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Standards of Practice: Guidelines for Thermal Ablation of Primary and Secondary Lung Tumors

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Introduction

The incidence of lung cancers continues to increase, and primary lung cancer remains the primary cause of cancer-related deaths in both women and men [1]. There are two main types of lung cancers: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The latter is further divided into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Treatments of primary lung cancers include surgical resection (including sublobar or wedge resection), radiotherapy (including three-dimensional conformal radiation or stereotactic body radiotherapy), chemotherapy, thermal ablation, or a combination of these treatment modalities. Only patients with stage I and stage II disease are considered to have early stage disease and are potential candidates for surgery [2]. On the other hand, SCLC is usually inoperable because this cancer has often spread by the time of diagnosis. Currently, the best survival in patients with NSCLC is obtained by surgical resection, with a 5-year overall survival commonly accepted to be 60–80% for stage I and 40–50% for stage II NSCLC [2]. However, most patients either have too a limited pulmonary function for surgical resection or are unable to tolerate surgery because of other comorbid medical conditions, especially patients with poor cardiopulmonary functions. In these high-risk patients, radiotherapy remains an option in a palliative setting. Nevertheless, radiotherapy offers overall survivals that are definitively worse than surgery at 5 years, ranging 6–27% [3]. Percutaneous thermoablation has also be found to be effective for treatment of pulmonal metastases, especially in patients with limited colorectal lung metastases. In case of concomitant extrapulmonary disease, an approach with thermoablation may be justified only if extrapulmonary disease can otherwise be controlled [3].

Image-guided percutaneous thermal ablation therapies are minimally invasive interventional techniques established in the local treatment of hepatic, renal, or osseous tumors [4–12]. Among these techniques, radiofrequency ablation (RFA) has now attained consideration for therapy of primary and secondary lung tumors [13–18]. Other thermal ablation techniques that have been used for treatment of pulmonary tumors include cryoablation [19], laser [20], and more recently microwave [21]. Thermal ablative techniques produce irreversible tumor tissue destruction through application of either hot or cold thermal energy. Planning, monitoring, targeting, and controlling this modality are performed with the help of different imaging modalities, including ultrasound, X-ray, computed tomography (CT), and magnetic resonance tomography.

Pretreatment Procedure

Medical history and physical examination of the patient as well as the results of recent imaging studies should be evaluated to determine the indication of thermal ablation. The indication for percutaneous ablation should be made by an interdisciplinary tumor board. Chest CT is the key

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imaging modality for the pretreatment evaluation of lung tumors; the size and location of the lesions and their relationship to vessels and bronchi must be assessed. CT is currently the most widely used imaging modality for initial planning, monitoring the placement of ablation's probe, and immediately assessing treatment response [3]. Biopsy is recommended before treatment or in the setting of ablation in cases of metastatic disease whenever the presentation is atypical [22]. Staging for a patients with metastatic disease should include abdominal and pelvic CT. Completing the staging with magnetic resonance imaging of the brain in patients with abnormal neurologic examination and with bone scans in patients with evidence of bone pain is indispensable. In patients with primary lung cancer who are candidates for curative intention to treat, whole body positron emission tomography (PET)-CT should be performed to search for distant metastases and to select patients with stage IA disease (Table 1) [23]. The superiority of fluorodeoxyglucose (FDG)-PET-CT over CT has been demonstrated for the staging of primary lung cancers [24].

Laboratory tests should include coagulation parameters (including complete blood count and international normalized ratio), and in patients with metastatic disease, appropriate tumor markers should be assessed. Anticoagulant medications should be discontinued before ablation. Pulmonary function tests are strongly recommended in patients with a history of lung surgery or pulmonary disease. Poor results of spirometry must be discussed by tumor board. The choice of thermal ablation is then an individual decision, based on the patient's risk–benefit relation. Theoretically, there is no lower limit of forced expiratory volume in 1 s or diffusion capacity in candidates for percutaneous thermal ablation [25].

