

CLINICAL GUIDELINE

Chinese expert consensus workshop report: Guidelines for thermal ablation of primary and metastatic lung tumors

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Abstract

Although surgical resection is the primary means of curing both primary and metastatic lung cancers, about 80% of lung cancers cannot be removed by surgery. As most patients with unresectable lung cancer receive only limited benefits from traditional radiotherapy and chemotherapy, many new local treatment methods have emerged, including local ablation therapy. The Minimally Invasive and Comprehensive Treatment of Lung Cancer Branch, Professional Committee of Minimally Invasive Treatment of Cancer of the Chinese Anti-Cancer Association has organized multidisciplinary experts to develop guidelines for this treatment modality. These guidelines aim at standardizing thermal ablation procedures and criteria for selecting treatment candidates and assessing outcomes; and for preventing and managing post-ablation complications.

Introduction

Lung cancer is the deadliest and most common cancer, with an annual incidence of about 2.5 million and more than 1.6 million deaths each year, worldwide.¹ The picture is even worse in China. According to the 2012 China Annual Cancer Report, the annual incidence of lung cancer is 57.63 per 100 000 and annual mortality 48.87 per 100 000, ranking China first in the world in absolute terms.² For early-stage non-small cell lung cancer (NSCLC), surgical resection remains the therapeutic choice for curative intent,³ but for various reasons about 80% of lung cancers cannot be removed surgically. Most patients with unresectable lung cancer can derive only limited benefits from traditional radiotherapy and chemotherapy. Therefore, many new local treatment methods have emerged, including local ablation therapy. Local thermal ablation is a minimally invasive technique that has been increasingly used to treat early-stage lung cancer.⁴ Percutaneous thermal ablation has been proved to be effective in treating lung metastases.⁵ The Minimally Invasive and Comprehensive Treatment of Lung Cancer Branch, Professional Committee of Minimally Invasive Treatment of Cancer of the Chinese Anti-Cancer Association organized multidisciplinary experts to develop these guidelines for thermal ablation of primary and metastatic lung tumors to provide guidance for clinicians.

Local thermal ablation techniques

Tumor thermal ablation is a therapeutic technique that directly causes irreversible injury or coagulation necrosis of tumor cells in one or more tumor lesions in a specific organ by utilizing the biological effects of heat. The techniques include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, laser ablation, and high-intensity focused ultrasound (HIFU),⁶ although laser ablation and HIFU are not commonly used to treat lung tumors.

Radiofrequency ablation (RFA)

RFA is currently the most widely used ablation technique for the treatment of solid tumors. With radiofrequency electrodes inserted into the tumor tissue and the application of 200–650 kHz frequency alternating current, mutual friction and collisions of ions within the tumor tissue produce thermal biological effects to raise the local temperature up to 60–120°C. When the tissue is heated to >60°C, cell coagulation necrosis may occur. RFA volume depends on the transfer of heat produced by local RFA and thermal convection between the blood circulation and extracellular fluid.^{6–9} In December 2007, the US Food and Drug Administration approved RFA for the treatment of lung cancer.⁹ Since 2009,

the NSCLC National Comprehensive Cancer Network (NCCN) Guidelines and China's Primary Lung Cancer Diagnostic and Treatment Practices (2011 edition) have both recommended RFA to treat patients with early-stage lung cancer who cannot tolerate surgical resection.

Microwave ablation (MWA)

MWA generally uses either of two frequencies, 915 MHz or 2450 MHz. In a microwave electromagnetic field, water molecules, protein molecules, and other polar molecules within tumor tissue vibrate at high speeds, resulting in collision and mutual friction between molecules. This can produce temperatures of 60–150°C in a short time, leading to coagulation necrosis of the cells.^{10–12} As ablation can concentrate microwave energy in a certain range, the desired target area can be effectively radiated. MWA has a higher convection and a lower “heat-sink” effect in the lungs.^{13–17}

Cryoablation

Argon-helium cryoablation is a currently mature cryotherapy, based on the principle that high-pressure argon gas may be cooled to –140°C, and helium can rapidly rise from –140°C to 20–40°C. The temperature gradient change can lead to: (i) protein denaturation of target tissues; (ii) cell lysis as a result of changes of the internal and external osmotic pressures and “freezing;” and (iii) tissue necrosis resulting from microvascular thrombosis.^{18–20} The “ice ball” observed under computed tomography (CT) or magnetic resonance imaging (MRI) can directly distinguish the ablation region and tumor boundary to determine the margin of freezing injury, which is generally within 4–6 mm of the margin of the ice ball.^{19,20}

