stage I NSCLC in whom no lymph node metastases are evident by imaging, lobectomy has been demonstrated to be associated with a lower recurrence rate and improved survival compared with sublobar resections (40,41). The reason for the improved results with lobectomy and mediastinal lymph node sampling is that microscopic lymphatic metastases, commonly present in hilar and ipsilateral mediastinal lymph nodes, are removed with this operation. Five-year survival rates in patients with stage I NSCLC who undergo lobectomy are approximately 70%. Sublobar resection, radiation therapy, and image-guided ablative

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Table 1
Stage Criteria in the TNM Staging System for NSCLC⁵⁸

Stage	Description
Primary Tumor (T)*	
TX	Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (e.g., not in main bronchus)
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are T2a if ≤ 5 cm) <ul style="list-style-type: none"> • Involves main bronchus, ≥ 2 cm distal to the carina • Invades the visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in different ipsilateral lobe
Nodal Involvement (N) (Regional Lymph Nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes including involvement by direct extension
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis

* Most pleural effusions associated with lung cancer are caused by tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is not bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2, or T3.

therapy are usually reserved for patients who cannot undergo lobectomy because of comorbid conditions.

In patients with pulmonary solid tumor metastases, metastasectomy and other sublobar resections are an accepted alternative technique to lobectomy (42–46). In properly selected patients, resection of pulmonary metastases may result in improved disease-free survival. In patients who are not operative candidates, focal ablative therapy potentially may be beneficial.

CURRENT STATUS OF RESEARCH REPORTING FOR IMAGE-GUIDED TUMOR ABLATION

In 2005, Goldberg and collaborators (47,48), on behalf of the SIR Technology Assessment Committee and the International Working Group on Image-Guided Tumor Ablation (SIRTAC/IWGIGTA), published their updated consensus report on standardization of terminology and reporting criteria for

generic image-guided tumor ablation. Because the editorial staffs of both *Radiology* and the *Journal of Vascular and Interventional Radiology* have agreed to adopt the recommendations offered by this group for publications, investigators in the field of image-guided thermal ablation are strongly encouraged to familiarize themselves with the content of this article and confirm that reports meet these standards. Brief highlights of their recommendations follow.

Tumor ablation is defined as “the

Table 2
IASLC Lung Cancer Staging Project: Proposed TNM Categories and Stage Groupings for NSCLC⁵⁸

T/M Descriptor	Sixth Edition TNM Staging	Proposed			
		N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (≥2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5–7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (>7 cm)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion	—	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	—	IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)	—	IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)	—	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Note.—When the T, N, and M categories have been assigned, this information is combined (stage grouping) to assign an overall stage of 0, I, II, III, or IV. Stage groupings in bold represent a change in status from Sixth Edition grouping. IASLC = International Association for the Study of Lung Cancer.

direct application of chemical or thermal therapies to a specific focal tumor (or tumors) in an attempt to achieve eradication or substantial tumor destruction." The generic term "image guidance" is preferred, as most tumor ablation can be performed with a variety of imaging modalities. Thermal ablation procedures are those that cause tumor destruction through application of thermal energy, either heat or cold.

Tumor ablation performed in one episode is termed a procedure or a session. A treatment refers to a completed effort to thoroughly ablate one or more tumors, and may involve more than one procedure or session. The number of sessions or procedures required to achieve a treatment should be reported.

The generic term used for thermal ablative device is "applicator." Appropriate terms used for specific energy forms are "electrodes" for RF ablation applicators, "antennas" for microwave applicators, "fibers" for laser applicators, and "cryoprobes" for cryoablation applicators.

RF ablation refers to electromagnetic energy sources with frequencies less than 30 MHz. The specific devices, the algorithm of energy depositions, and adjuvant therapies, if employed, need to be specified. Recommended terms for

specific types of RF electrodes include "multitined expandable electrodes," "internally cooled electrodes" (either single or cluster), and "perfusion electrodes." If adjuvant therapies are used, the rationale for use and specifics of technique should be detailed. Microwave ablation refers to electromagnetic tumor necrosis with devices that emit frequencies between 30 MHz and 30 GHz. Information provided should include the specific frequency and type and number of applicators used. "Laser ablation" is the appropriate term for ablation using light energy. Description of technique needs to include the laser light source, wavelength, description of the specific device employed, algorithms of energy application, laser power, duration of energy application, total energy applied, and type of energy application if multiple laser fibers are used. Focused ultrasound (US) ablation needs to be specified whether it is extracorporeal or directly introduced with applicators. Cryoablation applies to methods of tissue destruction using freezing. Reporting should include the low temperature achieved, gasses used, cryoprobe description and number, and numbers and duration of freeze/thaw cycles. If available, estimated distance between the location of the thermistor and the tip of the cryoprobe would be desirable.

