

Expert consensus on thermal ablation therapy of pulmonary subsolid nodules (2021 Edition)

ABSTRACT

The Expert Consensus reviews current literatures and provides clinical practice guidelines for thermal ablation of pulmonary subsolid nodules or ground-glass nodule (GGN). The main contents include the following: (1) clinical evaluation of GGN; (2) procedures, indications, contraindications, outcomes evaluation, and related complications of thermal ablation for GGN; and (3) future development directions.

KEY WORDS: Ground-glass nodule, lung cancer screening, pulmonary subsolid nodules, thermal ablation

INTRODUCTION

Lung cancer is the second most common cancer worldwide, and it has the highest mortality.^[1] Early detection, early diagnosis, and early treatment are important approaches to reduce mortality. In 2011, the National Lung Screening Trial reported for the first time that lung cancer mortality in high-risk populations could be reduced by 20% using low-dose computed tomography (LDCT) screening instead of standard chest X-ray.^[2] As LDCT screening programs have been widely carried out in recent years, asymptomatic pulmonary nodules have been detected in increasing numbers. The detection rate of pulmonary nodules in China is 20%–80%.^[3–6] However, more than >97% of the pulmonary nodules found by LDCT screening are benign. Lung cancer has a detection rate of only 0.7%–2.3%.^[2,4–8] A detection rate that is too high may lead to overdiagnosis, overtreatment, and waste of medical resources, and higher levels of anxiety in patients.^[9–13] Current guidelines for the screening and treatment of lung nodules are mainly derived

from the National Comprehensive Cancer Network, Fleischner Society, American College of Chest Physicians, Asian experts, and Chinese experts.^[14,15] No consensus has been reached on a set of guidelines up to this point because difference in professional background and hospital practice guidelines.

Even guidelines differ among practitioners, consistent principles are applied for the management of pulmonary nodules: Follow-up and surgical resection. With the development of surgery, particularly the universal use of video-assisted thoracoscopic surgery (VATS), outcomes have been improved and postoperative complications and mortality from early-stage lung cancer have been lowered,^[16–19] but there are still many unsolved problems.

A pulmonary nodule is often considered as a predictor of a precancerous lesion or early-stage lung cancer. However, lung cancer with ground-glass nodule (GGN) is characterized by “indolent” development, with distant metastasis in very few patients; it has a favorable prognosis with a 100% 5-year survival rate after surgery.^[20–27] It is a special subtype of lung cancer as it differs from traditional early-stage lung cancer. The following problems exist

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in the premature use of VATS to remove this type of lesion: (1) Premature surgical intervention for pulmonary nodules, particularly for precancerous lesions, will lead to early and unnecessary organ damage and lung function loss. Moreover, early surgery cannot significantly improve the overall survival of patients, when compared with patients whose intervention are follow-up and elective surgery. (2) There are no clear selection criteria for surgical intervention of multiple pulmonary nodules and no principles for the follow-up management of residual nodules. (3) Preoperative diagnosis of pulmonary nodules is made by imaging without pathological evidence. Surgical resection of pulmonary nodules may be unnecessary and causes postoperative complications when the lesions are founds benign.^[28-30] (4) As the population ages, increasing numbers of patients with early-stage lung cancer have been diagnosed above 75 years old, when surgery is almost impossible. Moreover, there are also problems with follow-up, such as follow-up intervals and termination. Each reexamination may trigger anxiety, affect the quality of life,^[31] and increase patient's exposure to X-rays. New approaches to manage lung nodules need to be explored to solve the above problems.

As a precise and minimally invasive technique, local thermal ablation has been applied in the treatment of early-stage lung cancer, and the number of patients treated is increasing rapidly every year.^[32-41] This technique is minimally invasive and has good efficacy, high safety, and repeatability. Thermal ablation for pulmonary nodules is being developed.^[42-50] The Expert Group on Tumor Ablation Therapy of the Chinese Medical Doctors Association, the Tumor Ablation Committee of the Chinese College of Interventionalists, the Society of Tumor Ablation Therapy of the Chinese Anti-Cancer Association, and the Ablation Expert Committee of the Chinese Society of Clinical Oncology provided the platform for multidisciplinary experts to formulate the 2021 Expert Consensus. The experts, from multiple disciplines, including thoracic surgery, medical oncology, imaging, radiotherapy, respiratory, interventional medicine, pathology, and traditional Chinese medicine, gathered together and aimed to achieve consensus for clinical practice and thermal ablation treatment for pulmonary subsolid nodules or GGN.

CONCEPT AND CLASSIFICATION OF GROUND-GLASS NODULE

Concept

Arising from various factors, pulmonary nodules cause pathological changes, such as reduction of air content in the alveoli, increase in cell number, proliferation of alveolar epithelial cells, thickening of the alveolar septum, partial congestion, and edema in terminal air sacs. In lung-imaging features, it is often manifested as focal and increased hazy opacities in the lung parenchyma, with preservation of the bronchial structures and vascular margins, clear or unclear boundary, a diameter ≤ 3 cm (round or quasi-circular shadow), and solitary or multiple pulmonary nodules, and without atelectasis, hilus lymph node enlargement, or pleural effusion.^[15,51-54]

Classification

Benign or malignant

(1) Benign: benign tumors, various infectious diseases, rheumatic diseases, congenital diseases, and pulmonary hemorrhage. (2) Malignant: Such as lung cancer, lymphoma, sarcoma, and pulmonary metastases, etc.^[55]