These three ablation techniques can all be used for local treatment of lung cancer, but have different advantages. For tumors with diameters ≤ 3 cm, all ablation methods can achieve good therapeutic effects. RFA electrodes can be adjusted to protect adjacent organs. For tumors larger than 3 cm, particularly those larger than 5 cm, MWA is significantly better than the other two techniques because of its consistently higher intratumoral temperatures, larger tumor ablation volumes, shorter ablation times, improved convection profile, and a larger power field that enhances treatment of perivascular tissue and, thus, limits the “heat sink” effect. Furthermore, multiple MWA antennas can be positioned into the target tissue and activated simultaneously, maximizing the ablation zone size. The “ice ball” formed in cryoablation produces a clear, easily monitored margin, and can be used to treat tumors near high-risk adjacent organs. Cryoablation is also less likely to cause local pain. For tumors ≤ 1 cm from the pleura or complicated with bone destruction as a result of bone metastases, cryoablation is significantly better than RFA

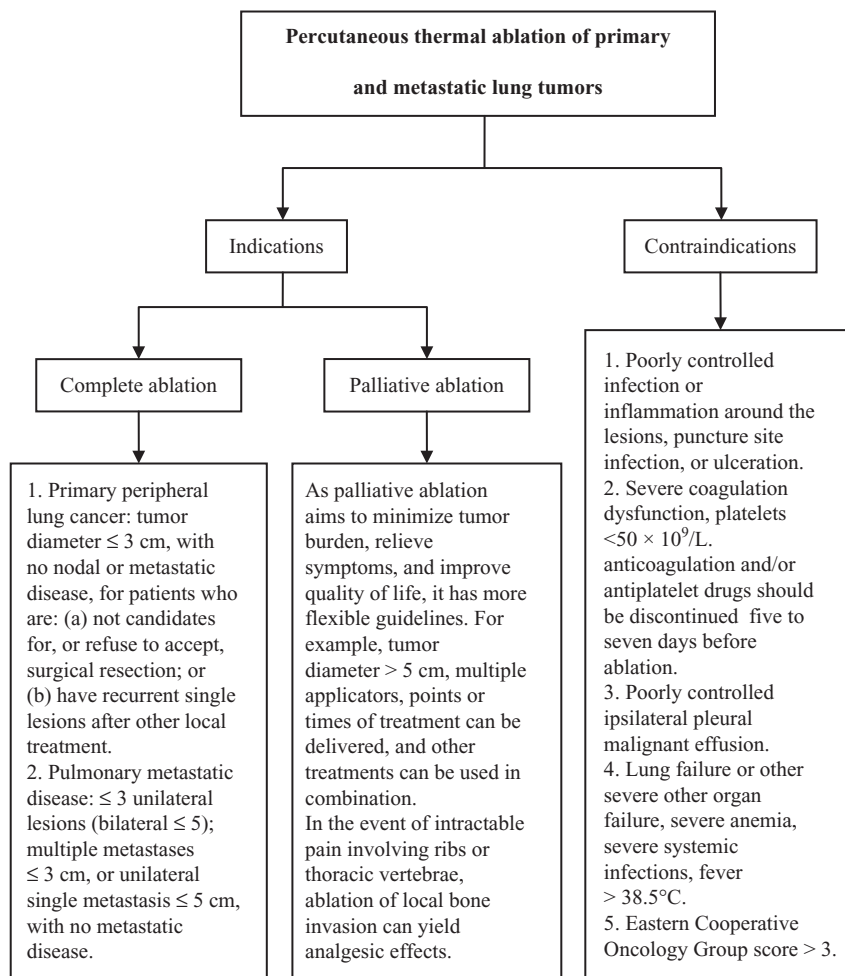


Figure 1 Decision chart for use of thermal ablation.

and MWA. However, cryoablation consumes platelets during treatment, and thus, should be avoided for patients with poor blood clotting function.

Procedure platform

Imaging guidance techniques for percutaneous thermal ablation include CT, MRI, and ultrasound. CT is the most commonly used image-guided technique in lung tumor ablation, followed by MRI. For tumors near or adherent to the chest wall in cases where the whole picture could be observed with ultrasound, ultrasound guidance can be used.