Tissue blood flow affects all methods of thermal ablation. The heat-sink effect refers to alteration of ablation zone size, morphology, and homogeneity caused by blood flow in blood vessels greater than 1 mm in diameter. Perfusion-mediated tissue cooling (or warming in the case of cryoablation) refers to ablation zone alterations induced by blood flow both in vessels greater than 1 mm and in the microcirculation. If techniques are used to reduce the effect of blood flow on tumor ablation, the specific technique used should be reported.

The specific imaging modalities and techniques used to plan, target, monitor, control, and assess therapeutic response to tumor ablation should be included in the reports. Regarding assessment of outcome, the imaging strategy and diagnostic criteria need to be specified. Usually, imaging findings after ablation reflect zones of diminished perfusion (eg, absence of contrast enhancement) or alterations in tissue appearance of signal intensity, echogenicity, or attenuation. The cited SIRTAC/IWGIGTA publication (47,48) details specific imaging findings during and after tumor ablation that should be addressed in reports of research results, including the presence of a transient hyperechoic zone, ablative margin, benign periablation enhancement, irregular peripheral enhancement, and involution of coagulation.

Specific recommendations were given regarding reporting tumor and ablation dimensions. The tumor targeted for ablation is referred to as the index tumor. As the time and effort expended to ablate tumors and the probability of complete tumor necrosis are highly dependent on tumor size, the actual dimensions of the index tumor, as well as the mean, SD, and range, should be included for the report. For the purposes of comparison of results between series or reports, tumors may be categorized as small when less than 3 cm in diameter, intermediate when between 3 and 5 cm in diameter, and large when exceeding 5 cm in diameter. Ideally, ablation zone descriptions would include all three dimensions. At a minimum, the short-axis diameter should be reported because that dimension is most closely related to the probability of ablation causing complete tumor necrosis and the number of applications required to completely ablate a tumor.

Technical success refers to the ability to treat the tumor per protocol with

Table 3
SIR Definitions and Grading System of Complications

Complication Category	Description
Minor	Require no therapy, result in no consequence Require nominal therapy, result in no consequence; includes overnight admission for observation only
Major	Require therapy and minor hospitalization (<48 h) Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 h) Result in permanent adverse sequelae Result in death

complete coverage. Alternatively, technique effectiveness refers to the ability to completely eradicate the index tumor(s) based on findings at follow-up. Complete tumor destruction may require more than one treatment session. Primary effectiveness rate is the percentage of tumors successfully eradicated by the initial procedure(s). Secondary or assisted effectiveness rates include those tumors thought initially to have been completely treated that developed local tumor progression that in turn was successfully eradicated by a repeated ablation. The SIRTAC/IWGIGTA committee recommended reporting only complete and incomplete status of tumor ablation. Given the absence of evidence of benefit for different degrees of incomplete tumor ablation, stratification based on the estimated portion of incomplete tumor ablation appears to be meaningless. In cases in which ablation is used for palliative symptom reduction, objective measures of symptom response should be used and presented in the reported results.

When tumor progression occurs after ablation, distinction should be made whether it involves local tumor progression, new tumors elsewhere within the treated organ, or distant metastases. Causes of mortality preferably differentiate those deaths caused by tumor progression from those caused by other comorbid conditions. They are also differentiated in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (49,50).

Complications are to be reported using the published SIR grading system (Table 3) as well as the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (49,50). Deaths are to be reported on a per-patient basis with particular emphasis on

deaths occurring within 30 days of an ablation procedure. The cause of mortality should be specified, including the likelihood of the death being procedure-related. Major complications are to be differentiated from minor complications, categorized according to SIR guidelines, and reported on a per-ablation procedure basis. Furthermore, the time of clinical manifestation preferably would be stratified as immediate (within 24 hours), periprocedural (within 30 days), or delayed (>30 days after ablation). For reporting pain following an ablation procedure, the committee proposed adoption of the Common Toxicity Criteria of the National Cancer Institute (50).

Clinical outcomes should include local tumor response, systemic tumor response, quality of life, and survival. When responding to quality of life outcomes, use of objective and preferably validated scales are encouraged. Imaging follow-up intervals should be specified. Imaging assessment of tumor control should include both the diameters of the index tumors and ablation zone as well as the presence or absence of tumor contrast enhancement. The appropriate length of follow-up will likely be a function of the tumor biology and aggressiveness. The report should include the mean and/or median length of follow-up as well as the ranges and/or SDs if appropriate.