Density

Pulmonary nodules can be divided into solid and subsolid. (1) Solid nodule: Computed tomography (CT) (lung window) shows a round or quasi-circular lesion in the lung, with increased density, which obscured all of the lung parenchyma within the vessel and bronchus. CT (mediastinal window) shows a lesion with soft tissue density. (2) Subsolid nodule:^[28,53,56,57] CT (lung window) shows a round or quasi-circular lesion of slightly increased CT attenuation, through which the normal lung parenchyma structures, airways, and vessels are visually preserved. CT (mediastinal window) shows nothing, but similar to ground glass opacity, thus it is also called a GGN or a ground-glass opacity (GGO). GGNs are radiologically divided into two categories: pure GGN (pGGN), which contain no solid component, and part-solid GGN, which contain both a pure GGN region and a consolidated region (also called mixed GGN-mGGN). GGN is an unspecific radiologic feature seen in numerous clinical conditions involving different pathologic processes. If GGN is malignant or potentially malignant, its pathology falls under lung adenocarcinoma-associated histological subtypes,^[53,58-61] including multiple progressing stages of adenocarcinoma, such as atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), microinvasive lung adenocarcinoma (MIA), and invasive adenocarcinoma (IAC). In accordance with WHO 2021's new classification, AAH and AIS are called precursor glandular lesions.^[62]

Size

(1) Micronodule, < 5 mm diameter (< 100 mm³ volume); (2) mininodule, 5–10 mm diameter (100–400 mm³ volume); (3) nodule, 11–30 mm diameter (> 400 mm³ volume).^[14,57]

Number

(1) Solitary nodule, with a single lesion; (2) multiple nodules, with ≥ 2 lesions.^[63-65]

Level of risk factor

(1) High-risk nodules:^[2,3,14,15] patients aged ≥ 50 years old with one of the following risk factors: (a) history of smoking (20 packs of cigarettes or more per year, in other words 400 cigarettes per year) and quits for less than 15 years; (b) history of known risk factors exposure (such as asbestos, beryllium, uranium, and radon); (c) history of chronic obstructive pulmonary disease (COPD), diffuse pulmonary fibrosis, or past medical history of tuberculosis; or (d) family history of lung cancer in a first-degree relative. (2) Low-risk nodules: patients without risk factors. In recent years, subsolid GGN has been found in many female patients aged 40–50 years old, with no smoking history or risk factors exposure, and have no complications with COPD or diffuse pulmonary fibrosis.^[3-5,66-68] The reason for this remains unclear. It may be that the estrogen receptor-induced signal pathway has contributed to the occurrence of lung adenocarcinoma in female patients.^[69] In addition, the potential factor that some nonsmoking females in China have a long history of passive smoking (from cigarettes or cooking) has not been ruled out.^[70]

COMPUTED TOMOGRAPHY IMAGING EVALUATION

Computed tomography scan parameters and measurement

Scan parameters

CT is the first choice for the diagnosis of GGN; CT scan detector ≥ 16 rows; and the collimation thickness is measured as follows: (1) 1-mm-thin-slice reconstruction. If thickness is < 1 mm, reconstruct without interval. If thickness is > 1 mm, reconstruct with an interval of 50%–80% of the collimation thickness. The reconstructed image matrix is 512×512 . (2) The total radiation exposure dose is 1.0 mSv, 120 kV, and mAs ≤ 40 . (3) Lung window: The window level is -700 to -600 Hounsfield units (HU), and the window width is 1500–1600 HU; mediastinal window: Window level is 30–70 HU, and the window width is 350–400 HU. (4) Scan range: At the end of deep inspiration, ask patient to hold their breath, scan from the apex of the lung to the costophrenic angle, with scan and sampling time not exceeding 10 s.^[2,14,71-73]

Measurement

The size, volume, density, shape, margin, internal structure, and growth of GGNs are critical technical parameters for making GGN treatment decisions, but there are uniform standards for the measurement and observation of these parameters.^[74,75] In line with the principles of practicability, operability, and repeatability, and supported by evidence-based medicine, the following consensus have been reached by the 2021 Expert Consensus: (1) Unit of measurement: millimeter or cubic millimeter; (2) Nodule size: maximum diameter of the transverse section in lung window image; (3) Nodule volume: calculated according to the segmentation result of the nodule and the number of voxels included in the nodule region; (4) measurement of consolidation in nodule: lung window and mediastinal window are combined in measurement, but priority is given to the lung window (to measure the maximum diameter

of the transverse section);^[76-78] (5) calculation of consolidation tumor ratio (CTR): the ratio of the maximum diameter of consolidation in the nodule transverse section to the maximum nodule diameter in the lung window image; (6) density, shape, margin, and internal structure: Combined use of lung window and mediastinal window images. Meanwhile, observation can be done on a different axis, and three-dimensional reconstruction can be performed if necessary; (7) volume doubling time (VDT): VDT is an important parameter for differentiating benign and malignant GGNs.^[79-81] Generally, VDT is ≥ 800 days for benign lesions, 400–600 days for precursor glandular lesions and microinvasive lesions, <400 days for invasive lesions, and conventionally, 100–300 days for lung cancer; (8) artificial intelligence (AI):^[82,83] considering the large differences within existing AI software, the same CT scanner model and the same software package should be adopted. Moreover, consecutive and long-term follow-up and reexamination should be carried out in the same medical institution so as to obtain valuable references from the AI results.

Computed tomography imaging analysis and nodule features

No unified standard for CT imaging has been formulated to distinguish between benign and malignant GGNs, so clinical prediction is often based on imaging characteristics of GGN, such as size, shape, margin, tumor-lung interface, internal structure, location, and dynamic changes in follow-up; of which the most important imaging characteristics are nodule size, internal structure characteristics (particularly the solid component), and the dynamic changes during follow-up.^[78,84,85]

Ground-glass nodule size

(1) Micronodule: <5 mm diameter (<100 mm³ volume), 95%–99% benign lesions; (2) Mininodule: 5–10 mm diameter (100–400 mm³ volume), 85%–90% benign or precursor glandular lesions; (3) nodule: 11–30 mm diameter (>400 mm³ volume). The GGNs that do not disappear or shrink and persist after 3–4 months of observation and follow-up, 60%–80% are precursor glandular or invasive lesions.^[63,81,86-90]

Shape

Most malignant GGNs are round or quasi-circular in shape, but irregular shapes are observed in a high proportion of malignant GGNs near the interlobular fissures or great vessels.