Thoracotomy or video-assisted thoracoscopic assisted techniques are generally used when: (i) the tumor is adjacent to critical structures, such as large blood vessels, the hilum, or heart; or (ii) the lesion was identified as unresectable after an earlier thoracotomy.²¹

Indications and contraindications

Because percutaneous thermal ablation of primary and metastatic lung tumors is still not an established treatment in general, the indications should be selected by an interdisciplinary board (Fig 1).

Complete ablation

Complete ablation refers to complete necrotic lesions of the local tumor tissue and a possible cure through thermal ablation.

Primary peripheral lung cancer

Among patients with primary peripheral lung cancer,^{22–27} complete ablation may be suitable for: (i) patients who are not candidates for curative surgical resection because of

cardiorespiratory comorbidity, insufficient vital lung function, or older age; (ii) patients who refuse to accept surgical resection; or (iii) patients with recurrent single lesions after other local treatment (including three-dimensional conformal radiation or stereotactic body radiotherapy). The maximum tumor diameter for thermal ablation is ≤ 3 cm, with no evidence of nodal or distant metastases.

Pulmonary metastatic disease

Intrapulmonary metastases,^{24,25,28–33} such as kidney, colorectal and breast cancers, sarcoma, melanoma, and hepatocellular carcinoma, may have good outcomes, depending on their biological characteristics. If the primary disease can be effectively treated, thermal ablation can be used on pulmonary metastases. However, use of thermal ablation should be limited to ≤ 3 unilateral lung lesions (bilateral ≤ 5) for multiple metastases, with maximum diameters of ≤ 3 cm, or ≤ 5 cm for a unilateral single metastasis with no metastasis at any other site. For patients with bilateral pulmonary metastatic disease, bilateral simultaneous ablation is not recommended.

Palliative ablation

The purpose of palliative thermal ablation is to minimize tumor burden, relieve symptoms caused by the tumor, and improve quality of life. For patients in whom complete ablation cannot be achieved, the indications are more flexible. For example, for target tumors >5 cm, multiple applicators can be delivered and other treatments can be used in combination. In the event of intractable pain involving ribs or thoracic vertebrae, ablation of local bone invasion can yield analgesic effects.^{25,34–37}

Contraindications

Because of excellent tolerance of percutaneous thermal therapy, identifying an absolute contraindication for lung thermal ablation is difficult, with the exception of patients with untreatable coagulopathies.^{5,7,10,11,24,38,39} However, caution should be exercised for patients with: (i) poorly controlled infection or inflammation around the lesions, puncture site infection, or ulceration; (ii) severe bleeding tendency, platelets $<50 \times 10^9/L$, or severely disordered coagulation, in whom anticoagulation and/or antiplatelet drugs should be discontinued at least five to seven days before percutaneous ablation; (iii) ipsilateral pleural malignant effusions that are not well controlled; (iv) severe liver, kidney, heart, lung or brain function insufficiency, severe anemia, severe dehydration and nutritional and metabolic disorders that cannot be corrected or improved in the short term, severe

systemic infections, high fever ($>38.5^\circ\text{C}$); or (v) Eastern Cooperative Oncology Group (ECOG) score > 3 .

Procedure preparation

Patient assessment and imaging

Complete history, physical examination, and recent image data should be carefully reviewed to assess each patient's thermal ablation indications. Selection of procedure should be based on multidisciplinary decisions, with the procedure discussion recorded. Contrast-enhanced chest CT (within 2 weeks) is a key imaging assessment before thermal ablation, in which the tumor's size, location, and relationship with neighboring vital organs, blood vessels, trachea or bronchi can be seen. As relevant staging and examinations are completed, positron emission tomography (PET)-CT scans are recommended if applicable to exclude or detect distant metastases.⁴⁰

Laboratory tests

Laboratory tests should include routine blood, urine, and stool tests, coagulation, liver and kidney function, blood glucose, tumor markers, blood type and other tests, electrocardiogram (ECG), cardiac ultrasound (optional for elderly patients), and pulmonary function test.

Pathological examination

For primary lung cancer, percutaneous biopsy or bronchoscopy should be performed before ablation to confirm the diagnosis. When metastatic lesions are not typical, biopsy is recommended before ablation.^{5,24,41}

Drugs and monitoring equipment

Drugs for anesthesia and analgesia, antitussives, hemostatics, and vasodilators and antihypertensive drugs, as well as rescue medicines and equipment, should be prepared preoperatively.