To facilitate reproducibility of results, the SIRTAC/IWGIGTA committee recommended that investigators specify a number of technical details. This list included the device manufacturer, the type and duration of energy applied, the number of treatment sessions for each tumor, the type of approach (eg, percutaneous, open, or laparoscopic/endoscopic), whether general

anesthesia or conscious sedation was used, type(s) of imaging guidance, whether the patient was hospitalized, the number of sessions required to achieve technical success, and rates of subsequent tumors requiring ablation. The reported patient population features should include inclusion and exclusion criteria; tumor type (including diagnostic proof), size, number, location, and stage; patient demographics and comorbidities; and the use, timing, and specific protocols of other oncologic therapies. Preferably, the report should include the number of patients, tumors, treatment sessions, and ablation procedures. The therapeutic goal (cure vs survival benefit vs palliation) should be stated.

Several recommendations were made regarding statistical evaluation. Primary and secondary endpoints should be clearly stated. Survival outcome should use Kaplan-Meier life-table analysis. In comparative studies, it is preferable to have patients randomized into treatment groups. Results should be reported on an intent-to-treat basis. Outcomes should be stratified by appropriate factors such as tumor type, grade, and stage, patient performance status, and comorbidities. Commonly reported outcomes used for comparison with alternative therapies include overall survival, disease-free survival, and quality of life.

The generic recommendations of the SIRTAC/IWGIGTA are to be followed. The remainder of the present article is intended to fine-tune reporting recommendations as they apply to thermal ablation of malignancies specifically located in the lungs. The topic of palliative thermal ablation of malignancies that arise within or invade the chest wall lies outside the scope of this report, and will be covered in a separate reporting standards publication on thermal ablation of musculoskeletal tumors.

DEFINE POPULATION

Patients with malignancies in the lungs present a wide range of clinical scenarios. Tumors may be primary to the lungs or metastatic deposits from elsewhere. The biologic aggressiveness and patterns of dissemination are reflections of the tumor cell type and clinical stage. The tumor size, number, location, and pattern and degree of

extrapulmonary spread are highly variable.

If anatomically and technically feasible, resection of the entire tumor burden—and in the case of patients with NSCLC, removal of draining lymphatic channels and regional lymph nodes that may harbor microscopic metastases—is usually the patient's best option for potential cure or prolonged survival. However, many such patients will not be optimal candidates for a surgical resection such as lobectomy with mediastinal lymph node sampling as a result of comorbid conditions such as chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, or advanced stages of malignancy. Some such patients may benefit from less invasive surgeries, thermal ablation, radiation therapy, or chemotherapy.

For clinicians, patients, and third-party payers to make rational evidence-based treatment decisions for patients who may have a wide range of clinical presentations, it is incumbent upon investigators to carefully define, describe, and stratify their subject populations. For both retrospectively accrued case series and prospectively enrolled series, thorough presentation of population demographics is necessary (discussed later). For studies that use prospective subject accrual, and for many case series, explicit description of enrollment inclusion and exclusion criteria should be given. Translatability of study results to other operators and centers, and over time, are central to advancement of lung cancer therapies.

Inclusion criteria are set to define the population believed most likely to benefit from the experimental therapy and are therefore eligible for treatment under the research protocol. Inclusion criteria should specify which tumor types are being studied. As tumor size and location strongly influence the probability of obtaining complete necrosis and causing complications, a definition of acceptable tumor diameter(s), number, and locations within the lungs needs to be stated. The method used to establish the diagnosis of lung malignancy, such as percutaneous biopsy, should be given. Demographic boundaries for enrollment of patient with lung cancers should be detailed. For example, a study may include patients with stage I NSCLC, ages between 18 and 85 years, with an

Eastern Cooperative Oncology Group performance score of 0–2, and a life expectancy of at least 3 months. Because thermal ablation has not been established as standard first-line therapy for treatment of lung cancers, the reason patients are included in the study should be explained. As an example, patients with stage I NSCLC may be included if they were not candidates for resection as a result of advanced comorbid conditions or refusal to undergo surgery. Other cases of advanced symptomatic malignancies may have been refractory to radiation therapy, chemotherapy, or opioid analgesics. A randomized controlled trial would need to carefully define those patients amenable to be enrolled in the experimental arm of thermal ablation and the control arm of standard therapy.

