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Advances in the Treatment of Pulmonary Nodules

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Abstract

Background: Early detection and accurate diagnosis of pulmonary nodules are crucial for improving patient outcomes. While surgical resection of malignant nodules is still the preferred treatment option, it may not be feasible for all patients. We aimed to discuss the advances in the treatment of pulmonary nodules, especially stereotactic body radiotherapy (SBRT) and interventional pulmonology technologies, and provide a range of recommendations based on our expertise and experience. ***Summary:*** Interventional pulmonology is an increasingly important approach for the management of pulmonary nodules. While more studies are needed to fully evaluate its long-term outcomes and benefits, the available evidence suggests that this technique can provide a minimally invasive and effective alternative for treating small malignancies in selected patients. We conducted a systematic literature review in PubMed, designed a framework to include the advances in surgery, SBRT, and interventional pulmonology for the treatment of pulmonary nodules, and provided a range of recommendations based on our expertise and experience. ***Key Messages:*** As such, alternative therapeutic options such as SBRT and ablation are becoming increasingly important and viable. With recent advancements in bronchoscopy techniques, ablation via bronchoscopy has emerged as a promising option for treating pulmonary nodules. This study reviewed the advances of interventional pulmonology in the treatment of peripheral lung cancer patients that are not surgical candidates. We also discussed the challenges and limitations associated with ablation, such as the risk of complications and the potential for incomplete nodule eradication. These advancements hold great promise for improving the efficacy and safety of interventional pulmonology in treating pulmonary nodules.

Plain Language Summary

This study provides an overview of the advancements in interventional pulmonology for the treatment of peripheral lung cancer patients. The challenges and limitations associated with ablation are also discussed, including the precise localization of lung nodules, evaluation of the ablation range

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under bronchoscopic guidance (due to the uncertainty in the dose-response relationship of energy conduction in lung tissue), reaching lung nodules without bronchial signs, replacing ablation catheters to increase the ablation range, as well as the risks of complications and potential residual mass formation. These advanced techniques have significant potential to enhance the efficacy and safety of interventional pulmonology in treating lung nodules. In summary, interventional pulmonology is becoming an increasingly important approach for managing lung nodules. While further research is needed to comprehensively evaluate its long-term effects and advantages, existing evidence suggests that this technology can provide a minimally invasive and effective alternative treatment method for selected patients with small malignant lung tumors.

Introduction

Lung cancer is one of the most common malignant tumors worldwide, with a high incidence and mortality rate [1]. Most patients are diagnosed at an advanced stage, which poses great challenges to treatment [2]. Early identification and treatment are crucial to improve the prognosis of lung cancer patients. The incidence of pulmonary nodules has been increasing in recent years due in part to the increased use and improved sensitivity of imaging modalities such as chest computed tomography (CT) scans [3]. Biopsy or surgical resection may be necessary to obtain a definitive diagnosis in cases where malignancy is suspected [4]. Although traditional surgical resection has achieved significant success in early-stage lung cancer treatment, some patients may not be able to tolerate surgery due to age, physical condition, or comorbidities, and respiratory dysfunction and complications may occur after surgery [5, 6]. With the development of respiratory intervention technology in recent years, minimally invasive therapies such as bronchoscopic ablation and stereotactic radiotherapy have received increasing attention in the treatment of early-stage lung cancer [7]. Minimally invasive therapies have advantages such as less trauma, faster recovery, and simpler operations [8]. These techniques can accurately locate and ablate tumors, maximize the preservation of lung function, and reduce the incidence of complications [9]. This article aimed to introduce the latest early-stage lung cancer treatment methods, focusing on minimally invasive therapies, and share our experiences in addressing potential issues that may arise during the procedures. Together with advancements in therapies, some of which can be administered via the bronchoscope, we are witnessing a new era in which bronchoscopy has the potential not only to diagnose early-stage lung cancer but also to provide treatment.

Treatment Strategies of Pulmonary Nodules

Surgical Resection

The management strategies for pulmonary nodules range from active surveillance with repeat imaging to more aggressive interventions such as biopsy or surgical resection [10]. For small, incidentally detected nodules that are deemed low-risk for malignancy based on imaging features and patient history, observation with repeat imaging at intervals of 6–12 months is a recommended management strategy [11]. If the nodule demonstrates stability over time, the interval between imaging studies may be lengthened, or the observation period may be discontinued [11]. In cases where there is concern for malignancy or if the nodule demonstrates concerning features such as growth, biopsy or surgical resection may be warranted. Biopsy can be performed through a variety of approaches, including transthoracic needle aspiration, bronchoscopy, or mediastinoscopy, depending on the location and size of the nodule [12].