Table 1 Comparison between the 6th and the 7th edition of the tumor, node, metastasis system classification of non-small cell lung cancer and the definition of N staging and M staging

Sixth edition	Seventh edition	N0	N1	N2	N3
T1 (=2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2 cm, ≤3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (>3 cm, ≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5 cm, ≤7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (>7 cm)	T3	IIB	IIIA	IIIA	IIIB
T3 (direct invasion)		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodule)		IIB	IIIA	IIIA	IIIB
T4 (other lobe)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral nodule)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral nodule)		IV	IV	IV	IV
M1 (distant metastasis)	M1b	IV	IV	IV	IV

Lymph node involvement (N staging): *N0* No regional lymph nodes involved, *NX* regional lymph node status cannot be assessed, *N1* ipsilateral nodes, *N2* extended ipsilateral mediastinal nodes involvement: paratracheal, aortic, and paraaortic, paraesophageal, and/or subcarinal, *N3* contralateral mediastinal and/or hilar nodes involved and/or supraclavicular nodes

Metastatic involvement (M staging): *M0* No metastasis, *MX* distant metastasis cannot be assessed, *M1a* metastasis in a contralateral lobe, malignant pleural, or pericardial effusion or pleural nodules, *M1b* distant metastasis

Thermal Ablation and Combined Therapies

Indications

Because percutaneous thermal ablation of primary and secondary lung tumors is still not an established treatment, patients should be selected by an interdisciplinary board.

Surgical resection for primary lung cancers is mainly performed in NSCLC stage I to IIIa disease (Table 1). In SCLC, surgical resection is reserved for selected patients with stage I and II disease. Pulmonary RFA of primary lung cancer should be reserved for patients who are not candidates for curative surgical resection as a result of cardiorespiratory comorbidity or insufficient vital lung function (Table 2) [26], and in cases where the maximum tumor diameter does not exceed 3.5 cm [18, 27–31]. Thus, size limitations mean that only stage IA and stage IB NSCLC may be treated by thermal ablation. Preliminary results suggest that RFA combined with radiotherapy

Table 2 Exclusion criteria for lobectomy for primary lung cancer

Major criteria
FEV1 ≤50%
DLCO ≤50%
Minor criteria
Age ≥75 years
FEV1 51–60% predicted
DLCO 51–60% predicted
Pulmonary hypertension (defined as a pulmonary artery systolic pressure >40 mmHg) as estimated by echocardiography or right heart catheterization
Poor left ventricular function (defined as an ejection fraction ≤40%)
Resting or exercise arterial po_2 ≤55
mmHg or Spo_2 ≤88%
pco_2 >45 mmHg

FEV1 Forced expiratory volume in 1 s, *DLCO* carbon monoxide diffusing capacity, *po2* partial O_2 pressure, *Spo*$_2$ O_2 saturation

Fulfillment of one major criterion or at least two minor criteria usually prevent a patient from being a candidate for surgical lobectomy for NSCLC. From [26]

improves local disease control and survival in patients with NSCLC [32].

In pulmonary metastatic disease, RFA has been mainly performed in patients with metastases from colorectal and lung cancers, renal cell carcinoma, melanoma, hepatocellular carcinoma, and sarcoma [25, 31, 33–38]. The maximum number of lung metastases that may be ablated is still not clearly defined. Most centers preferentially treats patients with five or fewer pulmonary metastases [25]. Combining RFA and surgery for treatment of a larger number of lesions in bilateral metastatic tumors may be a useful option for improving the chance of a cure and limiting disease invasiveness [39]. The use of percutaneous RFA combined with systemic chemotherapy may offer improved survival in patients with nonresectable colorectal pulmonary metastases [40]. Preliminary results of therapy that combines RFA with surgery or chemotherapy still need to be validated in prospective trials.

Contraindications

Because of excellent patient tolerance of percutaneous thermal therapy, it is difficult to identify an absolute contraindication for lung RFA, with the exception of untreatable coagulopathies. Anticoagulation and/or antiplatelet drugs should be discontinued at least 10 days before percutaneous ablation [41]. Warfarin should be discontinued 5 days before treatment and may be restarted 24 h after pulmonary ablation [3].