Exclusion criteria are necessary to maintain maximal patient safety and purity of data analysis. Patient factors may include extremes of age, advanced comorbidities, specific device risks such as cardiac pacemakers in patients undergoing RF ablation, history of allergies or contraindications to agents involved in performing the ablation or assessment of outcome (eg, iodinated contrast agent reactions or renal insufficiency), and potential risk to unborn fetuses. Other exclusion criteria exist to protect dependent patients such as minors, incarcerated patients, or patients unable to provide informed consent. Some exclusion criteria are in place to protect patients for whom benefit is unrealistic, such as a poor performance status (Table 4), limited life expectancy, or significant extrapulmonary malignant disease. Exclusionary limits on tumor number and size need to be stated. Some tumors may occur in locations likely to result in mechanical or thermal injury of critical nontargeted structures such as the heart, mediastinum, central airways, or brachial plexus. Criteria used to exclude treatment based on tumor location need to be specified. Patients with cancer frequently receive a variety of interdisciplinary therapies at different times during the course of their disease. These multiple therapies may confound interpretation of outcome responses and complications. If limitations are placed on permissible antecedent, concurrent, or subsequent therapy to thermal ablation, these exclusions need to be presented.

Table 4
Eastern Cooperative Oncology Group/
Zubrod Performance Status Scale

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; spends >50% of time in bed, but not bedridden
4	Completely disabled; no self-care; 100% bedridden

DEFINE OUTCOME OF THERAPY

Establishing the trial endpoints is both a function of the type of trial and a determinant of how the trial is to be structured. The appropriate measure of outcome will depend on the specific trial design and relative phase in the course of data maturity. Early phase prospective trials, analogous to chemotherapy phase I trials, usually evaluate issues of safety and, when relevant, most appropriate parameter or dose of an agent that has a potential range of operational or dose parameters. Outcome measures frequently include toxicity according to the Common Toxicity Criteria of the National Cancer Institute (50) and complications according to SIR guidelines (49), including mortality. Intermediate-phase prospective trials, analogous to phase II pharmaceutical trials, incorporate measures of therapeutic efficacy, typically as single arm trials. Common examples include complete necrosis or tumor response to treatment based on Response Evaluation Criteria In Solid Tumors, World Health Organization, or other anatomic imaging guidelines; tumor response based on serologic markers; tumor response based on surrogate functional imaging parameters such as contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging, diffusion-weighted MR imaging, or positron emission tomography (PET)

scanning; time to progression locally, within the treated organ, or overall; and tumor-free survival or overall survival. Late-phase trials, analogous to phase III pharmaceuticals trials, evaluate safety and efficacy comparing a group of patients undergoing the experimental therapy versus a comparable, preferably randomized, group of patients undergoing standard therapy.

In these prospectively enrolled trials, the primary endpoint is the outcome measure that is used to prove safety or efficacy and for which the trial is statistically powered to demonstrate significance. Ideally, the selected outcome measure is directly a function of the safety and efficacy of the therapeutic agent with few confounding variables. Secondary endpoints are the other important patient care efficacy and safety outcome measures that are concomitantly collected and evaluated, but for which the study is not powered to assess significance. Frequently, secondary endpoints include outcome measures such as overall survival that depend not only on the response of the index tumor to ablative therapy, but also on disease spread to other locations, additional therapies the patient receives, and comorbid conditions. Specific primary and secondary endpoints need to be detailed in all reported prospective trials.

Retrospective case series are usually less stringent but frequently less useful as well. Data collected will include those of primary or secondary interest to test a given hypothesis. However, primary endpoints are not strictly relevant because the trial is not powered prospectively. Nevertheless, the specific outcome data collected and analyzed should be listed.

PRETREATMENT EVALUATION

Patient Evaluation

Pretreatment evaluation of patients for thermal ablation must include assessment of demographics (age, sex, and any other variables relevant to risk of disease or complications). Any known or putative risk factors for lung cancer should be noted, such as smoking, occupational exposure, and interstitial lung disease. Because a large percentage of patients with NSCLC have a heavy smoking history, chronic pulmo-

Table 5
Criteria for Surgical Lobectomy for NSCLC

Major Criteria
FEV1 \leq 50%
DLCO \leq 50%
Minor Criteria
Age \geq 75 y
FEV1 51%–60% predicted
DLCO 51%–60% predicted
Pulmonary hypertension (defined as a pulmonary artery systolic pressure $>$ 40 mm Hg) as estimated by echocardiography or right heart catheterization
Poor left ventricular function (defined as an ejection fraction \leq 40%)
Resting or exercise arterial $pO_2 \leq$ 55 mm Hg or $SpO_2 \leq$ 88%
$pCO_2 >$ 45 mm Hg

Note.—Fulfillment of one major criterion or at least two minor criteria usually prevent a patient from being a candidate for surgical lobectomy for NSCLC. DLCO = carbon monoxide diffusing capacity; FEV1 = forced expiratory volume in 1 second; pO_2 = partial O_2 pressure; SpO_2 = O_2 saturation.

nary obstructive disease and other pulmonary and cardiac comorbidities are common and should be reported. These comorbidities are common reasons that patients with NSCLC cannot undergo lobectomy and are therefore candidates for thermal ablative therapy and other less invasive options (Table 5). Conversely, these same cardiopulmonary comorbidities frequently place these patients at higher risk of complications from ablative therapy. Other comorbidities must be reported, including essential hypertension, cerebrovascular disease, diabetes mellitus, and/or other malignancies. In addition to risk stratification for future treatment algorithms, this enables identification of patients who may have a lower tolerance for procedural complications.

