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CLINICAL GUIDELINE

Expert consensus on image-guided radiofrequency ablation of pulmonary tumors: 2018 edition

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Abstract

Lung cancer ranks first in incidence and mortality in China. Surgery is the primary method to cure cancer, but only 20–30% of patients are eligible for curative resection. In recent years, in addition to surgery, other local therapies have been developed for patients with numerous localized primary and metastatic pulmonary tumors, including stereotactic body radiation therapy and thermal ablative therapies through percutaneously inserted applicators. Percutaneous thermal ablation of pulmonary tumors is minimally invasive, conformal, repeatable, feasible, cheap, has a shorter recovery time, and offers reduced morbidity and mortality. Radiofrequency ablation (RFA), the most commonly used thermal ablation technique, has a reported 80–90% rate of complete ablation, with the best results obtained in tumors < 3 cm in diameter. Because the clinical efficacy of RFA of pulmonary tumors has not yet been determined, this clinical guideline describes the techniques used in the treatment of localized primary and metastatic pulmonary tumors in nonsurgical candidates, including mechanism of action, devices, indications, techniques, potential complications, clinical outcomes, post-ablation surveillance, and use in combination with other therapies. In the future, the role of RFA in the treatment of localized pulmonary tumors should ultimately be determined by evidence from prospective randomized controlled trials comparing sublobar resection or stereotactic body radiation therapy.

Introduction

Lung cancer is one of the most common malignant tumors worldwide, ranking first in terms of the proportion of deaths, while morbidity and mortality continue to increase. According to GLOBOCAN 2012 estimates published by the International Agency for Research on Cancer (IARC) under the World Health Organization (WHO), there were 1.825 million new lung cancer cases worldwide (1.242 million men and 583 000 women) and 1.59 million deaths (1.09 million men, ranking first; and 491 000 women, ranking second).[1] Lung cancer mortality has increased by 465% in China compared to 30 years ago, and approximately 600 000 people die of lung cancer each year.[2,3] According to National Cancer Registration Center estimates, in 2015 there were 733 000 new lung cancer cases (509 000 men, ranking first; and 224 000 women, ranking second) and 610 000 deaths (432 000 men and 178 000 women, both ranking first). China accounts for 35.8% of new lung cancer cases and 37.6% of lung cancer deaths worldwide. Five-year survival is 16.1%.[2]

While surgery remains the treatment of choice for early-stage lung cancer, only 1/4~1/3 of lung cancer patients are eligible for surgical treatment in clinical settings. The proportions of elderly and middle-aged lung cancer patients continue to rise as the population ages. These patients often are have other conditions and are therefore not eligible or cannot tolerate conventional surgical resection (Table 1).[4] Patients are divided into good-risk, high-risk, and medically inoperable groups according to surgical risk. Lobectomy and lymph node dissection remain the standard procedures for early-stage lung cancer patients in the good-risk group; sublobar resection (including segmental and wedge resection) can be performed for patients in the high-risk group; and for the medically inoperable group, tumor thermal ablation and stereotactic body radiation therapy (SBRT) are recommended. Tumor thermal ablation refers to in situ inactivation technology in which the coagulation necrosis of target tumors is directly caused by the biological effect of heat. It has the advantages of being minimally invasive, safe, conformal, repeatable, with reliable effectiveness and low cost, and enables rapid recovery with few complications. It has become the fourth leading treatment for tumors. Currently, the common minimally invasive ablation techniques for lung tumors include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, laser ablation, and other means at home and abroad. Since 2009, the National Comprehensive Cancer Network (NCCN) Clinical Guidance on Non-small Cell Lung Cancer (NSCLC) and *Standards for the Diagnosis and Treatment of Primary Lung Cancer in China* both recommend that RFA can be used for the treatment of early-stage lung cancer patients who cannot tolerate surgery.[5] In China, the use of RFA is restricted (*Medical Technologies with Restricted Clinical Application, 2015 Edition*).

Table 1 Criteria for surgical lobectomy for primary lung cancer[4]

Major criteria (at least 1 item)
$FEV_1 \leq 50\%$ predicted
DLCO ≤ 50% predicted
Minor criteria (at least 2 items)
Age ≥ 75 years
FEV_1 51–60% predicted
DLCO 51–60% predicted
Pulmonary artery pressure > 40 mmHg (estimated by echocardiography or right heart catheterization)
Left ventricular ejection fraction ≤ 40%
$PO_2 \leq 55$ mmHg or $SPO_2 \leq 88\%$ at rest or during exercise
$PCO_2 > 45$ mmHg

DLCO, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in one second; PCO_2, partial CO_2 pressure; PO_2, partial O_2 pressure; SPO_2, O_2 saturation.