Current management strategies for stage IA peripheral lung adenocarcinoma include surgical resection, either a lobectomy or sub-lobar resection, depending on factors such as tumor size and patient characteristics. Lobectomy remains the standard procedure for resectable non-small cell lung cancer (NSCLC); however, studies have shown that sub-lobar resection may be a viable option for select patients and can offer similar oncologic outcomes with less impact on lung function. In the multicenter, phase 3 trial (NCT00499330), Altorki et al. [13] evaluated the efficacy and safety between sub-lobar resection and lobar resection in NSCLC patients with tumor sizes ≤2 cm and node-negative disease (T1aN0). The patients undergoing sub-lobar resection had noninferior disease-free survival (DFS) compared with those undergoing lobar resection (HR, 1.01; 90% CI, 0.83–1.24). The two cohorts had similar overall survival (OS) (HR, 0.95; 95% CI, 0.72–1.26). The 5-year DFS and OS in the sub-lobar resection cohort were 63.6% and 80.3%, respectively, while 64.1% and 78.9% were in the lobar resection cohort. There were no statistical differences in the incidence of locoregional or distant recurrence between the two cohorts. However, the evaluation of pulmonary functions favored the sub-lobar-resection cohort. Advances in surgical techniques, such as minimally invasive

procedures, have made the surgical management of ground-glass nodules safer and more effective. Segmentectomy is also being evaluated as a treatment option for select patients with ground-glass-dominant lung cancer [14]. Lymph node metastasis status should be evaluated carefully before making treatment decisions, as this can affect the choice of surgical approach and adjuvant therapy [15]. In the single-arm, phase 3 trial (JCOG1211), Aokage et al. [16] evaluated segmentectomy in NSCLC patients with tumor sizes ≤3 cm, including ground-glass opacity (GGO) and predominant GGO. The results showed that the 5-year relapse-free survival of patients that underwent segmentectomy reached 98.0% higher than the pre-set threshold 5-year recurrence-free survival of 87% at 5.4-year median follow-up. Grade 3 or 4 early postoperative complications were observed in 2% of patients. However, no treatment-related deaths were observed. Segmentectomy is the potential standard treatment strategy for patients with predominantly GGO NSCLC with tumor sizes ≤3 cm including GGO even if it exceeds 2 cm [16].

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is considered a non-invasive treatment option for patients who are not suitable for surgery or refuse surgery. This treatment delivers high doses of radiation to the tumor with minimal damage to surrounding tissues [17]. SBRT has been shown to be effective in controlling local disease and achieving high rates of survival in select patients. Advances in local therapies, such as radiofrequency ablation (RFA) and SBRT, offer promising treatment options for patients with metastatic nodules and localized disease [18]. These modalities can be used alone or in combination with systemic treatments to achieve better outcomes and improve quality of life for patients with advanced lung cancer [19, 20]. However, the choice of treatment approach should be tailored to individual patient factors and should involve a multidisciplinary team of healthcare providers. SBRT has been increasingly used as a non-invasive treatment option for early-stage lung cancer [21]. The technique involves delivering high-dose radiation to the tumor using highly precise targeting techniques. Numerous studies have reported high rates of local control and OS with SBRT, with some reports suggesting comparable outcomes to surgery. SBRT has also been found to have a low incidence of complications and can be used to treat tumors located in difficult-to-reach areas of the lung [22].

The pooled analysis based on the STARS and ROSEL trials showed the stereotactic ablative radiotherapy (SABR) group had higher survival than the surgery group in operable early-stage NSCLC [23]. The single-arm prospective trial (NCT02357992) compared the long-term results between the enlarged NSCLC patients with tumor sizes ≤3 cm and N0M0 disease after SABR and propensity-matched patients after video-assisted thoracoscopic surgical lobectomy with mediastinal lymph node dissection (VATS L-MLND). The 3- and 5-year OS in the SABR cohort were 91% and 87%, respectively, while 91% and 84% were in the propensity-matched VATS L-MLND cohort. No substantial difference was observed in OS between the two cohorts ($p = 0.65$) [24].

Radiofrequency Ablation

RFA can use heat generated by high-frequency electrical currents to destroy cancer cells. RFA has been shown to be an effective treatment option for early-stage lung cancer, particularly for tumors that are small and located in the periphery of the lung [25]. Studies have reported high rates of local tumor control and survival with RFA, with some reports suggesting higher efficacy than traditional radiation therapy [26].

The prospective multicenter study (NCT00776399) evaluated the efficacy of RFA in patients with resectable colorectal cancer (CRC) lung metastases ≤3 cm. The 3-year OS rate reached 84%, and 9% of patients underwent local tumor progression. Among the 88 RFA sessions, a grade 5 adverse event (AE) was observed in one (1%) session, and grade 2 AEs were observed in 18 (20%) sessions [27].