Tumor Characteristics

Patients who are candidates for thermal ablation will generally present with stage I disease, ie, T1/2 N0 M0 disease (Table 1). Currently, tumor size should be recorded as the maximum unidimensional tumor diameter as seen on a CT scan displayed on lung windows, in ac-

cordance with the Response Evaluation Criteria In Solid Tumors adopted by the National Cancer Institute. When more detailed assessment of tumor size is recorded, including dimensions in three orthogonal axes, tumor volume estimated from the orthogonal diameters, or measurement of tumor volume using volume-rendering software, the method of volume estimation should be specified.

Nevertheless, tumor diameter is only one of several important determinants of technical success of thermal ablation. NSCLC location is an important determinant of ablation success. Perilesional air can produce a thermally insulating effect, resulting in more efficient thermal ablation. Therefore, a peripheral tumor surrounded by air and away from pulmonary vessels may be more likely to be completely ablated than a more central tumor. Tumor proximity to a major pulmonary vessel can result in residual viable tumor following thermal ablation as a result of heat-sink effects. Proximity to esophagus, pericardium, or mediastinum may be relative contraindications to percutaneous thermal ablation or require adjunctive techniques to prevent off-target heating of adjacent structures during the ablation procedure. Consequently, anatomic location of all treated tumors must be reported.

TREATMENT DESCRIPTION

Preablation Biopsy

Biopsy should always be performed before ablation to prove malignancy, as thermal ablation probably has no role thus far for treatment of benign lung disease. Biopsy can be performed at a separate sitting or during the same procedure before the introduction of the applicator. Specific cell type should be determined because management varies considerably. Small-cell lung cancer is usually considered a systemic disease and is treated with chemotherapy, whereas early-stage NSCLC is primarily treated with resection or other destructive techniques. A second small NSCLC could represent intrapulmonary metastasis (ie, stage IV disease) or a new primary NSCLC (ie, stage I disease). Metastases to the lung represent a wide range of diseases: some respond well to chemotherapy, others do not. In patients

with oligonodular metastatic disease, biopsy confirmation of the primary tumor or previously known metastatic disease is usually sufficient in the setting of newly developing or growing pulmonary nodules with imaging features consistent with metastatic lesions. In patients being treated for palliation, repeat biopsy is usually not required, provided imaging and serologic findings are strongly suggestive of malignancy. Results of biopsy, when performed, must be reported. Instances in which biopsy is not performed must be specifically described.

Method of Targeting and Monitoring

Thermal ablation of lung cancers may be performed with CT guidance with or without CT fluoroscopic control. The imaging method used must be described. When multitined expandable electrode systems or a configuration of multiple synchronously placed electrodes are used for RF ablation, final tine and electrode position before the application of RF energy should be verified with a scan volume through the treatment region. If routine image confirmation of applicator location is obtained, it should be reported as such. The goal of thermal ablation for lung tumors is to achieve a treatment margin that extends just beyond the margin of the tumor. CT imaging immediately after RF energy application to lung tumors will show a halo of ground-glass opacity, which is a marker of thermal changes within the lung. The exact relationship of these changes and cell death has not been entirely defined. Temperature readings may be of benefit, either acquired directly from the applicator if available or by remote sensors placed at the periphery of the tumor being treated. CT-guided cryoablation has the ability to monitor "ice ball" formation during ablation in soft tissue. However, precise ice ball visualization into normal aerated lung is less defined and unknown at this time. The exact distance of adequate treatment margins remains to be established; until further data become available, a circumferential treatment margin of 10 mm should be used. The method used to determine the extent of the estimated treatment margin must be reported.

Ablation Description

As specified in SIRTAC/IWGIGTA reporting standards (47,48), description must be given of the ablation device (ie, energy source and applicator) and treatment protocol used for thermal ablation. Adherence to the manufacturer's recommended treatment protocol and/or precise details and modification by the operator must be stated. The total procedure time and duration of energy application must be recorded. For RF ablation, this includes the energy source (ie, power, current) and algorithm (ie, impedance-based, pulsed) that is used, the number of overlapping ablations, the number of ablation sessions, and the treatment endpoint (ie, time, target temperature, maximum impedance). Details whether the electrode used was single or multiple cooled-tip, triple cluster, multitined expandable, or another type must be given. When bipolar electrodes become available, distinction between monopolar and bipolar devices must be made. The number of grounding pads, skin positioning, and skin preparation must be stated.