Patient with an Eastern Cooperative Oncology Group performance status of >2 or with a life expectancy of less than 1 year are not good candidates for lung ablation [3, 25].

Pretreatment Assessment, Procedural Features, and Postprocedural Care

Before ablation, complete history and careful clinical evaluation are mandatory with respect to coagulation tests. Pulmonal function tests are generally performed in patients with history of pulmonary disease or lung surgery, but no clear minimum values have been defined in the literature to exclude percutaneous thermal ablation as a treatment modality.

On the basis of patient or radiologist preference, the ablation procedure is performed via a sterile technique with the patient under general anesthesia or with local anaesthesia with conscious sedation. In a comparison of ablation procedures performed under conscious sedation or under general anesthesia, no differences in local tumor control were reported in a series of 26 treatments [42].

After an appropriate approach has been selected, the procedure involves inserting a thermoprobe through the skin directly into the target tissue under CT guidance. CT is the most accurate imaging modality for percutaneous thermal ablation procedures in the lung. Exact positioning according to the different manufacturer's recommendations is necessary and must be confirmed at least by two different planes at CT imaging. Vital signs (pulse, blood pressure, and oxygen) are monitored, and pain medication is administered on demand when the procedure is performed under conscious sedation. Lesions located near the pleura may be treated with RFA, which often requires pain management.

After confirming the correct applicator's position by multiplanar CT images, energy should be applied following the recommended algorithm for lung tissue ablation. During thermal ablation, the hyperattenuated opacity corresponding to tumor and surrounding coagulated lung is called ground-glass opacity (GGO), and it usually should be larger in size compared with the tumor size before ablation. The development of GGO in surrounding lung tumors, caused by thermal injury, should be monitored by intermittent CT imaging. The extent of the GGO surrounding the treated lesion on immediate postablation CT imaging has been shown to predict the effectiveness of thermal ablation. The tumor tissue is considered to be incorporated in the ablation zone when the GGO completely surrounded the tumor [31, 43]. The GGO should encounter the treated tumor with a circumferential margin of at least 5 mm for complete tumor ablation [44]. Other authors recommend that the area of postablation GGO should be 4 times the area of the tumor before ablation. The rate of complete ablation is 96% at 18 months when the ratio is higher than 4, versus 81% of complete response when this ratio is lower than 4 ($P = 0.02$) [14]. When GGOs are encountered in the targeted tissue with a circumferential safety margin of at least 5 mm, the probe may be removed, with coagulation of the puncture track at least 2 cm above the initial tumor borders [45]. CT imaging at the end of the ablation procedure is performed to exclude complications and to assess technical success. After the ablation procedure, the patient may be preferentially discharged 1 day after being informed about the risk of delayed pneumothorax [45]. We recommend that chest X-ray be performed 4 h after the procedure to exclude an asymptomatic pneumothorax.

Bilateral lung tumors should not be treated in the same session for safety reasons, particularly the increased risk of delayed pneumothorax [45].

For percutaneous thermal ablation of lung tumors, lesions with a distance of <1 cm from hilum, large vessel or main bronchi, esophagus, or trachea should be avoided [27, 33]. Direct contact with a vessel >3 mm or with the myocardium

has been already reported as a negative predictive factor for complete coagulation of lung lesions [46, 47].

CT imaging is the most widely used imaging modality for postprocedural assessment. The opacity increases in size from baseline to 1- to 3-month follow-up CT scans and then remains stable or decreases in size [43]. Follow-up CT imaging shows that the treated area can evolve in five different patterns: fibrosis, cavitation, nodule, atelectasis, and disappearance. None of these patterns gives valuable informations on local tumor progression [48]. Cavitation seems to occur more frequently in patients with lung cancer near the chest wall or in patients with emphysema [49]. In a recent study, criteria for a complete response were the decrease in longest tumor diameter of at least 30% compared with the diameter assessed at 1 month, and no evidence of contrast enhancement [31]. Intratumoral contrast uptake, tumor growth at the periphery of the ablation, or a 20% increase in longest tumor diameter strongly correlated with incomplete ablation [31]. At follow-up CT, the opacity will start to decrease in size as early as 4 weeks and up to 6 months [43].