A retrospective study compared the efficacy and safety between surgery and RFA in the treatment of oligometastatic lung disease with less than 5 pulmonary metastases ≤4 cm and no associated thoracic lymphadenopathy or pleural involvement. The RFA cohort had significantly older patients, with more extra-thoracic localization and bilateral tumor burden compared with the surgery cohort ($p < 0.05$). The 1- and 3-year OS rates for the surgery cohort were 94.8 and 67.2%, respectively, compared with 94 and 72.1% for the RFA cohort ($p = 0.46$). The 1- and 3-year progression-free survival (PFS) for the surgery cohort were 49.4% and 26.1%, respectively, compared with 38.9% and 14.8% for the RFA cohort ($p = 0.12$). There was also no significant difference in pulmonary progression rates or local tumor progression rates between the two cohorts. However, the RFA cohort had a significantly shorter hospitalization stay than the surgery cohort ($p < 0.01$). Thus, as a minimally invasive alternative, RFA had similar survival to surgery in the treatment of multiple or solitary lung metastases ≤4 cm in diameter with no thoracic lymphadenopathy or pleural involvement [28].

Microwave Ablation

Microwave ablation (MWA) is a newer technique that uses high-frequency electromagnetic waves to heat and destroy cancer cells [29, 30]. Compared to RFA, MWA has been shown to have a higher rate of complete ablation of tumors, leading to improved local control and survival rates [31, 32]. Some studies have reported 2-year survival rates of around 80% for patients with early-stage lung cancer treated with MWA.

The MALT study assessed the efficacy and safety of CT-guided MWA in patients with unresectable primary and metastatic lung tumors ≤4 cm. The results showed that technical success was achieved in all the 69 MWAs performed in 54 cases, and 61 (88.4%) MWAs were completed. No treatment-related complications or deaths were observed. The 1- and 2-year OS rates reached 98.0% and 71.3%, respectively. The CT-guided MWA is an effective and safe treatment strategy for malignant lung tumors ≤4 cm in size [33]. A retrospective study evaluated the short-term efficacy and safety of CT-guided percutaneous MWA to treat multiple synchronous lung GGOs. The technical success was achieved in all cases, and no surgery-related deaths were observed. The median follow-up was 18.1 months, and all cases are alive without tumor recurrence or local progression. CT-guided MWA is an effective and safe alternative approach in the treatment of multiple synchronous lung GGOs [34].

The meta-analysis evaluating the efficacy between RFA and MWA in lung cancer treatment showed that patients after RFA had higher estimated OS rates than those after MWA. However, there was no statistical difference in complete ablation rate, median OS, median PFS, median local tumor PFS, and AEs between the two cohorts. The analyses in subgroup stratified by tumor type demonstrated that patients with pulmonary metastases after RFA had higher median OS than those after MWA [35].

The retrospective study compared the efficacy and safety between percutaneous MWA and RFA in primary and secondary lung tumors. The mean tumor diameter in the RFA cohort was smaller than that in the MWA cohort ($p < 0.001$). At 1 month, no statistical difference was observed in the ablation volumes, 24.1 ± 21.7 (SD) cm^3 for the RFA cohort and 30.2 ± 35.9 (SD) cm^3 for the MWA cohort ($p = 0.195$). At a mean follow-up period of 488 ± 407 (SD) days, 6 out of 79 tumors (7.6%) developed local recurrence in the RFA cohort and 3 out of 81 (3.7%) in the MWA cohort ($p = 0.32$). More frequent pneumothoraces were observed in the RFA cohort (32/79, 40.5%) than in the MWA cohort (20/81, 24.7%) ($p = 0.049$). No statistical differences were observed in the mean hospital stay between the two cohorts ($p = 0.76$). Compared with RFA, MWA is an effective and safe thermal ablation technique for lung tumors, especially in cases where RFA has limited efficacy [32].

Cryoablation

Cryoablation involves freezing the tumor to destroy cancer cells. Cryoablation has been found to be a safe and effective treatment option for early-stage lung cancer, with studies reporting high rates of complete tumor destruction and minimal complications [36, 37]. Cryoablation may be particularly effective for tumors that are small and located near the center of the lung.

A multicenter, single-arm, prospective, phase 2 study assessed the local recurrence-free survival and safety after cryoablation in the treatment of pulmonary metastasis patients. After 12 months of initial treatment, 172 cases (85.1%) had no local recurrence response (local tumor efficacy) and 139 cases (77.2%) at 24 months. After the second cryoablation treatment of recurrent tumors, 184 out of 202 cases (91.1%) experienced secondary local no recurrence response (local tumor response) at 12 months, and 152 out of 180 cases (84.4%) experienced recurrence response at 24 months. The estimated OS rates at 1 and 2 years were 97.6% and 86.6%, respectively. The incidence of pneumothorax requiring the placement of pleural catheter was 26% (44/169). Out of 169 surgeries, 8 cases had grade 3 complications (4.7%) and 1 case had grade 4 complications (0.6%). Percutaneous cryoablation is an effective and safe treatment for pulmonary metastases [38].