Patient preparation

The patient and/or his/her family or representative must sign an informed consent form. The patient should fast four hours before local anesthesia, or abstain from solid food 12 hours and liquids four hours before general anesthesia. The patient should also undergo surgical skin preparation, if necessary, establishment of intravenous access, and oral antitussive before the procedure.

Anesthesia, procedural and post-procedural care

Anesthesia and disinfection

According to the patient's condition, general anesthesia or local anesthesia can be used for the procedure, while ensuring compliance with aseptic techniques.^{42,43}

Procedural and post-procedural care

After the proper ablation technique is determined, CT is one of the most common and accurate image-guided approaches. During the procedure, the thermal ablation applicator (electrode or antenna or probe) is directly inserted into the target tissue through the skin under CT guidance. After confirming that the ablation applicator is correctly positioned using multi-planar CT imaging, ablation is performed. Selection of lung tissue ablation parameters can be adjusted to the equipment manufacturer's recommended parameters.

A number of ablation patterns can be used based on the tumor size and location: (i) single session at a single point (e.g. lesions ≤ 3 cm); (ii) single session at multiple points (e.g. 3–5 cm); or (iii) single or multiple sessions at multiple points using multi-applicators (e.g. >5 cm, or palliative ablation). During the thermal ablation process, damage to lung tissue surrounding the tumor may lead to an opaque high-density area, called ground-glass opacity (GGO), appearing in the CT image. When the peripheral margin of the GGO in the target tissue expands 5 mm or more beyond the pre-procedure tumor borders, the ablation applicator can be pulled out. Due care should be taken to ablate the withdrawal path of the ablation applicator. A repeat large-range (preferably whole-lung) CT scan should be carried out at the end of the ablation procedure to identify any complications and assess technical success.

Monitoring the patient's heart rate, blood pressure, and oxygen saturation is necessary during the procedure; the patient should be closely observed for breathing, pain, cough, hemoptysis, etc. Symptomatic treatment should be delivered when necessary. Post-procedural attention to vital signs is recommended. Chest X-ray or CT scan can be performed after 24 to 48 hours to check for complications (such as asymptomatic pneumothorax or pleural effusion).

Follow-up and response assessment

Follow-up

Monthly contrast-enhanced chest CT scans are performed for the first three months after the procedure. After that,

contrast-enhanced chest CT or PET/CT scans and tumor markers are examined every three months, to detect whether local lesions have been completely ablated or if any new pulmonary lesions or extrapulmonary metastases have emerged. Contrast-enhanced chest CT is the standard method of evaluating ablation efficacy at present. If available, use of PET-CT in combination with contrast-enhanced CT can provide a more accurate assessment of the efficacy after ablation.^{24,40,44}

Post-procedure imaging characteristics and response assessment

Computed tomography-based efficacy assessment

After ablation, variations on contrast-enhanced CT scans will follow a pattern: the lesion will grow for one to three months after ablation, and remain stable or gradually involute and decrease in size after three months.^{44,45}

In the first week, the lesion may show low-density honeycomb-like or cavernous areas, and the area around the ablated tumor will be surrounded by concentric circles of different degrees of decay, known as the "cockade" sign (which is more obvious 24–48 hours after ablation). CT values (Hounsfield units) are reduced, and the lesion is enlarged compared with what it was before ablation, with a GGO-like reaction band around it. A GGO beyond the peripheral border of the tumor is thought to indicate complete tumor ablation.^{24,46,47} In the intermediate phase (1 week to 3 months), as the ablation zone increases constantly, a sharp enhanced ring may appear around the perimeter (benign periablation enhancement), known as the "egg shell" sign (a thin rim peripheral to the zone of ablation, a relatively symmetric and uniform process with smooth inner margin, that can measure 0.5–3 mm). In the late phase (after 3 months), the ablation zone remains stable compared with the baseline (CT findings at about 1 month after the ablation). Subsequent follow-up CT results of the lesion area may present different modes, such as fibrosis, cavities, nodules, atelectasis, and disappearance.⁴⁷

Assessment of local efficacy

The lesion at one month after ablation is used as the baseline to determine local efficacy.

Complete ablation is indicated by lesion disappearance, complete cavernous formation, fibrotic progression or scar, solid nodule involution or no change, without contrast-enhanced signs on the CT scan, and/or atelectasis.