For cryoablation, cryoprobe size, isotherm characteristics, probe positioning, duration of active freezing, duration of active thawing, and number of freeze/thaw cycles must be recorded. The method and frequency of monitoring ice ball formation must be provided. When thermocouples are used, the number, positioning and minimum temperature reached must be stated.

For studies reporting results of other thermal ablation modalities (eg, microwave, laser, or focused US), applicator and energy source characteristics and energy delivered must be reported.

In the case of RF ablation, the presence of circumferential ground-glass parenchymal opacities surrounding the index tumor is common, and may be predictive of complete tumor necrosis (51,52). The presence and degree of ground-glass parenchymal opacification should be reported in RF ablation series, and in other thermal ablation series if observed.

Adjunctive Technique

Adjunctive techniques may be used in some circumstances to displace at-risk structures away from the in-

tended ablation zone (53,54). These techniques include creations of a "window" of sterile water or similar nonionic solution (eg, dextrose in water) injected through a fine needle or catheter inserted between the tumor and the organ or structure deemed at risk (eg, between the location of the phrenic nerve at the level of the aortic arch and the lung mass). Deliberate temporary pneumothorax is another adjunctive technique described for treating lung masses adjacent to, but not involving, the heart or diaphragm. This technique involves percutaneous instillation of air into the pleural space without producing injury to the lung surface. When used, these techniques must be reported.

Anesthesia and Hemodynamic Monitoring

Thermal ablation of lung tumors may be performed with conscious sedation or general anesthesia. All patients will require hemodynamic monitoring in compliance with national hospital accreditation standards and local institutional standards. When conscious sedation is used, airway evaluation before and throughout the procedure is necessary, in particular with patients in the prone position. The method of anesthesia or sedation must be recorded, along with the methods used for patient monitoring. When endotracheal intubation is performed, this should be stated.

POSTTREATMENT EVALUATION

Imaging

The imaging findings after thermal ablation should be reported according to the recommended reporting guidelines of SIRTAC/IWGIGTA (47,48). Specifically, measures of technique effectiveness such as primary and secondary effectiveness rates, and measures of tumor progression including local tumor progression, new pulmonary tumors, and distant metastases should be reported. Local tumor progression is most common at the margin of the ablation zone (55). At present, limited data are available that correlate pathologic findings with imaging findings in humans who have undergone thermal ablation of lung malignancies. Nonethe-

less, radiologic imaging is likely to be the best available technique to estimate tumor viability. Imaging after thermal ablation to detect viable tumor can include noncontrast CT, contrast-enhanced CT, contrast-enhanced MR imaging, and PET imaging.

After ablation, the mass comprised of tumor and surrounding devitalized lung will usually increase in size compared with the tumor size before ablation (16,17). Imaging based on relative change in mass dimensions such as CT imaging using the Response Evaluation Criteria in Solid Tumors will likely be falsely categorized as disease progression, even if the entire tumor has undergone coagulation necrosis. Instead of basing volume changes on the preablation imaging, it is more appropriate to use the first cross-sectional imaging study after ablation as the baseline to evaluate subsequent imaging studies (8,16,17). Lesion diameter or volume changes over intervals of time during the course of treatment follow-up should be reported, with any further increase in size considered to represent local progression.

Viable tumor frequently enhances after administration of contrast material out of proportion to background nontumoral parenchyma. Nodular perilesional contrast enhancement has been shown to predict local tumor progression after thermal ablation of liver malignancies (52,55,56). CT nodule densitometry has been demonstrated to have a 98% sensitivity for detection of malignancy in solitary pulmonary nodules (57). Two centers have reported that contrast enhancement patterns within ablated pulmonary tumors were more sensitive for detection of local tumor progression than lesional enlargement (8,16). If centers include contrast-enhanced CT or MR imaging in follow-up imaging, details of the CT or MR imaging technique and diagnosis interpretation guidelines should be given.

In patients who have tumors documented to be [¹⁸F]fluorodeoxyglucose (FDG) PET-avid before ablation, FDG-PET scans obtained after ablation may provide an additional measure of tumor response and progression (12,15). A rim of FDG avidity is typically seen surrounding the ablated tumor for weeks to months after ablation (15). This rim represents hyperemic inflammatory tissue at the boundary of necrotic tissue and viable lung. Viable tumor tends to

appear as a discrete nodule of FDG uptake. Uniform FDG-PET scanning of all patients likely will not be feasible in many trials because some tumors will not be FDG-avid, and there is considerable variability in reimbursement practices among many third-party payers. In those trials that report PET results, a description of patient selection, reasons for exclusion, technique protocol, and standard uptake values should be detailed. If feasible, the PET scans should be performed in the same center for all studies.