Margin

Lobulated sign, spicule sign, pleural indentation sign, and vessel convergence sign of GGN often indicate the possibility of malignancy. Blurred margins and even exudations are observed in inflammatory GGN, whereas neat and smooth margins are observed in benign noninflammatory GGN. The sharp corner or fibrous cord on the margin of a GGN or a fibrous cord and pleural thickening around the margin often suggest that the nodule is benign.^[91-93]

Internal structure

(1) CT attenuation value: Reports differ greatly on CT

attenuation value for predicting pGGN as a precursor glandular or invasive lesion.^[53,94-99] CT values more than -450 HU usually suggests an invasive lesion, but their clinical application is unclear because of the small area of the GGN, which results in low repeatability of the measured attenuation value. (2) CTR: consolidation in mGGN is a major factor for prognosis. Pathologically, mGGN of ≥ 15 mm and CTR of $\geq 25\%$ usually indicate invasive lesions. The increase in CTR, or overall increase in GGN, or synchronous increase in both, indicates a high risk of invasive lung cancer.^[78,100-102] (3) Other signs of nodule: air bronchogram, vacuole sign, tortuosity, or dilation of blood vessels in the nodules also indicate that GGN tends to be IAC.^[103-105]

Follow-up

Follow-up is necessary after finding GGN. About 35%–45% of GGNs will disappear after 3–4 months of follow-up, so they are known as transient GGN, which is likely associated with inflammations.^[55,106-108] GGN that does not disappear after 3–4 months of follow-up is known as persistent GGN, which may be potentially malignant, and may turn malignant after a long period of development. Therefore, after GGN is discovered, a certain period of follow-up should be carried out by using the “Watchful-Waiting” method to observe the dynamic changes of GGN so as to determine the GGN.^[109-112] Follow-up strategies differ between pGGN and mGGN with patients, but malignancy can be considered in most cases if the following conditions are noted during follow-up: (1) Lesions grow (increased maximum diameter or volume) and VDT meets the growth law of tumors; (2) Lesion growth and consolidation are detected; (3) Lesions remain stable but more consolidations are detected; (4) Other malignant signs are observed, such as lobulation, spicule sign, pleural indentation, air bronchogram, vacuole sign, vessel convergence sign, and tortuosity or dilation of blood vessels in nodules. The growth of GGN and consolidation changes are key observation indicators during follow-up. GGN follow-up and intervention can be carried out by referring to Figure 1, based on the existing guidelines and research findings on follow-up.

POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY

Functional imaging is an important way to help distinguish between benign and malignant GGN; however, positron emission tomography/computed tomography (PET/CT) plays a limited role in the diagnosis of GGN lesions.^[99,124-127] (1) pGGN: PET/CT is not recommended for pGGN of any size; (2) PET-CT is not recommended for mGGN with a maximum diameter ≤ 10 mm and with a consolidation <5 mm; (3) PET/CT is recommended to identify the nature of mGGN with a maximum diameter between 11–15 mm and with a consolidation ≥ 5 mm; but PET/CT will raise the rate of false negatives; (4) PET/CT is recommended for mGGN with a maximum diameter >15 mm and with a consolidation of ≥ 5 mm when it is difficult to identify the nature of lesions, with a high positive rate; (5) PET/CT is recommended for GGN

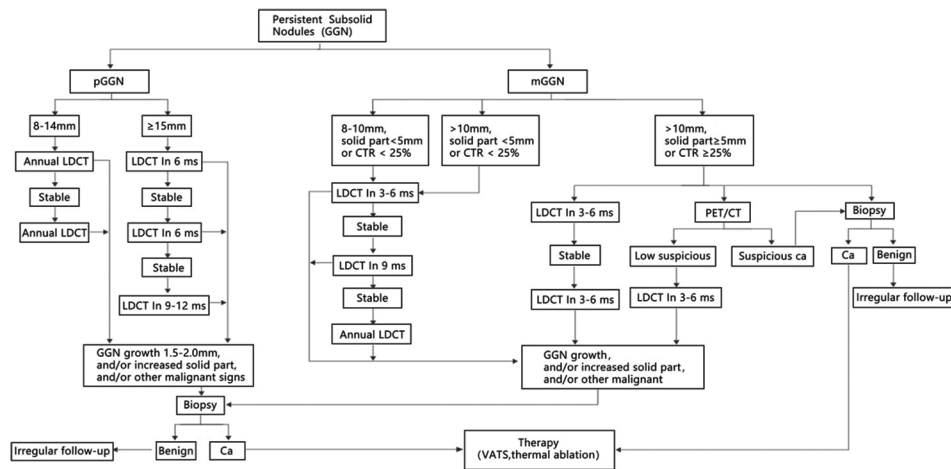


Figure 1: Clinical Follow-up and treatment of GGN. pGGN: (1) If the maximum diameter is <8 mm, routine follow-ups are not required, but subjects should be informed of its potential benefits and risks. (2) If the maximum diameter is between 8–14 mm and remains unchanged, annual routine follow-ups are required. (3) If the maximum diameter is ≥ 15 mm, reexaminations are required every 6 months for two consecutive times. If it remains unchanged, follow-ups can be performed every 9–12 months. mGGN: (1) If the maximum diameter is <8 mm, routine follow-ups are not required, but subjects should be informed of its potential benefits and risks. (2) If the maximum diameter is between 8–10 mm, consolidation is <5 mm, or CTR is <25%, and the lesions remain unchanged in CT, reexamination in 3–6 months and annual routine follow-ups are required afterwards. (3) If the maximum diameter is >10 mm, consolidation is <5 mm, or CTR is <25%, reexaminations are required every 3–6 months. If lesions remain unchanged, annual routine follow-ups are still required. (4) If the maximum diameter is >10 mm, consolidation is ≥ 5 mm, or CTR is $\geq 25\%$, reexaminations are required every 3–6 months. If lesions remain unchanged, reexaminations are required in 3–6 months. Other malignant signs include lobulation, spicule sign, pleural indentation, air bronchogram, vacuole sign, vessel convergence sign, and tortuosity or dilation of blood vessels in nodule. Multiple GGNs: Multiple GGNs are defined as the presence of two or more GGNs with maximum diameters of ≤ 30 mm in the lung, accounting for about 40%–50% of GGNs. By the occurrence interval of two or more ≥ 2 lesions, multiple GGNs can be divided into synchronous (interval <6 months) and metachronous (interval >2 years) types.^[60,64,113] Multiple GGNs can further be divided into many categories by the site of occurrence, such as the same lobe of the same lung, different lobes of the same lung, and different lobes of both lungs. Pathologically, multiple GGNs include multiple progressing stages of adenocarcinoma, such as AAH, AIS, MIA, and IAC, and even the coexistence of benign and malignant lesions.^[58,59,63,114] Multiple GGNs are diverse and complex, thus no consensus has been reached on the treatment method.^[65,115–117] Studies suggest that each lesion of multiple GGNs is an “individual” lesion.^[63–65,118–120] The treatment of multiple GGNs should follow the principle of “main,” then “minor.”^[31] The main lesion is often determined as the largest lesion, but sometimes, it is the lesion with high risk of malignancy. The prognosis of multiple GGNs depends on the size and consolidation of the main lesion and is generally not affected by the growth of minor or residual lesions or by the occurrence of new lesions^[65,119,121–123] Ca (cancer), LDCT (low dose computed tomography) GGN (ground-glass nodule), pGGN (pure GGN), mGGN (mixed GGN)