With the rapid development of imaging equipment and minimally invasive technology, the application of cryoablation technology in minimally invasive treatment of tumors is becoming increasingly frequent, mainly targeting early-stage tumor patients who voluntarily agree to ablation and late-stage tumor patients who cannot be surgically removed or tolerated [39]. Cryoablation ablation is more effective and safer for target lesions than other thermal ablation methods, such as MWA and RFA. While these local treatment options offer promising outcomes for patients with early-stage lung cancer, there are still debates around the optimal use of these techniques and their long-term safety and efficacy compared to traditional treatments such as surgery or radiation therapy [40, 41]. Despite the promising DFS rates observed in patients who have undergone percutaneous cryoablation for lung cancer, the risks associated with breaching the pleural surface underscore the potential benefits of utilizing bronchoscopic cryotherapy as a viable alternative for treating peripheral lung cancers. This technique involves the use of small cryoprobes

inserted into the lungs following confirmation of tumor location through radial-probe endobronchial ultrasonography (RP-EBUS) or electromagnetic navigational system (EMN). However, the primary challenge associated with this approach remains the limited capacity of the cold delivery probes to penetrate deep into the parenchymal tumors.

Bronchoscopy-Guided Ablation

Endobronchial Ultrasound-Guided Ablation

Although EBUS-guided ablation has been shown to have potential for local treatment of pulmonary nodules, there are still several challenges and limitations associated with this technique [42, 43]. For instance, the ablation zone can be affected by respiratory motion and airway anatomy, which may result in instability and errors in treatment efficacy. Additionally, the treatment depth is also an issue as EBUS ablation is typically limited to within a few millimeters of the tumor diameter. Therefore, due to the limitations and challenges of the technology, research into the use of EBUS for local treatment remains relatively limited. However, with advancements in technology, more and more studies will explore the application of this technique in lung cancer treatment and seek to address the difficulties and limitations associated with it.

This study aimed to evaluate the feasibility and efficacy of a new flexible cryoprobe for transbronchial lung parenchyma cryoablation. The authors used pigs as animal models and performed experiments by inserting the cryoprobe under bronchoscopic guidance. The results showed that this new flexible cryoprobe could accurately locate and cryoablate pulmonary lesions with minimal complications during the treatment. It is worth noting that although the results of this study showed good therapeutic effects of the flexible cryoprobe in pig lung models, further verification is needed in more models, and large-scale clinical trials are required to confirm the safety and efficacy of this technology. In addition, although this technology can be used to treat early-stage lung cancer, due to the difficulty of operation, longer treatment time, and relatively poor treatment experience, further optimization is needed in the actual application. Overall, this study provides a new cryoprobe technology that offers a new option for the treatment of early-stage lung cancer. However, further research and verification are needed, and more rigorous clinical trials are required to demonstrate its safety and efficacy [44].

Although these techniques have potential advantages in treating small, early-stage lung cancer, there are still some limitations and challenges. First, for tumors located in the periphery of the lungs, bronchoscopic treatment is more difficult due to the difficulty in accessing the area. Second, existing treatments generally have issues predicting treatment effectiveness, high recurrence rates, and many complications. Additionally, bronchoscopic treatments still require skilled physicians to handle devices and perform operations. However, with the continuous development of technology and clinical practice, more and more advantages of bronchoscopic treatments for early-stage lung cancer are emerging. However, after carefully designed research and large-scale clinical trials, these techniques may gradually develop into safe and effective treatment options [45]. Yuan et al. [46] reported the development and testing of a new minimally invasive ablation technique guided by flexible bronchoscopy and microwave technology in porcine lungs. Both in ex vivo and in vivo lung settings, the bronchoscopy-guided ablations proved to be effective, with no reported complications during or after the procedures. Within 24 h, coagulation necrosis was clearly apparent, and at 4 weeks, the repaired fibrous tissue was visible. This new technique which is feasible and effective in treating peripheral lung nodules has the potential to become a safe and minimally invasive option for the treatment of lung cancer.