Frequency of Imaging

The necessary frequency of imaging after thermal ablation is related to the natural history of NSCLC and metastases, which can vary widely as to rates of progression. For this reason it may be appropriate to perform CT imaging at 3-month intervals after an early scan (1–3 months) has been obtained that documents absence of viable tumor. Others will perform imaging more frequently within the first year after ablation (every 3–4 months), with the rationale that recurrent disease is most likely to occur during the first year after ablation. The timing of the first scan varies among institutions from 1 week to 1 month. PET/CT may be performed early and then every 6 months. Although the optimal frequency of follow-up imaging remains to be defined from a cost-effectiveness standpoint, for the purposes of study design, all patients within a study ideally should undergo imaging with the same frequency.

Serologic Marker Follow-up

In patients with metastases or primary bronchogenic carcinoid tumors, serologic markers such as carcinoembryonic antigen, chromogranin A, or α -fetoprotein may be elevated before ablation. Serial assessment of these serologic markers may be useful nonimaging methods of assessing tumor response and progression. When reported, patient selection features in addition to values should be given. To maintain consistency, laboratory studies should all be performed at one facility.

Follow-up Clinical Status

Evaluation of each patient's clinical status should be performed with at least the same frequency as follow-up imaging. These assessments should record the patient's general medical condition, pulmonary function, and any late complications possibly related to thermal ablation, including further respiratory compromise, pneumonia, empyema, and intercostal radiculopathy.

Functional Status

The potential benefit of thermal ablation in the management of patients with lung tumors needs to be defined in the context of an individual patient's functional status. Each patient's functional status should be recorded during every follow-up encounter with the same grading system (eg, Eastern Cooperative Oncology Group performance status) as was used in the pretreatment evaluation.

Duration of Follow-up

To become established as a local control technique for small-diameter NSCLC and metastases, percutaneous thermal ablation needs to achieve disease-free survival rates that are equivalent to those associated with other less-invasive nonsurgical options. Therefore, similar to any resection approach to a solid organ malignancy, 2- to 5-year follow-up, depending upon tumor type and patient population, will be necessary to make a valid comparison with other therapies.

ANALYSIS OF OUTCOMES

Intent-to-Treat Analysis

Patients in studies of thermal ablation of NSCLC should be considered to have undergone ablation if this was the intended treatment after randomization. For example, if a patient develops pulmonary hemorrhage and hemoptysis during insertion of an RF electrode, resulting in abandonment of the procedure, the patient should still be included as a patient in the RF ablation arm during subsequent outcome analyses. The intent-to-treat technique assigned to each patient should be reported and the success of the procedure(s) should be

evaluated against this intent-to-treat plan.

Life Tables

The single most important measure of outcome of percutaneous thermal ablation in lung tumors being treated for local control should be disease-free survival. Most clinical studies reporting survival data use Kaplan-Meier estimates or life tables. Many investigators refer to these techniques interchangeably, but they have important differences. Failure and censoring events in life-table analysis are clustered into fixed intervals of time, typically 3-month or 6-month windows. In small trials ($N < 200$), this clustering can produce inaccuracy in survival estimates, as a patient who survives 3 months and 1 day has the same statistical effect as a patient who survives 5 months and 29 days. In contrast, the Kaplan-Meier technique calculates survival from the actual time of the failure or censoring event. For this reason, all studies reporting survival data except for very large trials should use the Kaplan-Meier technique. Intergroup comparisons of survival estimates should be performed with an appropriate nonparametric technique, such as the log-rank test.

Stratification

In trials that involve large numbers of patients, subgroup analyses can be a powerful tool to help establish relative benefit or risk to specific patients, tumor, techniques, or situations. Depending on the study type, design, and size, meaningful stratification variable may include such items as demographic features; comorbid conditions; a history of irradiation to the target tumor; tumor type, stage, size, number, and location; technique variables; adjunctive therapies; and initial tumor response. When analysis of stratified variables is performed, the variables stratified, technique of analysis, and results, including measures of statistical significance, should be presented.