The principle of RFA is as follows. Alternating currents at a high frequency of < 30 MHz (normally 460–480 kHz) are used to make the ions in tumor tissues develop rapid turbulence and mutual friction, transforming radiofrequency (RF) energy into heat energy; as a result, the local temperature is escalated to 60–100°C, which causes the tumor cells to develop coagulative necrosis. The degree of coagulative necrosis depends on the temperature reached and the duration and the influence of factors, including heat conduction and heat convection, between circulating blood and extracellular fluid.[6] In 2000, Dupuy *et al.* reported the first clinical use of RFA to treat lung cancer.[7] In the same year, Cheng *et al.* reported their experience of treating 105 patients with lung tumors with high-temperature RFA of an anchored electrode under CT guidance in China, which started the application of RFA in clinical practice for lung cancer.[8–16] However, as an aerated organ, the lungs have spontaneous respiratory movements; lung tissue is rich in blood supply, and has a heat sink effect, high impedance ($509 \pm 197\ \Omega$ on average), and other characteristics; ground-glass opacity (GGO) around the tumor changes after ablation and is not consistent with the coagulated necrotic area of the tumor. As a result, RFA of lung tumors is characterized by difficulty in puncture positioning, a high local progression rate[10,17,18] special efficacy evaluation, and many surgical complications. In October 2014, Professor Bao-Dong Liu organized 11 well-known experts in the field of RFA of lung tumors in China who prepared the *Expert Consensus on Image-guided Radiofrequency Ablation of Pulmonary Tumors (2015 Edition)*, which was subsequently published in the *Journal of Chinese Lung Cancer*,[19] *Chinese Clinical Journal of Thoracic and Cardiovascular Surgery, Clinical and Pathological Journal, Journal of Thoracic Disease, Annals of Translational Medicine, Translational Lung Cancer Research,* and *Chinese*

Clinical Oncology.[20–25] The Consensus has played a positive role in promoting the development of RFA of pulmonary tumors in China since its publication, but further improvement is required. Therefore, on 3 December 2017, the Lung Cancer Prevention and Control Branch of the China International Exchange and Promotion Association for Medical and Healthcare organized a number of well-known experts in related disciplines to revise the Consensus in an attempt to further standardize procedure techniques, facilitate efficacy evaluations, minimize complications, and improve the therapeutic effectiveness of RFA of pulmonary tumors.

Imaging guidance

Computed tomography

Computed tomography (CT) is currently the most commonly used and accurate operating platform. It has high-density resolution and can provide a cross-sectional view of lesions. It can also clearly display relationships among the heart, large vessels, and lesions, and therefore can avoid puncturing the heart, great vessels, trachea, esophagus, and other important structures. Its advantages include accurate positioning, timely detection of complications, and capability for evaluating efficacy. However, it cannot monitor the puncture process in a real-time manner, and cannot provide static cross-sectional images, therefore repeated CT scans are required.

Ultrasound

Ultrasound can be performed in a real-time manner and requires a short surgical duration. However, it cannot display lesion or puncture sites as clearly and directly as CT and is only suitable for tumors near or closely attached to the chest wall in order to observe the full view.

Other techniques

Other new techniques include magnetic resonance, C-arm CT[26,27] positron emission tomography-CT (PET-CT),[28] CT-fiber bronchoscope,[29,30] and electromagnetic navigation bronchoscopy (ENB).[31]

Radiofrequency electrodes

Monopolar RF electrode

The monopolar RF electrode has one needle electrode, along with one or more electrode pads. Other designs include multi-tined expandable, internally cooled, and perfusion types.

Multi-tined expandable type

A coaxial electrode, made from multiple flexible electrodes placed in a 14–19 G trocar, is introduced into the tumor tissue. Using the propulsion device on the needle handle, the electrode is pushed out of the trocar to expand the arrays, thus enlarging the ablation area.

Internally cooled type

Using a hollow and dual-chamber design, the internally cooled type adopts an internal cooling method, during which the cooling water is circulated to the needle tip via an electric pressure pump, so as to cool down the needle electrode and prevent the drying and carbonization of tissues around the needle tip. This technique is helpful to decrease impedance and produces larger and more effective coagulative necrosis sites. The internally cooled type can be divided into single cluster and tri-needle cluster types, the latter of which has a larger ablation area after a single operation.

Perfusion type

The tip of the perfusion type has a small hole, through which liquid (typically normal saline) can be injected into the tissue to be ablated to increase electrical and thermal conductivity of the tissue, increase the ablation area, and prevent tissue carbonization.[32,33]

Multipolar RF electrodes

Multipolar RF electrodes are composed of two electrodes: active and dispersive electrodes. The tip of one electrode is both active and dispersive, and no dispersive electrode pad is required. For patients with metal implants or cardiac pacemakers, the multipolar RF electrode should be applied.

All three of these types can be employed in the RFA of lung tumors. Because patients have spontaneous breathing and large lung mobility, the multi-tined expandable type is recommended to facilitate the coverage of tumors and minimize lung injury, which can occur with the movement of an RF electrode. For tumors near the heart, great vessels, trachea, esophagus, and other important structures, however, the parallel single-needle types may be safer.

Indications and contradictions

Indications

Curative ablation

Curative ablation can achieve the complete necrosis of lung tumor tissue and may cure the condition and/or prolong survival.

Primary lung cancer[34]

Early-stage peripheral NSCLC (sized ≤ 3 cm, without lymph node or distant metastasis); patients with systemic poor heart and lung function, elderly patients, and/or patients who refuse surgery. Primary lung cancer includes multiple primary lung cancers (MPLC).

Pulmonary metastases[35]

The primary lesion has been effectively controlled; ≤ 3 unilateral lung metastases; ≤ 5 bilateral lung metastases; and/or a maximal tumor diameter of ≤ 3 cm.