Incomplete ablation is indicated by incomplete cavernous formation, with some solid or liquid components remaining and irregular peripheral or internal enhancement signs on

CT scans; partial fibrosis, with solid residues in the fibrotic lesion, which presents as irregular peripheral or internal enhancement signs on CT scans; and/or solid nodules with unchanged or increased size, which also present as irregular peripheral or internal enhancement signs on CT scans.

PET-CT may be the most accurate means of determining the local response after ablation, but it has a high false-positive rate three months after ablation. For various reasons, PET-CT has not been widely applied in the field of tumor ablation, but if applicable, it is recommended for follow-up assessment of ablation response.^{48–50}

Clinical outcomes assessment

Regular follow-up is based on the local efficacy assessment, to monitor improvement in quality of life (such as pain relief, as evaluated by a numeric rating scale). Overall survival is recorded during follow-up, as survival is the most important indicator of clinical outcomes. Patient survival at one, two, three, and five years should be followed.

Complications and treatment

Percutaneous lung tumor ablation is a relatively safe topical treatment. The incidence of complications is reported according to the classifications of the Imaging-guided Tumor Ablation International Working Group of the Society of Interventional Radiology.⁵¹

Major complications can cause death or disability, hospitalization or clinical treatment, increased level of care or prolonged hospitalization, including blood transfusions or thoracic drainage. In the event of death, the relationship with the ablation should be noted. Minor complications include cases of pneumothorax that do not require drainage.

Side effects include adverse outcomes associated with treatment, which may happen often, but rarely cause substantial damage, including pain, pleural reaction, small amounts of pulmonary bleeding, bloody sputum, small amounts of pleural effusion, and post-ablation syndrome. According to the time of occurrence, they are classified as immediate complications (<24 hours after ablation), perioperative complications (24 hours–30 days after ablation) and delayed complications (>30 days after ablation).

Pain

After a procedure under local anesthesia, patients may experience varying degrees of pain. Pain control treatment is often particularly necessary for the ablation of lesions near the pleura. If the pain is severe, opioid medications can be increased, and the proper amount of sedatives can also be used. Post-procedural pain is usually mild and will last for

several days, or up to two weeks in certain patients, but moderate or severe pain is rare. Non-steroidal analgesic drugs can be used for pain control.

Post-ablation syndrome

Post-ablation syndrome occurs in approximately two thirds of patients, as a result of the absorption of necrotic substances and release of inflammatory cytokines. This syndrome is transient and self-limiting; its symptoms include low-grade fever, general malaise, fatigue, vomiting, and so on, which generally last three to five days, or (less often) up to about two weeks. Symptomatic treatment is often sufficient, in addition to non-steroidal drugs when necessary. A small dose of short-term glucocorticoids in conjunction with enhanced supportive treatment can be helpful.

Pneumothorax

Pneumothorax is the most common post-ablation complication, with an incidence rate of 10–60%,^{52,53} and is more common with emphysema, male patients, age > 60 years, tumor <1.5 cm, tumor in the lower lobe, >3 puncture for a single tumor in lung tissue, multiple tumors and multiple puncture and ablations, and a long part of the ablation path through lung tissue or through a large fissure.^{54–56} Most cases of pneumothorax can be easily treated or are self-limiting. Fewer than 10% of cases need thoracic drainage. If there is still a gas leak after thoracic drainage, continuous suction, pleurodesis, endoscopic injection sclerotherapy, tracheal valve implantation and other means can be used.⁵⁷ The patient should also be observed for delayed pneumothorax (i.e. ≥72 hours after ablation).⁵⁸

Pleural effusion

A small amount of pleural effusion is usually observed after 1–60% of ablation procedures,⁵² and is thought to be a sympathetic response to thermal damage; 1–7% of patients require puncture/catheter drainage for the pleural effusion. Risk factors for pleural effusions include large lesions, ablation of multiple lesions at one time, lesions near the pleura (<10 mm), and prolonged ablation.⁵⁴

Bleeding

The incidence of bleeding is 3–8% during ablation,^{51,52} but hemoptysis is extremely rare.^{52,59,60} In the event of moderate or severe hemoptysis, ablation should be carried out immediately with intravenous hemostatic infusion. As ablation itself can cause blood coagulation, bleeding will gradually stop as the ablation progresses. As a result, the incidence of major bleeding is not high during the procedure. Obviously, large

blood vessels or atelectatic lung tissue should be avoided as much as possible. Postoperative hemoptysis is often self-limiting, and can last three to five days. In cases where conservative treatment fails, embolization or exploratory thoracotomy can be performed.