PET-CT seems to be the most accurate modality in patient follow-up after thermal ablation [27]. A recent study with FDG-PET-CT at 24 h, at 1 and 3 months after ablation reported false-positive results at 24 h and 1 month as a result of postablation inflammation and concluded that the 3-month PET-CT results in fewer false-positive studies [50]. Another group demonstrated that FDG-PET-CT findings at 6 months after ablation correlates better with clinical outcomes at 1 year [51]. Because this technique is not widely used after thermal ablation, clear recommendations for PET-CT after lung tumor ablation are not yet possible.

Radiofrequency Ablation

During monopolar RFA, an alternating high-frequency current is produced by a radiofrequency generator and oscillates in a closed-loop circuit between one radiofrequency applicator and one or more large grounding pads placed on the patient's skin. RFA destroys targeted tissue by heating cells to over 60°C to obtain an irreversible protein denaturation. The targeted tissue is therefore heated through ionic agitation [52, 53]. Radiofrequency applicators have different designs: straight needle, expandable needle, and internally cooled single or cluster monopolar and bipolar needles. When bipolar or multipolar probes are used, grounding pads are not necessary [54]. The expandable monopolar radiofrequency probe is helpful for lung ablation because it is less prone to migration when prongs are deployed in the soft lung parenchyma. Another advantage is for ablation of small lung tumors: a direct puncturing of the lesion is not necessary as long as the deployed electrodes encompass the targeted tumor. Algorithms for lung ablation are specific and are generally different from those for liver ablation. A lower power (30–40 W) for energy application is generally recommended [14].

Cryoablation

The destructive effects of freezing tissue can be grouped into two major mechanisms, one immediate and the other delayed, as studied at the end of the 1990s by Gage and Baust [55]. In the freezing phase of cryoablation, the formation of intracellular and extracellular ice crystals occurs, and this effect can change in size and location depending on tissue type, proximity to the cryoprobe, and presence of blood flow during the process. Near the tip of the cryoprobe, there is a prevalence of intracellular ice formation as a result of the rapid rate of cooling, which guarantees almost immediate cellular death. The other effect on the tissue is extracellular ice nucleation, which prevails during the low-rate ice formation; this occurs at the periphery of the ice ball. This phenomenon is due to dehydration of cells after the increase of osmolarity in extracellular compartment. During the hours after the procedure, the damage is perpetrated by ischemia. The endothelial damage results in increased permeability of the capillary wall, edema, platelet aggregation, and microthrombi formation. Many small blood vessels are completely occluded by thrombi 4 h after thawing. Large arterioles may remain open for 24 h [56]. The CT findings of ice-ball formation in the lung parenchyma are difficult to appreciate until the initial thaw [57, 58].

Microwave Ablation

Microwave ablation is less reported for pulmonary treatments than for radiofrequency technology, but this modality has some theoretical advantages for lung ablation, such as less severe heat sink effect and a faster and higher heating. Moreover, microwaves are not limited by tissue boiling, lower thermal conductivity of lung parenchyma, or increased impedance of charred tissues [25, 59]. An experimental study comparing the relative effectiveness of microwave ablation versus RFA in the lung shows that coagulation produced by microwave was larger in diameter and more circular than the coagulative area achieved with a similar-sized radiofrequency applicator [60]. Microwave ablation for clinical uses generally operates with electromagnetic waves at frequencies ranging from 915 and 2,450 MHz, resulting in dielectric heating to cytotoxic

levels through rapid rotation of water molecules [25]. The design of microwave antennas is either straight needle with varying active tips 0.6–4.0 cm in length, or an antenna with one to three loops [25].