Comparison with Other Nonsurgical Therapies

To become established as a local control technique for NSCLC, thermal ablation needs to (i) achieve equivalent safety and efficacy to state-of-the-art ra-

Table 6
Classification of Complications of Percutaneous Lung RF Ablation

Complication	Class
Abscess	Infectious/inflammatory
Allergic/anaphylactoid reaction	Contrast-related
Angina/coronary ischemia	Cardiac
Bronchopleural fistula	General nonvascular
Death related to procedure	Death
Death unrelated to procedure (30-day mortality)	Death
Empyema	Infectious/inflammatory
Hypotension	Cardiac
Hematoma bleeding, pleural	Vascular
Hematoma bleeding, puncture site	Vascular
Idiosyncratic reaction	Medication-related
Myocardial infarction	Cardiac
Nerve injury	Neurologic
Pleural effusion	Respiratory/pulmonary
Pneumothorax	Respiratory/pulmonary
Pulmonary embolism	Vascular
Respiratory failure	Respiratory/pulmonary
Sepsis	Infectious/inflammatory
Skin burn	Device-related
Stroke	Neurologic
Tumor seeding	General nonvascular
Unintended perforation of hollow viscus	General nonvascular
Vagal reaction	Cardiac

diation therapy and (ii) be cost effective. Whenever possible, randomized trials should include economic evaluation of thermal ablation compared with the alternative treatment. Blinded studies regarding the type of thermal therapy during lung cancer treatment (eg, RF ablation vs cryoablation) may not be possible. However, follow-up imaging can be evaluated in a core laboratory with observers blinded to therapy.

COMPLICATIONS

All complications of the ablation procedure should be reported, including those that do not appear related to the procedure. Recognized and/or potential complications of lung thermal ablation are given in **Table 6**. Complications within 30 days are presumed to be procedure-related. Complications beyond 30 days may be procedure-related and also need to be reported. The classification system used by SIR (49) for grading complications and the National Cancer Institute Common Terminology Criteria for Adverse Events (50) must be used (**Table 3**).

QUALITY OF LIFE

A validated instrument for measuring quality of life should be used

at baseline and during each follow-up encounter, such as the Short Form 36, European Organisation for the Research and Treatment of Cancer QLQ-C30 instrument, or Functional Assessment of Cancer Therapy-General questionnaire.

COSTS AND COST EFFECTIVENESS

When reporting costs of lung ablation, authors should report direct costs associated with the procedure (eg, thermal applicators, CT interventional suite time, and hospital stay) and indirect costs (eg, need for increased imaging follow-up to detect residual or recurrent disease). These costs are then combined for a study patient cohort as a cumulative numerator for measurement of cost effectiveness. The denominator of cost effectiveness is the number of quality-adjusted life-years derived for the study population, yielding the cost-effectiveness ratio of dollars per quality-adjusted life-year. This should also include sensitivity analysis and discounting. These cost-effectiveness data will become critical in comparing percutaneous thermal ablation with other ablative and nonsurgical therapies.

Table 7
Recommendations for Reporting Standards

Procedure	Required	Highly Recommended	Recommended
Preablation evaluation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Population description	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Clinical indication for RF ablation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anatomic location of tumor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tumor staging	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Biopsy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Study design			
Inclusion criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Exclusion criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comorbid diseases	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Functional status	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ablation description			
Ablation device description	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Treatment endpoint	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Energy and duration of RF ablation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Number of ablation zones	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Method of targeting and monitoring	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adjunctive techniques	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anesthesia	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hospital days	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Complications			
Immediate	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30-day	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Late complications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Postablation evaluation			
Follow-up imaging at regular intervals	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Follow-up of clinical status	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Technique effectiveness	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tumor progression	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Survival	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Disease-free survival	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Quality of life assessment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Uniform duration of follow-up	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Need for additional ablation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Costs	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Cost effectiveness	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

RECOMMENDATIONS

Disease-free and overall survival should be determined with the Kaplan-Meier technique. An initial intent-to-treat basis should be used for evaluating patient outcomes after randomization. Comparison with other nonsurgical approaches is ideal, rather than case series of patients treated only with thermal ablation. A thorough description of complications, both in the immediate peri-procedural period and within 30 days of the procedure, is needed. Measurement of quality of life should be performed with a previously validated instrument, preferably one that has been developed for oncology patients. Determination of costs and cost effectiveness is recommended. A summary of recommended items to be included in re-

ported trials of thermal ablation of lung cancers is presented in **Table 7**.

CONCLUSION

Percutaneous ablation of lung tumors is becoming an established, minimally invasive therapy for many patients in whom conventional therapy fails or who are poor surgical candidates. To optimize its clinical potential, percutaneous thermal ablation ultimately must be supported by compelling randomized prospective trials in which it is used alone and in combination with other modalities. Rigorous earlier-phase trials are important to optimize ablation technique and lay the necessary research groundwork before large, expensive, lengthy definitive ran-

domized controlled trials are performed. The goal of this document is to provide recommended definitions to enable uniform reporting of these trials.

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