Palliative ablation

Palliative ablation can maximize the induction of coagulative tumor necrosis and thus achieve the purposes of lowering tumor burden, relieving symptoms, and improving quality of life.

Primary lung cancer (PLC)[16,36–42]

The tumor is > 3 cm; multiple points or times of treatment can be delivered; and/or other treatments can be used in combination. Palliative ablation is recommended in China in the following cases:

- Solitary pulmonary recurrence following surgery for primary lung cancer;
- Progression or relapse of lung tumor after radiochemotherapy or molecular targeted therapy for peripheral NSCLC;
- Progression or relapse of lung tumor after radiochemotherapy for peripheral small cell lung cancer;
- Peripheral lung cancer complicated with malignant pleural effusion following thoracoscopic pleural biopsy/pleurodesis;
- In the event of intractable pain when ribs or thoracic vertebrae are involved, ablation of the local bone invasion can yield analgesic effects.

Pulmonary metastases

The number and size of pulmonary metastases exceed the limitations of curative ablation.

Contraindications

Absolute contraindications

Patients with a tendency for severe bleeding, platelets > 50×10^9/L, and platelet function disorders that cannot be corrected (prothrombin time > 18 seconds and prothrombin activity < 40%). Anticoagulation and/or antiplatelet drugs should be discontinued at least five to seven days prior to ablation.

Table 2 Eastern Collaborative Oncology Group/Zubrod performance status scale

Physical status	Description
0	Asymptomatic: Fully active, able to carry on all pre-disease activities without restriction
1	Symptomatic but fully ambulatory: Restricted in physically strenuous activity
2	Symptomatic, < 50% in bed during the day awake: Ambulatory and capable of all self care
3	Symptomatic, > 50% of time spent in bed, but not bedridden: Capable of only limited self-care
4	Bedridden: Completely disabled, cannot perform any self-care, totally confined to bed

Relative contraindications

Extensive extrapulmonary metastasis and a predicted survival of < 3 months; serious complications, infection, low immune function, and renal insufficiency; pacemaker and metal implants; Eastern Collaborative Oncology Group (ECOG) performance status (PS) scale > 3 (Table 2).

Examinations and staging

Pre-procedure examinations

Routine examinations

Routine blood, urine, stool, liver/kidney function, coagulation function, and lung function tests, detection of tumor markers, blood type examination, infection screening, and electrocardiogram (ECG) are performed within two weeks before the procedure.

Medical imaging

Chest contrast-enhanced CT should be performed within two weeks before the procedure. To define the staging, abdominal ultrasound, bone scan, skull magnetic resonance imaging (MRI), PET-CT, or other examinations are performed.

Pathological examinations

Trans-thoracic needle aspiration (TTNA) or bronchoscopy should be performed. For suspected mediastinal lymph node metastasis, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or mediastinoscopy can be performed.

Clinical staging

See Tables 3 and 4.

Table 3 Proposed T, N, and M descriptors for the eighth edition of the TNM classification for lung cancer

Primary tumor (T)	
T_X	Primary tumor cannot be assessed or proven by the presence of malignant cells in the sputum or bronchial washings and cannot be 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, not more proximal than the lobar bronchus under bronchoscopy. The main bronchus is involved, but the carina is not (superficial diffuse type, regardless of size).
T1a(mi)	Minimally invasive adenocarcinoma
T1a	Tumor ≤ 1 cm in greatest dimension
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension
T1c	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 5 cm or tumor with any of the following *(T2 tumors with these features are classified as T2a if ≤ 5 cm):* The main bronchus is involved, but the distance from carina is < 2 cm and the carina is not involved; or invades the visceral pleura; or is accompanied by complete atelectasis or obstructive pneumonia.
T2a	*Tumor > 3 cm but ≤ 4 cm in greatest dimens*ion
T2b	*Tumor > 4 cm but ≤ 5 cm in greatest dimension*
T3	Tumor > 5 cm but ≤ 7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	Tumor > 7 cm in greatest dimension or is associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
Regional lymph nodes (N)	
N_X	Regional node metastasis cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
Distant metastasis (M)	
M_X	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

TNM, tumor node metastasis.

Pre-procedure preparations

Planning

The body position and puncture pathway are determined based on the location, size, number, and shape of the tumor, as well as its relationships to the heart, great vessels, trachea, esophagus, and other important structures, as shown on CT or PET-CT.

Equipment and instruments

The equipment and instruments used include a CT machine, RF generator, RF electrode, drainage bags for thoracentesis or chest tube drainage, ECG monitor, oxygen inhalation device, and an ambulance.

Preparation of drugs

Anesthetic, analgesic, and antitussive drugs, as well as drugs for hemostasis, expanding coronary artery, and lowering blood pressure, should be prepared.