Transbronchial Brachytherapy for Pulmonary Nodules

Brachytherapy is a commonly used technique for the treatment of lung cancer that involves localized intratumoral irradiation. This can be performed using different methods such as direct implantation of radioactive seeds, CT or ultrasonographic guidance, and delivery through an after-loading catheter inserted through the working channel or parallel to the flexible bronchoscope [47]. In one study, high-dose-rate transbronchial brachytherapy was carried out to treat 2 patients with peripheral lung cancers. The procedure involved placing an applicator carrying a dummy source into the bronchus with the help of fluoroscopic guidance. Radiation was delivered in three fractions at 1-week intervals, using a radiation dose of 24 Gy at a radius of 10 mm from the center of the applicator. A single patient was administered a 15 Gy radiation dose, leading to a significant 75% reduction in tumor size. Moreover, the combination of endoluminal brachytherapy with guided/navigational bronchoscopic methods like RP-EBUS and EMNs has also been explored as an effective treatment option [48]. In a case study, EMN with dedicated catheter was applied to localize a peripheral lung cancer, and high-dose-rate brachytherapy was performed using 192Ir at a boost of 5 Gy three times

weekly, resulting in a partial radiographic response and complete histopathologic response at 12-month follow-up [49].

RFA and MWA are two percutaneous techniques used for the treatment of early-stage NSCLC [50, 51]. However, these methods are associated with a high incidence of complications such as pneumothorax, hemothorax, and bronchopleural fistula. Especially pneumothorax was reported in between 10% and 57% of cases [52]. In light of the proven antitumor benefits associated with percutaneous RFA and MWA for peripheral lung tumors, as well as the belief that endobronchial approaches may entail fewer instances of pneumothorax compared to transthoracic techniques, there has been a concentrated push to develop ablation modalities that can be administered via the working channel of a flexible bronchoscope. Ten patients with stage IA lung cancer underwent bronchoscopy-guided RFA using internally cooled probes. The probes were inserted within the tumors using CT imaging guidance prior to surgical resection. The ablated area achieved with the 10 mm catheter tip was 12 mm × 10 mm, with demonstrated coagulation necrosis and destruction of alveolar space. Ablation with smaller catheter tips resulted in smaller tumor areas. The coagulation necrosis area increased with larger tips and longer ablation times, but residual tumor cells were present in all patients. No major complications were reported [53].

In the study by Koizumi et al. [22], 20 patients with early-stage NSCLC with 23 peripheral lung lesions received CT-guided bronchoscopic cooled RFA. The majority (82.6%) of patients achieved local disease control, and there were no serious complications reported. Interestingly, the 5-year survival rate for these treated patients was 61.5%, which is a favorable comparison to the 5-year survival rate of less than 50% reported in early-stage cancers treated with SBRT. Due to the notably lower incidence of complications, particularly the reduction in pneumothoraces, bronchoscopic techniques for treating peripheral lung cancer with RFA probes may become more preferred over percutaneous RFA technologies.

Challenges and Recommendations

How to Achieve Precise Positioning of Pulmonary Nodules

Bronchoscopy-guided ablation is a minimally invasive procedure that uses a bronchoscope to deliver heat or cold energy directly to cancerous tumors in the lungs. One of the major challenges of this technique is achieving precise positioning of pulmonary nodules. To perform bronchoscopy-guided ablation, a bronchoscope equipped with a small camera and a specialized instrument is inserted through the mouth or nose and guided to the site of the tumor. Once the instrument is in place, energy is delivered to the tumor to destroy the cancer cells. However, achieving precise positioning can be difficult because pulmonary nodules can be small and difficult to visualize with the bronchoscope. Moreover, the movement of the airways during breathing can cause the tumor to shift, making it even harder to target accurately. To overcome these challenges, several techniques have been developed. Image-guided navigation systems use CT or magnetic resonance imaging (MRI) to create a three-dimensional (3D) map of the lung and guide the bronchoscope to the tumor with greater accuracy. Another approach is to use electromagnetic tracking technology to monitor the position and movement of the bronchoscope in real-time and adjust its position accordingly. In conclusion, achieving precise positioning of pulmonary nodules during bronchoscopy-guided ablation is a significant challenge. However, with advances in technology, such as image-guided navigation and electromagnetic tracking, physicians can improve their ability to target tumors with greater precision, leading to improved outcomes for patients with lung cancer.

How to Evaluate the Range of Bronchoscopy-Guided Ablation (There Is Uncertainty in the Dose-Effect Relationship of Energy Conduction in Lung Tissue)

Another challenge in bronchoscopy-guided ablation is how to evaluate the range of the treatment and ensure that the desired area of tissue is adequately covered while avoiding damage to surrounding healthy tissue. This is particularly challenging since there is uncertainty in the dose-effect relationship of energy conduction in lung tissue.