Laser Interstitial Tumor Therapy

Laser interstitial tumor therapy is another thermal technique that uses light energy (mostly infrared) that is absorbed and converted into heat. Light and therefore energy is transmitted through fiberoptic cables that are inserted into the target tissue by means of introducer sheath. The source of heat is mostly a Nd:YAG laser with a wavelength of 1,064 nm. Cell death follows protein denaturation causes by photon delivery [25]. Similar to RFA, the extent of coagulation is limited by tissue charring near the fibers. New systems have introduced cooling that permits a longer energy application. Multiple laser fibers may be used simultaneously [25].

Outcomes and Effectiveness

Clinical results of percutaneous pulmonal RFA have been mainly achieved in patients with unresectable lung tumors. A systematic review found 17 studies reporting the efficacy of pulmonal RFA [61]. The reported median rate of complete ablation was 90% for a median tumor size of 2.2 cm, with a high variability, ranging 38–97% of primary and metastatic lung tumors. Median survival ranged 8.6–33 months, and the overall 3-year survival rate ranged 15–46% [61].

In studies with pulmonary RFA and curative intention to treat, survival rates are significantly better than for palliative situations. One of the first studies, from Fernando et al., reported survival data after 21 ablations in 18 marginal surgical candidates with NSCLC. With a median follow-up of 14 months, mean survival was 21 months, and mean progression-free survival was 17.6 months for stage I disease and 15 months for all other NSCLC [36]. At the present time, various groups have reported 1-year and 2-year survival rates ranging 78–95% and 57–84%, respectively [3].

Long-term outcomes for patients have been reported. Simon et al. reported in a cohort of 153 consecutive patients a 5-year overall survival of 27 and 57% after RFA of nonoperable NSCLC and lung metastases, respectively [17]. A significant difference between the survival curves was associated with large (>3 cm) or small (≤3 cm) tumor diameter. In a study that included patients with colorectal lung metastases, a 5-year overall survival rate of 35% was reported [62]. Two other prognostic factors were found to be carcinoembryonic antigen levels and extrapulmonary disease.

Kodama et al. retrospectively evaluated a series with 44 patients after RFA of unresectable recurrent NSCLC. A total of 55 lung RFA sessions were performed for a 5-year overall survival rate of 55.7%. Tumor size was an independent prognostic factor in multivariate analysis, with 60.5% 5-year survival in 38 patients who had NSCLC measuring <3 cm [63].

There are several parameters for a successful thermoablation of lung tumors, but similar to ablation of liver or renal tumors, one of the most important prognostic factors is the size of the target lesion, with the cutoff value being 3.0 cm [33, 47, 61, 64], with <50% complete necrosis in lesions 3–5 cm in diameter. Similar to surgical data, complete tumor destruction and lack of extrapulmonary disease lead to a survival benefit [65]. Advantages of RFA over surgery include the possibility of performing multiple sessions, even in patients with limited pulmonary reserve, as well as repeating the treatment with a relatively low risk of complications. The maximum number of metastases that can be treated effectively has not been established. In a retrospective study that included 39 patients with unresectable metastases from renal cell carcinoma who were treated with RFA, curative ablation was intended in patients with six or fewer lesions measuring <6 cm, whereas palliative ablation with mass reduction was performed in patients with more than six metastases or with tumors larger than 6 cm. There were significant differences in the overall survival rates between the curative and palliative groups, with 5-year survival rates of 100 and 52%, respectively, thus suggesting that patients with up to six metastases may benefit from thermal ablation [65] when complete ablation is obtained [66]. Among the different pulmonary tumors (primary lung cancer; and metastases from renal cell carcinoma, lung cancer, or hepatocellular carcinoma), tumor type did not significantly influence local tumor control [67].

A combination of RFA and conventional radiotherapy has already shown a better local control and survival than radiotherapy alone. Grieco et al. reported a 3-year survival of 57% after combined therapy in 41 patients with NSCLC (stage Ia, 21; stage Ib, 17; stage IIb, 3) [68]. Yan et al. achieved an overall median survival of 33 months in 55 patients with colorectal pulmonary metastases [69]. Similar survival rates have been reported by different groups in colorectal lung metastases, with overall survival ranging 64–78% [14].