Patient preparation

(i) an informed consent form is signed by the patient and/or his/her family (representative); (ii) the patient must fast, with no food or water four hours before the

Table 4 Proposed stage groupings for the eighth edition of the TNM classification for lung cancerr

Occult carcinoma	T_X	N_0	M_0
Stage 0	Tis	N_0	M_0
Stage IA	$T_{1a,b,c}$	N_0	M_0
Stage IB	T_{2a}	N_0	M_0
Stage IIA	T_{2b}	N_0	M_0
Stage IIB	T_1	N_1	M_0
	T_2	N_1	M_0
	T_3	N_0	M_0
Stage IIIA	$T_{1,2}$	N_2	M_0
	T_3	N_1	M_0
	T_4	N_0	M_0
Stage IIIB	$T_{3.4}$	N_2	M_0
	$T_{1.2}$	N_3	M_0
Stage IIIC	$T_{3.4}$	N_3	M_0
Stage IVA	Any T	Any N	$M_{1a,b}$
Stage IVB	Any T	Any N	M_{1c}

TNM, tumor node metastasis.

procedure; (iii) prepare the skin if necessary; (iv) establish intravenous access; (v) orally administer an antitussive drug before the procedure, as necessary; and (vi) conduct pre-procedure education.

Procedures

Body position

When selecting the patient's body position, the puncture pathway needs to be considered. The principle when selecting the puncture pathway is to determine the shortest puncture distance avoiding bones, lung fissure, lung blisters, and other important structures. The principle of the selection of body position is that it is easy to immobilize the patient and the patient is relatively comfortable.

Monitoring of vital signs

The heart rate, blood pressure, and oxygen saturation must be monitored during the ablation process, and the patient should be closely observed for breathing, pain, cough, hemoptysis, and so on. Symptomatic treatment should be delivered when necessary.

Table 5 ASA physical status classification system

ASA class	Physical status
ASA 1	Healthy and fit patient with normal organ functions
ASA 2	With mild systemic disease (excluding surgical conditions) and sound functional compensation
ASA 3	With severe systemic disease, with functional limitation but still able to cope with daily activities
ASA 4	With severe systemic disease that is a constant threat to life, loss of ability to perform daily activities
ASA 5	A moribund person who is not expected to survive without surgery
ASA 6	A person declared brain-dead whose organs are being removed for donor purposes

ASA, American Society of Anesthesiologists.

Disinfection and anesthesia

The skin is disinfected with iodine tincture and ethyl alcohol and then covered with sterile towels. The puncture site is anesthetized by local infiltration of 1~2% lidocaine up to the pleura. Conscious sedation or general anesthesia is recommended under the following conditions: (i) pediatric patients; (ii) patients who cannot cooperate during the procedure; (iii) if a long procedure is expected to be required; and (iv) if the tumor is close to the parietal pleura and thus may cause sharp pain. Pre-anesthesia evaluation should be based on the American Society of Anesthesiologists (ASA) classification system (Table 5), and only patients with a class of < 3 can undergo RFA.

Puncturing and insertion[43]

The scope of each CT scan includes the target tumor. The RF electrode is inserted into the target tumor via the puncture site under CT guidance. After the RF electrode is confirmed to be in the predetermined position by CT imaging, ablation is performed. To ensure complete ablation of the target tumor, under the premise of safety, the coverage scope of the RF electrode should include the target tumor and lung tissue 0.5~1.0 cm around the tumor (i.e. the "ablation area").

Ablation

Treatment parameters are set based on the model of RFA generator, type of RF electrode, tumor size, and relationships between the tumor and its surrounding structures (the selection of lung tumor ablation parameters can be adjusted depending on the equipment manufacturer's recommended parameters). After ablation, the puncture pathway should also be ablated before withdrawal of the RF electrode to minimize tumor implantation and bleeding.

Small tumors

Patients with tumors sized ≤ 3 cm may receive a single ablation.

Middle-sized tumors

Patients with tumors sized 3–5 cm should receive single multi-focused ablation.

Large tumors

Patients with tumors sized > 5 cm should receive single multi-focused ablation, sequential ablation by radiotherapy, or repeat ablation if necessary.

Tumors in special sites

For lesions near the heart, major vessels, trachea, bronchus, esophagus, and diaphragm, single-electrode puncturing is recommended; the direction of the puncture should be parallel with the major structures and maintained > 0.5 cm.

Post-procedure scan

A repeat CT scan should be performed immediately after the ablation to assess whether the procedure has been successful (whether the treatment has been completed according to the ablation procedures or whether the tumor has been fully covered by the ablation). The patient should be observed for possible complications.

Post-procedure management

The patient is asked to take a supine position for 2–4 hours, during which time the vital signs are monitored. Chest X-ray or CT scan can be performed after 24–48 hours to determine if there are any complications (such as asymptomatic pneumothorax or pleural effusion).

Complications and treatment

Radiofrequency ablation is a relatively safe local treatment. Complications are graded according to the criteria of the International Working Group on Image-guided Tumor Ablation under the Society of Interventional Radiology (SIR) (Table 6).[44] Complications are classified according to the time of occurrence as: immediate (≤ 24 hours after RFA), periprocedural (24 hours to 30 days after RFA), and delayed (> 30 days after RFA).