patients with other solid nodules in lungs or have a medical history of malignant extrapulmonary tumor; (6) PET/CT can also provide an important basis for the selection of biopsy sites.

BIOPSY

Biopsy is an important approach to identify the property and determine the treatment method of GGN. Image-guided percutaneous thoracic needle biopsy (PTNB) and transbronchial lung biopsy are the most common nonsurgical approaches.

Percutaneous thoracic needle biopsy

PTNB should be guided by CT images. Chest CT images can clearly show the size, shape, and location of the lesion, as well as relationships of the lesion with ribs, mediastinum, interlobular fissures, and blood vessels, contributing to the design of puncture routes, early detection, and timely treatment of complications.^[128]

Indications

Please refer to Figure 1. pGGN: (1) Biopsy is not recommended

for lesions with maximum diameters <8 mm; (2) A maximum diameter of 8–14 mm, and lesion growth or consolidation is found during follow-up; (3) A maximum diameter of ≥ 15 mm, and lesion growth or consolidation is found during follow-up. mGGN: (1) Biopsy is not recommended for lesions with a maximum diameter <8 mm, a consolidation of <5 mm, or CTR <25%; (2) A maximum diameter between 8–10 mm, a consolidation of <5 mm, or CTR <25%, and lesion growth or more consolidations are found during follow-up; (3) A maximum diameter >10 mm, a consolidation of <5 mm, or CTR <25%, and lesion growth or more consolidations are found during follow-up; (4) A maximum diameter >10 mm, a consolidation ≥ 5 mm, or CTR $\geq 25\%$, and lesion growth or more consolidations are found during follow-up; (5) A maximum diameter >10 mm, a consolidation of ≥ 5 mm, or CTR $\geq 25\%$, and malignancy is highly suspicious with PET-CT examinations [Figure 1].^[129–136]

Contraindications

Absolute contraindications: (1) Platelet count $< 50 \times 10^9/L$; (2) Serious bleeding tendencies and coagulation disorders that cannot be improved in the short term (prothrombin

time >18s, prothrombin time activity <40%).^[128,130] Relative contraindications: (1) Severe cachexia and cardiopulmonary insufficiency; (2) Significant infectious lesions on puncture routes; (3) Severe COPD, emphysema, pulmonary fibrosis; (4) Severe pulmonary arterial hypertension; (5) Patients using mechanical ventilation (ventilators); and (6) Patients with psychotic episode.

Diagnostic accuracy of percutaneous thoracic needle biopsy

(1) 70%–75% for pulmonary nodules with diameter ≤8 mm; (2) 80%–85% for pulmonary nodules with a diameter between 9–10 mm; (3) 85%–95% for pulmonary nodules with a diameter between 11–20 mm; (4) 55%–65% accordance rate with adenocarcinoma subtypes after surgery.^[136–141]

Auxiliary technologies for percutaneous thoracic needle biopsy

(1) Biopsy after ablation:^[142–148] pulmonary parenchyma bleeding during PTNB is the main factor affecting diagnostic accuracy but can be decreased by biopsy after ablation because microwave or radiofrequency ablation can coagulate blood vessels with approximately 2 mm diameter in the lungs. Please refer to relevant literatures for specific technical operations;^[142–146] (2) Three-dimensional template technique:^[149,150] because breathing requires a large range of motion of the lungs, it is difficult to perform PTNB, particularly the biopsy of GGN on lower lobes. Application of a three-dimensional-printed coplanar template combined with fixed needle technique can make the GGN relatively fixed, so as to reduce the impact of breathing on biopsy and increase the accuracy of biopsy.

Bronchoscopy

Traditional techniques include bronchoscopy biopsy and brush biopsy under direct vision. Perspective transbronchial lung biopsy and bronchoalveolar lavage can obtain cytological and histological information but play a limited role in the diagnosis of GGN. Other new technologies include endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB), virtual bronchoscopic navigation, and electromagnetic navigation bronchoscopy (ENB), which guides an ultra-thin bronchoscope to enter Grade 5 to Grade 8 bronchi for the biopsy of GGN.^[151–153]

THERMAL ABLATION TECHNOLOGY AND IMAGE GUIDANCE

As a precise, minimally invasive treatment technology, tumor thermal ablation utilizes biological effects of heat to directly cause irreversible injury or necrosis of tumor cells in one or more tumor lesions that are located in a certain organ. Radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation are the main technologies for GGN.^[32,33,154]

Radiofrequency ablation

Currently, RFA is the most widely used ablation technique for the treatment of solid tumors. Through inserting radiofrequency electrodes into the tumor tissue and the application of 375–

500 kHz frequency with alternating current, mutual friction, and collisions of ions within the tumor tissue produce thermal biological effects to raise the local temperature up to 60°C–120°C. When the tissue is heated to >60°C, cell coagulation necrosis may occur. The RFA volume depends on the thermal conduction of local RFA and the thermal convection between circulating blood and extracellular fluid.