During bronchoscopy-guided ablation, a specific amount of energy, either heat or cold, is delivered to a targeted area of tissue to destroy cancer cells. However, the amount of energy needed to achieve the desired effect can vary depending on several factors, including the size and location of the tumor, as well as the type of energy used. Therefore, it is important to carefully monitor the patient during the procedure to assess the response to the treatment and adjust the energy delivery as necessary. One approach to evaluate the range of bronchoscopy-guided ablation is to use imaging techniques such as CT or MRI to confirm the location and extent of the tumor before and after the ablation procedure. This can help identify any residual disease and ensure that the desired area of tissue has been effectively treated. In addition to imaging, other methods such as biomarker analysis and

tissue sampling can also be used to evaluate the effectiveness of bronchoscopy-guided ablation. Biomarkers, such as circulating tumor DNA or tumor markers, can be monitored before and after the procedure to assess the response to treatment. Tissue samples can also be taken and analyzed for evidence of cell death and changes in gene expression associated with treatment response. In summary, the evaluation of the range of bronchoscopy-guided ablation is a complex issue that requires careful monitoring of the patient during and after the procedure. Imaging techniques, biomarker analysis, and tissue sampling can be used to assess the effectiveness of the treatment and ensure that the desired area of tissue has been adequately covered while minimizing damage to surrounding healthy tissue.

How to Reach Pulmonary Nodules without Bronchus Sign

The challenges associated with navigating through multiple subsegments during bronchoscopy, coupled with the propensity for endobronchial path selection errors, represent significant hurdles to this diagnostic approach. To address these difficulties, virtual bronchoscopic navigation (VBN) coupled with fused fluoroscopic guidance has been developed. This innovative technology reconstructs a three-dimensional image of the bronchial pathway and generates a virtual image of the lesion using two-dimensional CT scans, enhancing navigation and facilitating diagnosis via highlighted lesion visualization on the fluoroscope screen. Vessel mapping is utilized to avoid sampling from large vessels. Furthermore, bronchoscopic transparenchymal nodule access and guided transbronchial needle aspiration have been introduced, both of which require puncturing through the airway wall to create a point of entry. These techniques enable access to lesions regardless of their size, proximity to the airway, presence of a bronchus sign, or location within the lung [4, 54].

Robotic-assisted bronchoscopy (RAB) is a novel technique that uses a robotic arm to guide a flexible bronchoscope to the site of lung nodules, providing a higher degree of precision and accuracy. RAB has emerged as a promising tool in the diagnosis and treatment of lung cancer, particularly for the positioning of pulmonary nodules. One of the major advantages of RAB is its ability to access hard-to-reach areas of the lung with greater precision. The robotic arm allows for more accurate and steady control of the bronchoscope, which enables the physician to navigate through the complex anatomy of the lungs more easily. During RAB, computer software guides the robotic arm to the target area based on CT scans or other imaging techniques. This allows the physician to plan the trajectory of the bronchoscope in advance, which can help minimize the risk of damage to surrounding healthy tissue. RAB also features advanced imaging capabilities that can help improve the accuracy of nodule localization. The system is equipped with high-resolution cameras and video scopes that provide clear images of the lung nodules, allowing the physician to visualize the location and size of the tumor with greater clarity. The system can also use real-time tracking to adjust the trajectory of the robotic arm to ensure that the bronchoscope stays on course, even when the patient breathes or moves [55–58].

How to Change the Ablation Catheter to Increase the Ablation Range

Changing the ablation catheter to increase the ablation range is one of the challenges in bronchoscopy-guided ablation for the treatment of lung cancer. Here are some potential solutions.

Ablation after Flex needle puncture involves using a small flexible needle to puncture the lung tissue, followed by the insertion of the ablation catheter through the puncture site. This approach may allow for access to more difficult-to-reach areas of the lung and increase the ablation range. Umbrella-shaped radiofrequency ablation needle has a wider diameter at its base than at its tip, allowing for a larger ablation range. It also has an expandable umbrella-like structure at its tip, which can help to anchor the catheter in place and prevent it from moving during the procedure. Ablation needle for the water sac is designed to be used when there is an accumulation of fluid around the lung, known as a water sac. The needle can be inserted into the sac and used to ablate the tumor, potentially increasing the ablation range and improving treatment efficacy. A perforated radiofrequency catheter for ablation has a catheter with multiple tiny holes along its length, allowing for a larger ablation range. The holes also allow for better heat dissipation, reducing the risk of damage to surrounding healthy tissue.

Each of these solutions may offer advantages in terms of increasing the ablation range and improving treatment efficacy. However, they also require careful consideration of factors such as patient anatomy, tumor location, and potential risks and complications. The choice of approach will depend on the specific needs of the patient and the judgment of the treating physician.

In addition, intraoperative confirmation of cone-beam CT (CB-CT) is an important issue in bronchoscopy-guided ablation for the treatment of lung cancer.