Complications after RFA for lung tumors can be categorized into puncture-related (such as pulmonary hemorrhage, hemothorax, pneumothorax, cardiac tamponade, air embolism, etc.) and ablation-related (such as chest pain, pleural reactions, cough, skin burns, etc.) complications.[45] The mortality of RFA for lung tumors ranges from 0% to 5.6%.[46] RFA mortality of a sample size of > 100 cases is reported in the literature at 0–2.2%, with incidences of minor and major complications of 3–24.5% and 21.3–64.9%, respectively. Causes of death include hemorrhage, pneumonia, worsened pulmonary fibrosis, pulmonary embolism, acute heart failure and respiratory failure.[47,48] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 is recommended to evaluate response.[49]

Table 6 SIR definition and grading system of complications

Classification	Definition
Side effects	Pain
	Post-ablation syndrome
	Asymptomatic pleural effusion
	Injury of the adjacent structures but without any consequence
Minor complications	Require no therapy, result in no consequence
	Require nominal therapy, result in no consequence; includes overnight admission for observation only
Major complications	Require therapy and minor hospitalization (< 48 hours)
	Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 hours)
	Result in permanent adverse sequelae
	Result in death

SIR, Society of Interventional Radiology (US).

Pain

Pain is often assessed using CTCAE v4.03: 1, mild pain; 2, moderate pain limiting instrumental activities of daily living; and 3, severe pain limiting self-care activities of daily living.

Intra-procedure pain

1 Etiology: Procedures under local anesthesia are often associated with varying degrees of pain, which may be caused by stimulation of the pleural nerve by heat conduction. In their univariate and multivariate analysis, Okuma *et al.*[50] found that the occurrence of pain was significantly correlated to the short tumor distance from the chest wall (< 1 cm).
2 Treatment: If the pain is severe, complete anesthesia of the pleura is required. The following techniques may be required: the use of analgesics or even conscious sedation/anesthesia; the target temperature is lowered to 70°C before it is gradually increased several minutes later; the 3D reconstructed CT images are observed to determine if the electrode needle is approaching the pleura, and if so, the electrode needle may need to be rotated before ablation; or the RF electrode may be inserted into the thoracic cavity to separate the visceral from the parietal pleura, forming an artificial pneumothorax.[51,52]

Post-procedure pain

Post-procedure pain is usually mild (levels 1–2) and will last for several days, or up to two weeks in certain patients, but does not require special management. While moderate or severe pain is rare, non-steroidal analgesic drugs can be administered as treatment.

Post-ablation syndrome

Post-ablation syndrome occurs in 6.6–22.2% (mean 18%) of patients.[46] It is a transient self-limiting syndrome characterized by a low fever and other discomfort. Fever may be assessed using CTCAE v4.03: 1, 38–39°C; 2, 39–40°C; 3, > 40°C for < 24 hours; and 4, > 40°C for > 24 hours.

1 Etiology: The severity and duration depend on the tumor necrosis volume and the patient's general condition. The symptoms last two to seven days in most patients but may last two to three weeks in patients with larger ablated tumors.
2 Treatment: Most symptoms are transient and self-limiting, and symptomatic treatment is often sufficient. In a small number of patients, a small dose of short-term non-steroidal drugs (glucocorticoids) is helpful when necessary.

Pneumothorax

The incidence of pneumothorax is 5–63%.[46,49] Pneumothorax may be assessed using CTCAE v4.03: 1, asymptomatic, clinical or diagnostic observations only, intervention not indicated; 2, symptomatic, intervention indicated (e.g. tube placement without sclerosis); 3, sclerosis and/or surgical intervention and hospitalization indicated; and 4, life-threatening consequences, urgent intervention indicated. Nour-Eldin *et al.* divided pneumothorax into mild (≤ 2 cm), moderate (2–4 cm), and severe (> 4 cm) by lung surface retraction.[53]

Intra-procedure pneumothorax

1 Etiology: According to Hiraki *et al.*, the risk factors of intra-procedure pneumothorax include: male gender (with larger vital capacity); no history of pulmonary surgery (without pleural adhesions); a greater number of tumors ablated (multiple punctures), involvement of the middle or lower lobe (with larger lung mobility); small and deep lesions increase the length of the aerated lung traversed by the electrode (difficult to locate and multiple punctures are required); and large tumors (requiring multi-focused ablation, repeated punctures, cluster needle, and ablation duration > 3 hours).[54] Sano *et al.* demonstrated that older age, use of a multi-tined expandable RF electrode, and high-power output were hazards related to the development of pneumothorax.[55] Kennedy *et al.* conducted a meta-analysis of the results of 1916 pulmonary tumor ablation procedures in 10 retrospective studies and found that increased age, male gender, no history of pulmonary surgery, and a greater number of tumors ablated are high risk factors of the development of pneumothorax.[56] In conclusion, the incidence of pneumothorax is related to greater age, emphysema, tumor diameter, lesions in the lower part of the lung, aerated lung parenchyma traversed by the needle track for a distance, and traversal of a major pulmonary fissure. During RFA of upper lobe lung tumors, the incidence of pneumothorax is high as a result of the high alveolar pleural pressure gradient.[54]
2 Treatment: A mild pneumothorax may not require management. Moderate to severe pneumothorax can be treated by thoracentesis or by placing a chest tube drainage device.[57] It has been reported that 3.3–38.9% (mean 11.0%) of patients require the placement of a chest tube drainage device.[46] Hiraki *et al.* found that high risk factors of pneumothorax requiring chest tube drainage include: no history of surgery of the ipsilateral lung ($P = 0.002$); the use of a cluster needle ($P < 0.001$); and tumors located in the upper lobes (i.e. because the pleural pressure gradient of alveoli of the upper lobes is high and a large amount of air continuously enters the chest when the patient is upright) ($P < 0.001$).[54] After pneumothorax occurs, a decision to terminate or continue the positioning procedure of the RF electrode depends on factors such as whether the pneumothorax is relieved after the extraction, whether the RF electrode can be accurate positioned, and the clinical symptoms of the patient. If pneumothorax is reduced after treatment, the patient has no symptoms, and the RF electrode can be accurately positioned, continuing the procedure is recommended; otherwise it may be necessary to place a chest tube drainage device and operate after the pneumothorax and patient's symptoms are relieved. If the patient still has air leakage after the thoracic closed drainage, continuous negative pressure suction, pleurodesis, a sclerosis agent injection, placement of a valve into the trachea, and other techniques can be performed.[58]
3 Prevention: In general, the incidence of pneumothorax increases three-fold when the puncture needle: (i) passes through the interlobular fissure; (ii) passes through the bullae of lungs; or (iii) is oblique to the pleura. The keys to reducing the occurrence of pneumothorax are a skilled puncture technique, fast needle insertion, accurate puncture, and avoiding multiple punctures. Normal saline or anesthetic can be injected into the pleural juncture via the injection hole, thus allowing the extrapulmonary tissues to thicken. After the RF electrode needle is removed, the patient lies in a position with the puncture side below, and oxygen inhalation can reduce the incidence of pneumothorax.