Microwave ablation

It generally uses either of these 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 raise temperatures to 60°C–150°C in a short time, leading to coagulation necrosis of the cells. MWA has a higher convection and a lower “heat sink” effect on the lungs.^[32,33,54]

Cryoablation

(1) Argon--helium cryoablation is a mature cryoablation therapy. The principle is based on Joule–Thomson theory, the target tissue could be cooled to −140°C with high-pressure argon and then rapidly heated up to +20°C to +40°C from −140°C with helium. (2) Liquid nitrogen cryoablation: Liquid nitrogen can cool target tissues to −196°C, while ethanol can heat target tissues to 80°C. The ablation process consists of successive freezing–thawing cycles, which induce cell death by protein denaturation, membrane disruption, and microvascular thrombosis.

All three technologies have been applied in GGN.^[43–47,155,156] However, the lungs and GGN have relatively special tissue structures, MWA has certain advantages in treating GGN due to higher convection and lower thermal precipitation in the lungs, and it has been the most widely applied technique in clinical practice.^[41,45,46,48,50]

Image guidance

CT is the most common image guidance technology applied in ablation therapy for GGN. This procedure is recommended under lung window settings or under appropriate window width and window level, with a CT slice thickness of 2–2.5 mm.

INDICATIONS AND CONTRAINDICATIONS

Prognosis of lung cancer is mainly affected by hilar and mediastinal lymphatic metastases and distant metastases. GGN like lung adenocarcinoma is a special subtype of lung adenocarcinoma, mainly with local and slow growth and almost no lymphatic or distant metastasis in AAH, AIS, and MIA. Lymphatic or distant metastasis is also rarely seen, even in IAC, with a maximum diameter ≤30 mm and CTR ≤50%.^[20–27] Thermal ablation is one of the most effective methods for local treatment, can treat GGN through thermobiological effects. It is possible to achieve curative ablation, leading to complete necrosis of lung tumors.^[32,157]

Indications

Peripheral GGN: (1) Patients who cannot tolerate surgical resections due to poor cardiopulmonary function or advanced age (> 70 years); (2) Patients who refuse surgical resections; (3) Patients who cannot tolerate or who refuse a second surgery for new or remaining lesions after their first surgical resection; (4) Multiple GGNs (ablation of the main lesion first, followed by consideration of ablation of minor lesions according to their development); (5) Severe pleural adhesion or atresia of the pleural cavity caused by various factors; (6) Single lung; and (7) Patients with severe anxiety, which cannot be alleviated by psychotherapy or medication. The above patients need to have biopsy-proven as AAH, AIS, MIA, or IAC (for patients with GGN-like IAC, distant metastases should be excluded).

In clinical practice, there are some patients who refuse both biopsy and surgery: (1) Patients with high-risk factors, malignant signs in imaging findings, such as lesions with a maximum diameter of ≥ 15 mm, spicule sign, lobulation, vacuole sign, pleural indentation, vascular changes, GGN growth in dynamic observation, and presence or increase of consolidation; (2) patients with no high-risk factors but with malignant signs in imaging findings, such as lesions with a maximum diameter of > 15 mm, spicule sign, lobulation, vacuole sign, pleural indentation, vascular changes, GGN growth in dynamic observation, and presence or increase of consolidation; (3) patients with extreme tension and anxiety after GGN detection who cannot be alleviated by psychotherapy or medication;^[10,31,158,159] (4) patients with a suspicion of lung cancer that a biopsy is too risky or difficult.^[160,161] For the above four categories of patients, it is recommended that a discussion to hold with a multidisciplinary team (MDT) to formulate a preliminary diagnosis and treatment opinion, and that final diagnosis and treatment opinions be made by shared decision-making (SDM)^[162-165] on the basis of a MDT. If the opinion of SDM is “direct ablation without biopsy, or synchronous ablation and biopsy,” then the medical staff, the patient, and their family members (or guardians, etc.) can follow the instructions based on the opinion of SDM. SDM^[166,167] is an important component of evidence-based medicine that has attracted increasing attention as a new medical model.

Contraindications

Absolute contraindications

(1) Platelet count $< 50 \times 10^9/L$; (2) Serious bleeding tendencies and coagulation disorders that cannot be improved in a short time (prothrombin time > 18 s, prothrombin time activity $< 40\%$); (3) Severe pulmonary fibrosis and pulmonary arterial hypertension; and (4) Withdrawal of anticoagulant therapy and/or antiplatelet drug within 5–7 days before ablation.

Relative contraindications

(1) Poor control of pleural effusion; (2) severe hepatic, renal, cardiac, pulmonary, or cerebral insufficiency; (3) severe anemia, dehydration, and severe disorders of nutrient metabolism, which cannot be cured or improved in a short time; (4) severe systemic infection

and fever ($> 38.5^\circ\text{C}$); (5) Eastern Cooperative Oncology Group score > 3 ; (6) psychotic episode; (7) combined with other tumors that have widespread metastases and expected patient survival period < 6 months; (8) for patients with implanted cardiac pacemakers, cardiac function should be fully evaluated before RFA. Pacemakers can be stopped during RFA and restored postoperatively.

PROCEDURE PREPARATION

Evaluation and imaging examination of patients

Patients' medical history, physical examination findings, and recent medical images should be carefully reviewed to evaluate indications for thermal ablation. A MDT (from the departments of thoracic surgery, oncology, respiratory diseases, radiotherapy, interventional medicine, imaging, and pathology) is recommended for discussion and decision-making on the selection of indications. SDM should be carried out if necessary. Thin-slice chest CT (thickness ≤ 1 mm, within 1 month; enhancement is not required) is an essential imaging examination and should be carried out before the procedure. CT images will show the size, shape, internal structure, and location of the GGN and its relationships with important adjacent organs, blood vessels, trachea, or bronchi. If stage IA GGN is highly suspected, PET/CT or other general medical examinations can be conducted before the procedure so as to exclude or determine distant metastases.