CB-CT is a type of imaging technology that uses cone-shaped X-ray beams to create 3D images of the lungs and surrounding tissue. It can provide real-time guidance during the ablation procedure, helping physicians to ensure that the catheter is properly positioned and that the ablation is effectively treating the tumor. There are several ways to perform intraoperative CB-CT confirmation. One approach is to use a mobile C-arm system, which can be moved into position around the patient during the procedure. This allows for real-time imaging and visualization of the ablation catheter and surrounding tissue, allowing physicians to adjust the position of the catheter as needed for optimal treatment efficacy. Another approach is to use a dedicated CB-CT scanner, which is typically located within the operating room. This allows for more detailed imaging of the lungs and surrounding tissue, providing greater accuracy and precision in the placement of the ablation catheter. However, this approach may be more time-consuming and expensive than using a mobile C-arm system. Regardless of the method used, intraoperative CB-CT confirmation can help to improve the safety and efficacy of bronchoscopy-guided ablation for lung cancer. It provides real-time imaging and guidance, allowing physicians to ensure that the catheter is properly positioned and that the ablation is effectively treating the tumor. This can help reduce the risk of complications such as bleeding or damage to surrounding healthy tissue while improving treatment outcomes and patient satisfaction [59].

How to Confirm Radical Ablation Has Been Achieved or whether the Ablated Nodules Have Been Completely Covered after Ablation

Confirming radical ablation and complete coverage of ablated nodules are important concerns after ablation surgery for the treatment of lung cancer. Here are some potential ways to address these issues.

Imaging screening such as CT scans or positron emission tomography (PET)/CT scans can be used to assess the extent of ablation and monitor for any residual tissue or new tumor growth. These studies can be performed at regular intervals after the ablation procedure to ensure complete ablation has been achieved. A biopsy of the treated area can confirm that the ablated tissue is free of cancer cells. This may be done during the ablation procedure or at a later time point. If residual cancer cells are detected, additional treatment options can be pursued. Patients should be closely monitored after the ablation surgery, with regular follow-up visits to assess lung function, symptoms, and potential complications. Further imaging or biopsies may be performed if necessary. The Thoracic Imaging and Interventional Therapy group has developed consensus guidelines for the evaluation of patients after lung ablation. These guidelines provide recommendations for imaging protocols and follow-up schedules to ensure the best possible outcomes for patients.

It is important to note that, while ablation surgery can be an effective treatment option for lung cancer, it is not always curative. Close follow-up and monitoring are essential to ensure that any remaining cancer cells or new tumors are detected early and appropriate treatment options are pursued.

How to Deal with the Diagnosis of Pulmonary Nodules for Source-Limited Centers

Several bronchoscopic guidance modalities have been developed to improve the diagnostic yield of conventional bronchoscopy, including RP-EBUS, VBN, and electromagnetic navigation bronchoscopy (ENB). However, certain hospitals may not have access to such navigation devices due to financial limitation and a lack of sophisticated operator. These source-limited centers face unique challenges in effectively diagnosing pulmonary nodules. A feasible and economical bronchoscopic navigation method for guiding peripheral pulmonary nodule biopsy is lacking. Zhong et al. [60] developed a feasible and economical method of hierarchical clock-scale hand-drawn mapping for bronchoscopic navigation (HBN) with a comparable diagnostic yield to VBN. The HBN system could serve as a non-inferiority method for guiding peripheral pulmonary lesion biopsy compared with VBN system.

Without navigation systems, these centers may rely on traditional bronchoscopy techniques, which can present limitations in terms of accuracy and precision when targeting smaller or peripheral lesions. In such cases, alternative diagnostic modalities, such as CT-guided biopsies or transthoracic needle aspirations, may be considered. However, these alternatives carry their own risks and limitations, including potential complications and the need for specialized expertise and equipment.

To address the resource constraints faced by these centers, efforts could be made to provide training and support in advanced bronchoscopy techniques, such as R-EBUS or ENB. These techniques, although requiring initial investment, have shown promise in improving the diagnostic yield for peripheral pulmonary nodules, even without the use of navigation systems. Additionally, collaboration between source-limited centers and larger institutions with access to advanced equipment and expertise could facilitate referrals and consultations, providing patients with access to more comprehensive diagnostic options.

Table 1. Comparison between intervention modalities in the treatment of peripheral pulmonary nodules