Delayed pneumothorax

The incidence of delayed pneumothorax is approximately 10%, is observed 24 hours after ablation, and can be managed as described above.[59,60] Some authors have proposed

that no history of surgery to the ipsilateral lung, deep lesions, and GGO of the target tumor adjacent to the pleura after RFA are high risk factors for delayed or recurrent pneumothorax.[53] After ablation of the needle pathway, the peripleural tissue is dry, which negatively impacts elastic recoiling and closure of the needle hole. Bronchial pleural fistula may occur and even develop into tension pneumothorax, which requires special attention.

Subcutaneous emphysema

The incidence of subcutaneous emphysema is 0.2%.[61] When pneumothorax occurs during RFA, if the pleural cavity is attached, the air enters the skin along the puncture route and forms subcutaneous emphysema. If the pneumothorax is mild or treated, subcutaneous emphysema can gradually be absorbed.

Pleural effusion

A small amount of pleural effusion is usually observed after ablation, with an incidence rate of 1.3–60% (median 13.4%).[46] CTCAE v4.03 can be applied: 1, asymptomatic, clinical or diagnostic observations only, intervention not indicated; 2, symptomatic, intervention indicated (e.g. diuretics or limited therapeutic thoracentesis); 3, symptomatic with respiratory distress and hypoxia, surgical intervention including chest tube or pleurodesis indicated; and 4, life-threatening respiratory or hemodynamic compromise, intubation or urgent intervention indicated.

1 Etiology: The development of pleural effusion is related to pleural irritation resulting from heat. Risk factors leading to the occurrence of pleural effusion include the use of a cluster electrode, decreased distance to the nearest pleura, and decreased length of the aerated lung traversed by the electrode.[54]
2 Treatment: General observation or conservative treatment is sufficient. In cases of moderate to severe pleural effusion, thoracentesis/suction or chest tube drainage is required. However, the proportion of patients requiring thoracic drainage is < 10%.
3 Prevention: The ablation site should be located as far as possible from the pleura.

Hemorrhage

The incidence of intra-procedure hemoptysis ranges from 3.3% to 18.2% (mean 11.1%),[46] and the incidence of major hemoptysis is extremely low. The incidence of pulmonary hemorrhage is 0–11% (7.1%), which is inconsistent with incidence rates of hemoptysis and post-procedural bloody sputum. The incidence of hemothorax is 1.9–16.7% (4.3%). CTCAE v4.03 can be applied: 1, mild symptoms, intervention not indicated; 2, moderate symptoms, medical intervention indicated; 3, transfusion, radiologic, endoscopic, or surgical intervention indicated (e.g. hemostasis of bleeding site); and 4, life-threatening respiratory or hemodynamic compromise, intubation or urgent intervention indicated.

1 Etiology: No specific risk factor has been determined.[50] It is reported that the development of hemorrhage may be correlated with the small lesions, long needle pathway, co-existence of chronic obstructive pulmonary disease, and pulmonary arterial hypertension.
2 Treatment: Ablation should be immediately performed once intraprocedural hemoptysis occurs, which is also beneficial for hemostasis. Pulmonary hemorrhage can be absorbed spontaneously. Post-procedural bloody sputum is often self-limiting, and can last three to five days. If a small amount of pleural fluid is found during the procedure, the patient should be closely observed and may receive conservative treatment. The presence of moderate to severe pleural effusion suggests active bleeding, which needs to be treated by thoracentesis/suction or chest tube drainage. According to published literature, approximately 10% of patients require thoracic closed drainage, together with the use of hemostatic drugs. If conservative treatment fails, embolization or exploratory thoracotomy can be performed.
3 Prevention: Because ablation itself can cause blood coagulation, bleeding will gradually stop with the progress of ablation. When making the puncture, the blood vessels and atelectatic lung tissue should be avoided. Platelet count, blood coagulation function, and the use of hemostatic drugs should be taken into consideration before commencing the procedure.