Laboratory examinations

Laboratory examinations should include a routine blood test, urine test, and stool test, as well as an examination of coagulation function, liver function, kidney function, blood sugar, tumor marker, blood type, electrocardiogram, lung function, and Doppler echocardiography (optional for elderly patients).

Pathological examinations

PTNB or fiber optic bronchoscopy biopsies can be performed to make final diagnosis before the procedure.

Drugs and monitoring equipment

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

Patient preparation

The patient or their family or guardians must sign the informed consent form. The patient should fast for 4 h before local anesthesia or abstain from solid food for 12 h and liquids for 4 h before general anesthesia. The patient should also undergo surgical skin preparation and be administered an oral antitussive drug before the procedure. The patient should receive pre-procedure education (such as breathing training).

ANESTHESIA AND DISINFECTION

According to patients' condition, general anesthesia or local

anesthesia can be used for the procedure. The puncture point is locally infiltrated with 1%–2% lidocaine. General anesthesia is recommended for the following patients: children, patients who cannot cooperate during the procedure, patients with expected long procedure time, and patients with tumor close to the wall of the pleura, which may cause intensive pain. During the procedure, strict aseptic technique should be followed.

PROCEDURE

After an appropriate ablation technique is selected, ablation is performed. Guided by CT scan (the most common and accurate imaging guidance method), the thermal ablation applicator directly and accurately punctures through the skin and advances into the target tissue. The procedure of ablation is shown in Figure 2.

Planning

Preprocedure planning is critical toward ensuring procedure success, which mainly includes the following steps: (1) Determining the “gross tumor region (GTR),” which can be defined by imaging, including the location, size, shape, and its relationship with adjacent organs; (2) selecting the appropriate body position and the punctured sites on the body surface; (3) determining the puncture path: the path from the puncture site to the deepest border of the lesion (“target-skin distance”); and (4) preliminarily determining the ablation parameters.

Targeting

After anesthesia, in accordance with the GTR in pre-procedure planning, the ablation applicator is used to puncture at the puncturing site on the body surface, and advance layer by layer along the predetermined puncture path, which is the “target-skin distance” determined in pre-procedure planning. Three-dimensional reconstructed images obtained by CT scans are used to observe the relative location of the ablation applicator inside patient’s body until it reaches the target lesion.

Ablation

According to the size and location of GGN, multiple modes can be applied for ablation of the target tissues: (1) Single site in one session for completing the ablation; (2) multi-site in one session for completing the ablation; (3) multi-applicator and multi-site in one session (each session has three or fewer lesions) or multi-site in multi-session for completing the ablation with an interval of approximately 15 days between lesions in both lungs. The ablation parameters (temperature, power, time, and cycle, etc.) vary between different devices.

Monitoring

During the procedure, the applicator is monitored with CT to observe any “off-target,” whether the applicator should be adjusted, whether the pre-planning range of ablation is achieved, or whether there are any complications (such as hemorrhage or pneumothorax) during the procedure. During the procedure, due to the damage caused by thermal ablation to the lung tissue adjacent to GGN, there could be an opaque, high-density area around the tumor, which is called GGO. When the GGO around the GTR is greater than the GTR border before ablation, the ablation applicator can be pulled out. The target tissue at this time is defined as the post-ablation target zone (PTZ). During the procedure, patient’s vital signs should be monitored closely, as well as any complications such as cough, hemoptysis and pain. Symptomatic treatment should be provided if necessary.

Intraprocedural modification

The operator can utilize image-based information obtained during monitoring to modify the ablation treatment as needed in order to achieve the best outcome. Intraprocedural modification may simply be the repositioning of an applicator and adjusting the parameters of the ablation on the basis of physician experience and imaging findings, or it could be as sophisticated as an automated system that automatically terminates the ablation at a critical point during the procedure. For example, operator can adjust the applicator border for GGN ablation if the border of a tumor surrounded by blood vessels indicates incomplete ablation based on the physicians’ experience.

Assessment of immediate treatment response

A repeat (preferably whole-lung) CT scan should be carried out at the end of the procedure in order to assess immediate response including the following: (1) Preliminarily evaluating the technical success; (2) Observing the ablation margin. When ablation is performed with a curative intent, assessment should demonstrate that the PTZ encompasses the GTR including a circumferential ablative margin (GGO: at least 5 mm); (3) Identifying any complications. The patient can return to the ward if the blood pressure, heart rate, and blood oxygen saturation are normal, and there is no hemoptysis, shortness of breath, chest tightness, dyspnea, and other symptoms.

Postprocedure management

Vital signs should be monitored, and the chest radiograph or CT scan should be taken in 24–48 h, which is aimed at observing the occurrence of complications (such as asymptomatic pneumothorax or pleural effusion).

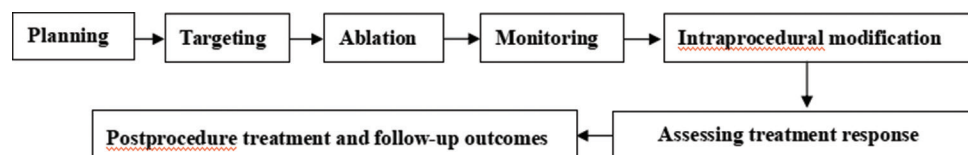


Figure 2: Ablation procedure

FOLLOW-UP AND OUTCOMES

Follow-up

The first chest CT should be performed at 1 month after the procedure, whereas the second one should be performed after 3 months to observe any complications and to determine if complete ablation of local lesions is achieved. Thereafter, chest CT should be performed every 6 months, mainly to observe relapses of local lesions, formation of scars, and if there is any new lesion in the lungs. Annual chest CT should be performed after two years.