Intervention modalities	Efficacy	Survival	Complications	Inclusion cases	Reference (DOI)
Surgery					
Lobar resection	5-year RFS: 71.2%	5-year DFS: 64.1% 5-year OS: 78.9%	NA	T1aN0 (tumor size, ≤2 cm)	10.1056/NEJMoa2212083
Sub-lobar resection	5-year RFS: 70.2%	5-year DFS: 63.6% 5-year OS: 80.3%	NA	T1aN0 (tumor size, ≤2 cm)	10.1056/NEJMoa2212083
Stereotactic body radiation therapy (SBRT)	5-year cumulative incidence: 17.6% 3-, 5-year CSS: 95%, 92%	3-, 5-year OS: 91%, 87% 3-, 5-year PFS: 80%, 77%	No grade 4–5 toxicity and a single case each (1/80, 1.3%) of grade 3 dyspnea, grade 2 pneumonitis, and grade 2 lung fibrosis	T1N0M0 (tumor size, ≤3 cm)	10.1016/S1470-2045(21)00401-0
Percutaneous ablation	1-, 2-, 3-, 4-, and 5-year CSS: 94%, 74%, 72%, 60%, and 60%	1-, 2-, 3-, 4-, and 5-year OS: 92%, 78%, 62%, 57%, and 41% 1-, 2-, 3-, 4-, and 5-year DFS: 86%, 66%, 66%, 59%, and 37%	Pneumothorax (13–58%), hemoptysis (5–50%), pleural effusion (3.6–12%), pain (9.3%), infection/pneumonia (0–1.8%)	NA	10.1007/s00330-020-07634-7
Bronchoscopic ablation	Resulting response rate: 47.8% Local control rate: 82.6%	Median PFS: 35 months 5-year OS: 61.5%	No serious adverse event	T1-2aN0M0 and not surgical candidates because of comorbidities	10.1159/000430825

RFS, recurrence-free survival; OS, overall survival; PFS, progression-free survival; CSS, cancer-specific survival; DFS, disease-free survival.

Ablation Combined with Immunotherapy

Beyond its ability to induce tumor apoptosis and necrosis, cryoablation has been shown to facilitate the diffusion of tumor-derived autoantigens into the bloodstream, thereby stimulating the host immune system and promoting a robust antitumor immune response against both primary and metastatic tumors. Given the recent progress in the field of immune checkpoint inhibitor research, which has demonstrated that lung cancer can be treated with immunotherapy, there has been growing interest in exploring the relationship between cryoablation and lung cancer immunotherapy [61]. Not all patients respond to immune checkpoint inhibitors. The use of cryoablation involves the destruction of cancerous tissue through freezing. Unlike ablative methods that rely on heat, cryoablation induces cell death in tumors via osmosis and necrosis. It has been postulated that the necrosis caused by cryoablation retains the intracellular contents of cancer cells, which may then prompt the immune system to launch a specific immune response. In theory, this immune response could extend beyond the ablated tissue and induce what is called the "abscopal effect." However, this effect is rarely observed in practice. By combining cryoablation with immunotherapy, it is possible to enhance the effects of both treatments and promote a more robust immune response against cancer cells [62].

Discussion and Conclusions

This article aimed to highlight the efficacy and advantages of surgical resection, SBRT, percutaneous ablation, and bronchoscopic ablation as treatment options for malignant pulmonary nodules (Table 1). The field of interventional pulmonology has witnessed rapid advancements in the treatment of malignant pulmonary nodules. SBRT, percutaneous ablation, and bronchoscopic ablation techniques have emerged as effective alternatives to surgical resection, showcasing comparable efficacy and survival rates with reduced adverse effects. The ongoing development of minimally invasive procedures holds great promise for optimizing patient

outcomes and should be considered as integral components in the comprehensive management of malignant pulmonary nodules. In comparison to traditional surgical treatment and SBRT, therapeutic bronchoscopy for lung nodules offers several distinct advantages. First, it eliminates the need for thoracotomy or incisional surgery, thereby avoiding procedure-related complications and reducing recovery time. This leads to reduced hospitalization, alleviates patient burden, and facilitates quicker return to normal activities. From a cost-effectiveness standpoint, therapeutic bronchoscopy represents a relatively economical option. Surgical interventions and SBRT typically require a greater allocation of medical resources, including operating room facilities, anesthesiologists, and radiation therapy equipment. In contrast, therapeutic bronchoscopy requires fewer resources in terms of equipment and manpower, thus resulting in cost savings. Additionally, therapeutic bronchoscopy can often be performed on an outpatient basis, reducing patient visits and transportation expenses.

In summary, therapeutic bronchoscopy as a minimally invasive diagnostic tool offers certain advantages and cost-effectiveness in the assessment and treatment selection of pulmonary nodules. However, in clinical practice, physicians need to carefully weigh the pros and cons of various treatment options and make individualized treatment decisions based on patient-specific considerations. Bronchoscopy-guided ablation for early lung cancer is a new technology that requires selecting the appropriate population, precise positioning, and improving ablation instruments to expand the ablation range and reduce complications caused by ablation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Investigation, formal analysis, conception, and design: Quncheng Zhang, Xiaoju Zhang, and Xuan Wu; drafting of the manuscript: Quncheng Zhang, Xuan Wu, Huizhen Yang, and Peiyuan Luo; acquisition and analysis of the data: Nan Wei, Shuai Wang, Xingru Zhao, and Ziqi Wang; helpful guidance and suggestions: Felix JF Herth. All coauthors edited and approved the final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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