Cough

CTCAE v4.03 can be applied: 1, mild symptoms, nonprescription intervention indicated; 2, moderate symptoms, limiting instrumental activities of daily living, medical intervention indicated; and 3, severe symptoms, limiting self-care activities of daily living.

1 Etiology: A severe intraprocedural cough may result from the stimulation of alveoli, bronchi, or pleura after the local temperature is increased. A post-procedure cough is often an inflammatory response caused by local tumor tissue necrosis and thermal injury to the surrounding lung tissue after ablation.
2 Treatment: A cough can be alleviated immediately after oral administration of an antitussive agent or an injection of lidocaine via the injection hole in the RF electrode. In some patients, however, the cough will not cease until ablation is completed. Patients with a post-

procedure cough may be appropriately administered drugs for curing the cough and reducing phlegm.
3 Prevention: Oral administration of an antitussive drug 30 minutes before the procedure may help to alleviate the cough response.

Vagal reaction

CTCAE v4.03 can be applied: 3, present; 4, life-threatening consequences, urgent intervention indicated.
1 Etiology: The procedure stimulates the vagus nerve that dominates the parietal pleura. The resulting vagus nerve excitement can slow down the heart rate, and even cause cardiac arrest. The dose of local anesthesia may also be insufficient. Vagus nerve excitement occurs because some patients have limited knowledge about the disease and may feel fearful of treatment, or reach a state of high tension; or if the lesion is located < 1 cm away from the pleura.
2 Treatment: When a vagal reaction occurs, the procedure should be suspended to allow complete local anesthesia. Atropine, sedatives, and other drugs should be properly applied.
3 Prevention: Adequate periprocedural communication may help the patients to mentally relax; otherwise the adjacent pleura should be completely anesthetized.

Pulmonary inflammation

The incidence of pneumonia ranges from 6% to 12% (mean 9.5%) and that of lung abscess is 1.9~6.6% (mean 6.4%).[46] CTCAE v4.03 can be applied: 2, moderate symptoms, oral intervention indicated (e.g. antibiotic, antifungal, antiviral); 3, IV, antibiotic, antifungal, or antiviral intervention indicated, radiologic, endoscopic, or operative intervention indicated; and 4, life-threatening consequences, urgent intervention indicated. Bronchiolitis obliterans organizing pneumonia (BOOP), a reactive pneumonia after ablation, is very rare and may be distal obstructive pneumonia caused by bronchial stenosis and occlusion resulting from granulation tissue hyperplasia[62] Incidence is 0.4% (3/840). It is characterized by nonspecific symptoms, such as fever, cough, sputum, and dyspnea. CT imaging shows peripheral nodes on the lungs, GGO, or patchy gas-containing shadows. Antibiotics are not effective, but steroidal drugs are effective.
1 Etiology: High risk factors of pulmonary inflammation include patients aged > 70, with low immunity or after radiation therapy, systemic chronic obstructive pulmonary disease, interstitial pneumonia and diabetes mellitus, and tumors > 4 cm.
2 Treatment: If the body temperature remains > 38.5°C five days after the procedure, lung infection should first be considered. A chest X-ray plain film or chest CT scan (recommended) should be taken to confirm, and antibiotics should be adjusted according to culture results of sputum, blood, or fester. If chest X-ray plain film or chest CT scan indicates an intrapulmonary/thoracic abscess, catheterization should be performed for drainage. Such infection can develop into acute respiratory distress syndrome (ARDS) or even death.
3 Prevention: Pulmonary function should be comprehensively evaluated before the procedure, and severe pulmonary diseases should be treated.

Rare complications

Other potentially fatal complications include bronchopleural fistula, air embolism, pulmonary artery pseudoaneurysm, and cardiac tamponade. Other severe complications include injury to adjacent nerves (e.g. the brachial plexus, and the intercostal, phrenic, and recurrent laryngeal nerves are heat-sensitive), implantation metastasis, pulmonary abscess, and skin burns.[63]

Follow-up and efficacy evaluation

Follow-up

A general evaluation includes the patient's symptoms and signs, tumor markers, T cell subsets, physical status score, lung function, and quality of life. A chest CT examination is often selected to evaluate local efficacy, and a PET-CT examination can be selected for patients with other conditions. CT or PET-CT is mainly used to evaluate whether the target tumor is completely ablated, and whether there is local progress, new lesions, and so on. Chest enhanced CT should be re-examined four to six weeks after the procedure, and used as the baseline for evaluation. Chest CT should be re-examined every three months in the first two years after the procedure and every six months thereafter. PET-CT should first be re-examined three to six months after the procedure, then every six months, and subsequently once every year after two years. PET-CT is more accurate in determining efficacy and can reveal the presence of extrapulmonary metastasis. Long-term evaluation of efficacy includes progression-free survival (PFS, i.e. the duration between the beginning of treatment and imaging progress or death), overall survival (OS), and cancer specific survival (CSS). Technical efficiency and safety evaluations are followed up for at least six months; short-term efficacy is followed up for at least one year, mid-term for at least three years, and long-term for at least five years.