Long-term follow-up for patients undergoing percutaneous cryoablation is lacking at this time. The most important series of lung cryoablation treatments was published in 2005 by Wang et al. [57]. In this study, 187 patients with 234 lesions were treated for lung tumors with

cryoablation. The extent of ablation was an independent predictor for duration of recurrence-free and overall survival in patients with lung malignancies. Even in patients with masses >3.0 cm in diameter, complete ablation provided a better survival rate and longer progression-free duration than did partial ablation [66].

Only few series have been published reporting survival data after microwave pulmonary ablation. In one of the largest series, Wolf et al. reported a 1-year local control rate of 67% with a mean of 16.2 months to the first local recurrence after microwave ablation in 50 patients with 82 intrapulmonary lesions. Kaplan–Meier analysis yielded an actuarial survival of 55% at 2 years after microwave ablation and 45% at 3 years [21]. More recently, complete microwave ablation was achieved in 95 (73.1%) of 130 metastatic lung lesions from different primary tumors [70]. Successful tumor coagulation was significantly more frequent for lesions <3 cm in diameter than for those >3 cm.

Complications

Complications within 30 days after thermal ablation may be procedure related and should be reported according to the Society of Interventional Radiology classification system [71]. Percutaneous lung RFA is considered as a relatively safe procedure, with an overall procedure-related morbidity rate ranging 15.2–55.6% (median 35.7%) and a mortality rate ranging 0–5.6% [61]. Some patients will experience mild to moderate periprocedural pain or raised body temperature (as a result of release of cytokines and serum inflammatory mediators) during or immediately after ablation. Pain can usually be managed with pain medication or nonsteroidal anti-inflammatory drugs. Pneumothorax and pleural effusions are the most common periprocedural complication, occurring in nearly 40% of patients [72]. In a study by Hiraki et al., the incidence of pneumothorax was 52% after 224 pulmonary RFA procedures. The frequency of chest tube placement in this study was 21% [73], and 11% was the median rate of chest tube placement in a systematic review [61]. Manual aspiration during ablation should be considered as a valuable option for thin pneumothoraces to avoid excessive coagulation of atelectatic lung parenchyma during energy application. Delayed pneumothorax at follow-up has also been reported [45]. Underlying bronchopleural fistula along the coagulated former radiofrequency applicator track seems to correlate with the onset of delayed pneumothorax. Thus, track ablation along the access paths should be performed to avoid tumor cell seeding or bleeding, but should be limited to 2–3 cm outside the ablated tissue to minimize the risk of bronchopleural fistula [45]. The most frequent complications reported in human use of lung cryoablation include cough, hemoptysis, fever, pneumothorax, and hemothorax. In mediastinal masses, a rare complication has been laryngeal recurrent nerve damage [57].

Pneumonia and pulmonary abscess are reported parenchymal complications. The risks of infectious complications seem to be higher in primary tumors, in compromised lung parenchyma, and in previously irradiated lung. However, prophylactic antibiotics have not been proven to reduce infectious rates [33].

Conclusion

Percutaneous thermal ablation of primary and metastatic lung malignancies is clearly feasible, is cheaper, results in a shorter recovery time, and offers reduced morbidity and mortality. Because there are still uncertainties regarding the clinical efficacy of lung thermal ablation, patients should be informed about the benefits and risks of the procedure, and the treatment's indication should be discussed by a tumor board. One of the unanswered questions is the impact on survival of metastatic lymph nodes in patients with lung cancers, because lymph nodes will generally not be treated by percutaneous thermal ablation. Another open question is which patients might benefit from adjuvant or neoadjuvant treatments combined with thermal ablation. With the further development of percutaneous ablation procedures—for example, with microwaves as well as with minimally invasive surgical techniques—debates have emerged regarding the optimal therapeutic approach in patients with lung tumors.

Conflict of interest The authors declare that they have no conflict of interest.

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