Postprocedure imaging characteristics and response assessment

Local response

Computed tomography imaging characteristics

After thermal ablation, due to bleeding, edema, exudation, and infiltration of inflammatory cells around the ablation zone, PTZ will be significantly larger than the original tumor GTR. This imaging characteristic will last for 3 months. Therefore, the traditional Response Evaluation Criteria in Solid Tumors is not suitable for the evaluation of local efficacy after thermal ablation. After the ablation, CT characteristics are as follows: PTZ will be enlarged in the first 1–3 months, remain stable or gradually involute, and decrease in size after 3 months. (1) Early phase (within one week). There are three layers: (a) The inner layer is solid, honeycomb-like, or hypo-attenuating bubbles can be observed within PTZ; (b) the intermediate layer is the GGO. It is generally believed that GGO should be at least 5 mm beyond the GTR border to achieve complete ablation of the GGN; (c) the outer layer. There is a reaction zone outside the GGO layer, with density slightly higher than that of the GGO. This typical imaging characteristic is called the “cockade” or “fried eggs” sign, which is more obvious in 24–48 hours after ablation. (2) Intermediate phase (one week to three months). As the ablation zone increases constantly, the GGO disappears, and a sharp enhanced ring may appear around the perimeter (benign peri-ablation enhancement), which is known as the “egg shell” sign (a thin rim peripheral to PTZ, formed by a relatively symmetric and uniform process, with smooth inner margin, measuring 0.5–3 mm). (3) Late phase (after 3 months), the PTZ remains stable when compared with that at baseline, which is generally found by CT at about 4–6 weeks after ablation). Subsequent follow-up CT results of PTZ may present several different patterns, such as fibrosis, cavities, nodules, atelectasis, disappearance, enlargement (possible hyperplastic fibrosis, progression, or recurrence).^[32,168] The characteristics of imaging changes after cryoablation are different from the imaging after RFA and MWA, but the above process can be used as reference.

Assessment of local response

The response is determined by comparing the CT images to the baseline of the lesion at 4–6 weeks after ablation. (1) Complete ablation (with any one of the following patterns): (a) lesion disappears; (b) cavity completely

forms; (c) fibrosis or scar; (d) solid nodule involution or no change, without contrast-enhanced signs on the CT or any fluorodeoxyglucose (FDG) uptake on the PET/CT; (e) atelectasis, lesion in atelectasis without contrast-enhanced signs on the CT or any FDG uptake on the PET/CT. (2) Incomplete ablation (with any one of the following patterns): (a) cavity partially forms, with some typical GGNs remaining, irregular peripheral or internal enhancement signs on the CT, or intense FDG uptake on the PET/CT; (b) partial fibrosis, with consolidation in lesions, and the CT scan of the consolidation is enhanced or PET/CT shows that tumors have metabolic activities; (c) solid nodules, with no change or increase in size, which present as irregular peripheral or internal enhancement signs on CT, or intense FDG uptake on the PET/CT. (d) atelectasis, lesion in atelectasis with contrast-enhanced signs on the CT or intense FDG uptake on the PET/CT; (3) local progression (with any one of the following patterns): (a) enlarged by 10 mm, with enlarged irregular or typical GGN signs on the CT or enlarged intense FDG uptake on the PET/CT; (b) local, newly developed lesion, with typical GGN signs on the CT or newly developed intense FDG uptake on the PET/CT.

Clinical outcomes

Regular follow-up should be performed to assess local response. The following are longitudinal follow-up guidelines: (1) Technical success and early safety data: minimum 6-month follow-up; (2) preliminary clinical outcomes: Minimum 1-year follow-up; (3) intermediate data: Minimum 3–5-year follow-up; (4) long-term data: at least 6–10-year follow-up.

COMPLICATIONS AND MANAGEMENT

Ablation of pulmonary nodules is a relatively safe local therapy. The complications reported are based on the classifications of the American Society of Interventional Radiology (SIR) criteria [Table 1].^[169] The definition of a major complication is an event that leads to substantial morbidity and disability, which increases the level of care required, or leads to hospital admission or one that substantially lengthens hospital stay (SIR classifications C-E). The complication includes any conditions that require blood transfusion or interventional drainage procedure. Any patient death within 30 days of image-guided GGN ablation should be addressed (SIR classification F). All other complications are considered minor. According to the time of occurrence, the complications are classified into immediate complication (<24 h after procedure), perioperative complication (24 h – 30 days after procedure), and delayed complications (>30 days after procedure).

Side effects

Pain

After a procedure under local anesthesia, patients may experience varying degrees of pain (particularly for the ablation of lesions near pleura where analgesic therapy is generally necessary). If the pain is severe, the amount of analgesic drug (such as an opioid) can be increased, as well

Table 1: The American Society of Interventional Radiology classification system for complications by outcome

Classification	Definition
Side effects	Pain Postablation syndrome Asymptomatic pleural effusion Nonconsequential damages to adjacent structures
Minor complications	No therapy, no consequence Nominal therapy, no consequence; includes overnight admission for observation only
Major complications	Require therapy, minor hospitalization (≤ 48 h) Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 h) Permanent adverse sequelae Death

as giving appropriate amount of sedatives. Postprocedural pain is usually mild, which can last for several days, but may last for 1–2 weeks in some patients. Moderate or severe pain is rare. Nonsteroidal drugs can also be administered to relieve pain.

Postablation syndrome

About one-third of patients may suffer from postablation syndrome, which is caused by the absorption of necrotic substances and the release of inflammatory cytokines. Low-grade fever, fatigue, general malaise, nausea, and vomiting are the most common symptoms, which generally last for 3–5 days. In special cases, nonsteroidal drugs and small doses of glucocorticoids can be used in the short term.

Cough

Cough is a very common symptom during ablation. Severe cough may cause or aggravate pneumothorax or subcutaneous emphysema, sometimes rendering the ablation antenna off-target. Some patients might not be able to tolerate the procedure due to severe cough. The reasons for cough may be the stimulation of alveoli, bronchial intima, or pleura caused by increased local temperature during the procedure. Postprocedure cough is caused by the inflammation of tissue necrosis and heat injury around the lung tissues. Oral codeine is helpful to prevent coughing if it is given one hour before the procedure. The procedure is not affected by mild cough. For the postprocedure cough, antitussive, expectorant, and necessary antibiotics should be given as appropriate.