Pleural reaction

Ablation stimulates the vagus nerve that dominates the parietal pleura, and vagus nerve excitement can slow the heart rate, and even cause cardiac arrest. When this happens, the ablation should be suspended to allow complete local anesthesia. Atropine, sedatives and other drugs should be properly applied.

Infection

The incidence of lung infection caused by ablation is 1–6%.^{52,59–61} Prophylactic antibiotics can be used 30 to 60 minutes before the procedure, and once again in 24 hours, and can be extended to 48 to 72 hours for patients older than 70 years, or for those with chronic obstructive pulmonary disease, poorly controlled diabetes, tumors > 4 cm, or low immunity. If the temperature is still > 38.5°C at five days after the procedure, lung infections should be first suspected. Antibiotics should be adjusted according to sputum, blood or pus culture results. Pulmonary or chest abscesses can be drained using tube placement. Also, note that as interstitial pneumonia often occurs after radiotherapy, ablation increases the risk of secondary infection.⁶¹

Less common complications

Individual reports included cases of bronchial fistula, acute respiratory distress syndrome, thermal burns or frostbite in non-target areas, cold shock, thrombocytopenia, tumor seeding via needle, nerve damage (brachial plexus, intercostal, phrenic, recurrent laryngeal nerves, etc.), pulmonary or air embolism, and myocardial infarction. Individualized treatment should be given in such cases.

Ablation in combination with other therapy

Ablation in combination with other therapy methods is an important part of current cancer research, including combinations of ablation with surgery, chemotherapy, radiation and/or molecular-targeted drugs and the like. The combination of ablation and radiotherapy can improve local tumor control and prolong survival, while not evidently increasing adverse reactions.^{62–64} Although few studies have been pub-

lished on ablation with chemotherapy in NSCLC, the combination can control localized tumors and prolong patient survival.^{65–68}

Conclusion

Minimally invasive therapy appears to be the direction of future lung cancer treatment development. In particular, imaging-guided percutaneous thermal ablation techniques have the following advantages in treating lung tumors: minimal invasiveness, good therapeutic effects, safety, fast recovery, relatively simple procedure, and wide applicability. The best reported one, three, and five-year overall survival rates after RFA for NSCLC are 97.7%, 72.9%, and 55.7%, respectively,⁶⁹ with a procedural mortality rate of <1%.⁷⁰ Such clinical evidence indicates that this technique will be more widely used in treating lung tumors in the future, and it could become a new treatment modality following surgery, radiotherapy, and chemotherapy. Clinically, however, thermal ablation is used much less often to treat primary and metastatic lung cancer patients than surgery, radiotherapy, and chemotherapy.^{71–75} Further work is needed to change the knowledge of thermal ablation techniques among traditional oncologists, making the treatments universal and standardized.

However, thermal ablation as the treatment of primary and metastatic lung tumors has some current problems: (i) although thermal ablation technology has become an important facet of multidisciplinary lung cancer treatment, especially for the early lung cancer patients who cannot be tolerate surgical resection (for whom it is likely to become the treatment of choice), large-scale, multi-center, randomized, prospective clinical trials are still lacking; (ii) no prospective, multi-center comparative clinical trials with other conventional treatments (such as stereotactic radiation therapy) have been performed; (iii) few clinical trials use thermal ablation in combination with other treatments (such as radiotherapy, chemotherapy and molecularly targeted therapy);^{76–79} (iv) as a relatively new modality, thermal ablation has not been subjected to the volume of clinically based refinements to improve local complete ablation rates and reduce local recurrence (for example) as have more traditional modalities; (v) because of differences in equipment manufacturers and performance, and because the technique is just emerging, professional skill varies greatly among clinicians, which complicates the formation of standard guidelines; (vi) compliance with current international criteria in terms of outcome determination after thermal ablation can be difficult, as existing imaging methods do not always reflect outcomes after thermal ablation with a desirable level of precision, so development of recognized outcome criteria in line with thermal ablation technology itself has a long way to go; (vii) palliative ablation in the comprehensive treatment of

lung cancer has yet to be fully explored; and (viii) basic research in topics, such as complex thermal field distribution and effects on the immune system, is still lacking.

Disclosure

No authors report any conflict of interest.

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