Changes in imaging findings in the ablation zone[64,65]

CT changes

Early phase (within 1 week)

The most common post-RFA imaging findings include intralesional bubbles and cone-shaped sectorial hyperemia

Table 7 Modified RECIST criteria used to evaluate treatment response

Effectiveness	CT (size)	CT (density)	PET
Complete ablation	Shrinks or unchanged	Without an enhanced zone	Without a metabolic zone
Incomplete ablation	Remains unchanged or is enlarged	No change in the enhanced zone	With a highly metabolic zone that remains unchanged
Local progression	Enlarged by > 10 mm	Newly developed enhanced zone	Newly developed highly metabolic zone

CT, computed tomography; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

or rim of hyperemia characterized by GGO that may circumferentially or partially envelop the target tumor. However, GGO alone may overestimate the effectiveness of procedure. Ghost cells may be seen in this zone during pathological examination. This may be explained by the rapid coagulative necrosis of the tumor and the destruction of microcirculation after heat ablation, which may prevent the release of intracellular lysosomal enzymes. The infiltration of inflammatory cells can also delay cell autolysis. Nicotinamide adenine dinucleotide diaphorase (NADH) in vitro/in vivo staining and other special staining methods can be applied for differential diagnosis.

Intermediate phase (1 week to 3 months)
In the intermediate phase, the ablation zone will continue to be larger, compared with the original tumor, but should be smaller relative to the early phase as a result of regressing parenchymal edema, inflammation, and hemorrhage.

Late phase (after 3 months)
At three months, in general, the size of the ablation zone should be the same size or larger than the baseline tumor, and by six months, the size of the ablation zone should be the same or smaller than the tumor before ablation, which may be shown in different morphologies (e.g. fibrosis, cavity, nodules, atelectasis, and disappearance or in combination).

PET-CT changes
On PET images, increased metabolic activity after two months, residual activity centrally or at the region of the ablated tumor, or the development of nodular activity at the site of the original tumor nodule is suggestive of recurrence. The results can be described using standard uptake value (SUV).

Evaluation of local efficacies

Modified RECIST (mRECIST) can be used to evaluate local efficacies (Table 7).[66]

Complete ablation
Complete ablation is achieved when CT imaging indicates that the target tumor has disappeared or if there is no enhanced cavity, solid nodules, atelectasis, or fibrosis on enhanced images. PET-CT indicates that the target tumor has no radionuclide activity or has a normal SUV value.

Incomplete ablation
Incomplete ablation is considered if any of the following occurs: incomplete necrosis formation, with some solid or liquid components remaining and enhanced signs on the CT scan; partial fibrosis, with solid residues in the fibrotic lesion that present contrast enhanced signs on the CT scan; or solid nodules of unchanged or increased size that present enhanced signs on the CT scan. PET-CT indicates that the target tumor still has radionuclide activity or has an abnormally high SUV value after the procedure.

Local tumor progression
Local tumor progression is considered after complete ablation of the target tumor if the CT indicates scattered, nodular, and irregular eccentric enhancement around the tumor has recurred. If PET-CT indicates that the target tumor has no radionuclide activity or a normal SUV value, radionuclide activity or an abnormally high SUV value recurs. Repeat ablation or other treatment is required in patients with local progression.

Primary and secondary technique efficacy
Primary technique efficacy is defined as the percentage of target tumors successfully eradicated following the initial procedure or a defined course of treatment. The secondary efficacy rate is defined as including tumors that have undergone successful repeat ablation following the identification of local tumor progression.

Follow-up and outcomes
During the one to five year follow-up period, the patient's survival conditions are recorded.

RFA combined with other treatments

Radiofrequency ablation, as a local minimally invasive ablation technique, may be combined with other treatment to improve efficacy. The combination of RFA with surgery,[39] radiotherapy,[67,68] chemotherapy,[69] and molecular

targeted drugs[38,70,71] can increase the local control rate and prolong survival. A decision whether to administer chemotherapy or molecular targeted drugs can be made following the results of gene testing.

Conclusions

Recent studies have shown that following RFA, early-stage NSCLC patients who cannot tolerate surgical resection (tumor diameter ≤ 3 cm) have one, three, and five-year survival rates of 90%, 70%, and 50%, respectively, and a mortality rate of < 2%.[72] This clinical evidence leads us to believe that RFA may become a new treatment modality following surgery, radiotherapy, and systemic therapy. However, the efficacy of RFA still needs to be validated in prospective, randomized, multi-center clinical trials,[73] and comparison with other treatment, including surgery,[74–77] ablation[78] and SBRT[79–82] is necessary.

In summary, the effectiveness and safety of RFA for the treatment of pulmonary tumors has been well demonstrated by clinical trials. However, as the equipment and instructions used between centers differ, the publication of this consensus document may facilitate the standardization of this technique during its promotion. Although the development of this consensus document was based on many international guidelines, the latest domestic and international progress, serious discussions, and repeated revisions, some errors and limitations may remain. Therefore, a more optimized clinical guideline on RFA that meets the real conditions in China is planned after the application of this document in clinical settings.

Disclosure

No authors report any conflict of interest.

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