Complications

Pneumothorax

Pneumothorax is the most common complication after ablation, with an incidence of 50%. Pneumothorax is more common in the following conditions: emphysema, male, age >60 years old, GGN in the lower lobe, >3 punctures for a single GGN in the lung tissues, multiple GGNs and multiple puncture and ablations, and a long part of the ablation path goes through the lung tissues or through a large lobe

fissure. Most cases of pneumothorax can be easily treated or are self-limiting. In 15% of pneumothorax cases, chest tube placement for drainage is required. If there is still a gas leakage after thoracic drainage, continuous negative suction, pleurodesis, endoscopic injection sclerotherapy, tracheal valve implantation, and other measures can be employed. In addition, the occurrence of delayed pneumothorax should be monitored.

Pleural effusion

A small amount of pleural effusion is often observed after ablation, with an incidence rate of 30%. The occurrence of pleural effusion is associated with increased pleural temperature during the procedure, which may indicate that pleural effusion is related to pleuritis induced by thermal injury. Approximately 5% of pleural effusions require puncture/catheter drainage. Risk factors for pleural effusion include large lesions, single ablation for multiple lesions, lesions close to the pleura (<10 mm), and long procedure duration.

Hemorrhage

The incidence of hemorrhage during ablation is 3%–8%. Hemorrhage may present as hemoptysis, hemothorax, hemorrhagic shock, and acute respiratory failure, but it mainly presents as hemoptysis and hemothorax. (1) Hemoptysis: the incidence of massive hemoptysis is very low during ablation. Risk factors for intraparenchymal hemorrhage include: (a) lesion has a diameter <1.5 cm wherein the applicator need to be adjusted in order for to enter the targeted small lesions; (b) lesions located in the middle and lower lung, where the lesions are more easily influenced by respiratory movement and more difficult to be punctured. In addition, the blood vessels are more easily damaged by the movement of the applicator tip; (c) the path of the applicator penetrating the lung tissues is more than >2.5 cm, where these lesions are closer to the hilum and surrounded by large blood vessels; (d) the pulmonary vessels are penetrated through the ablation path; and (e) application of multipolar ablation applicator. If there is moderate hemoptysis, the ablation should be performed immediately with intravenous administration of hemostatic drugs. Ablation itself can coagulate the blood; thus, the hemorrhage will gradually stop during the ablation. During the puncture, the larger blood vessels or atelectasis in the lung tissues should be avoided. Most cases of postprocedure hemoptysis are self-limiting and only last for 3–5 days. For patients who are not suitable for conservative treatment, interventional embolization or thoracotomy can be conducted. (2) Hemothorax: the internal thoracic artery, the intercostal artery, or other arteries are damaged during puncture. During puncture, the aforementioned arteries should be avoided. If there is hemothorax, the patient should be closely monitored and actively treated with conservative treatment. For the patients who are not candidates for conservative treatment, interventional embolization or thoracotomy can be conducted.

Infection

The incidence of pulmonary infection caused by ablation is 1%–6%. Prophylactic antibiotics can be used 30–60 min before the procedure and once again in 24 h and can be extended to 48–72 h for patients >70 years old or those with COPD, poorly controlled diabetes, ablation >3 unilateral GGNs, or low immunity. If patient's body temperature is still >38.5°C at 5 days after the procedure, lung infections should be suspected. Antibiotics should be adjusted according to sputum, blood, or pus culture results. Pulmonary or chest abscesses can be drained using chest tube. It is worth mentioning that because interstitial pneumonia often occurs after radiotherapy, ablation increases the risk of secondary infection.

Cavitation

The formation of cavitation is common after lung ablation, which may be regarded as a natural outcome after ablation and the cause of serious complications, such as infection and hemorrhage. The incidence of the cavitation is about 14%–17%. In most patients, cavities occur between 15 days and 1 month after the procedure and are absorbed within 2–4 months. Risk factors for cavitation are proximity of the GGN to the chest wall and pulmonary emphysema. Cavitation infection and abscess formation should be considered when there is fever and weakness. In addition, the *Aspergillus* infection should be noted. Cavitation-induced recurrent hemorrhage can be treated with interventional embolization if patients are not suitable for conservative treatment.

Other rare complications

There were cases reporting complications such as bronchial pleural fistula, acute respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, nontarget thermal injury or frostbite, rib fractures, thrombocytopenia, nerve injury (brachial plexus, intercostal, phrenic, laryngeal), pulmonary embolism, systemic air embolism, pericardial tamponade, and so on. Each case should be treated individually.

CONCLUSIONS

On the one hand LDCT lung cancer screening has played a positive role in the detection of early stage lung cancer and the reduction of lung cancer mortality, but on the other hand it also causes a series of social, psychological and economic issues for patients. Therefore, efforts to balance the cost and benefit of the LDCT lung cancer screening and MDT discussion opinions from multiple dimensions to maximize the benefits and minimize the risks for patients. In addition, LDCT is only one imaging technology for lung cancer screening, and the combined screening mode of biomarkers and imaging may be more helpful for early diagnosis of lung cancer. Therefore, the search for biomarkers with high sensitivity and specificity is one direction for cancer screening in the future.

Local surgical resection treatment is still the main therapy for GGN. As a minimally invasive local therapy, thermal ablation

has shown certain advantages in treating GGN (particularly multiple GGNs). Afterall, there are still many challenges to overcome for applying thermal ablation for GGN. (1) From the perspective of clinical practice, the number of cases of thermal ablation to treat GGN is relatively smaller than that of VATS. (2) There is a lack of long-term (>10 years) follow-up on clinical outcomes. (3) There are few clinical trials on the use of thermal ablation for GGN. It is necessary to perform a prospective, randomized controlled, multicenter clinical trial of thermal ablation for GGN. (4) How to reach precise location, improve the positive rate of biopsy, and improving rates of complete ablation will be some focus areas for future studies. (5) Electromagnetic navigation bronchoscopy-guided thermal ablation for GGN is developing, and has shown certain advantages, but it may be difficult to popularize. (6) Basic research, such as complex thermal field distribution, is lagging. (7) Different types of the thermal ablation applicator should be developed for better control of size and shape of the ablation zone.

In the near future, we believe that thermal ablation will challenge surgery and become a novel therapy for GGN.

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Conflicts of interest

There are no conflicts of interest.

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