

Reviewer A

The section that follows should be rewritten to be clearer in terms of what is being suggested:

However, in patients with multiple pulmonary nodules, balancing the extent of pulmonary resection with loss of pulmonary function and perioperative risk is very important and also very difficult. In patients undergoing lobectomy/sublobar resection (segmental resection and wedge resection), FVC% predicted decreased by 23.3%/17.0%, 12.3%/6.4%, and 8.5%/4.1% at 2 weeks, 6 months, and 1 year after surgery from preoperative baseline, respectively, whereas FEV1 %predicted decreased by 21.7%/15.5%, 11.6%/6.0%, and 8.4%/4.0%, respectively, from preoperative baseline 16 . DLCO %predicted at 6 months and 1 year after surgery in patients with lobectomy/sublobar resection decreased by 14.4%/7.1% and 13.4%/7.3% from preoperative baseline, respectively.

Reply 1: Thanks for your review. In the second paragraph of discussion part, we cite these relevant data to illustrate that lobectomy and sublobar resection have a greater loss of lung function, and in the case of multiple pulmonary nodules, multiple lung resections will inevitably result in a greater loss of lung function. We added some sentence before and after this part to help understanding the purpose of showing these data. Because traditional surgery impairs lung function to such an extent that multiple lung resections for multiple primary lung nodules may not be the best option, we have begun to think about new strategies for the treatment of multiple primary lung nodules. In a later section from line 335, we describe the solution, our hybridized surgical protocol that resolves the paradox of multiple primary nodule treatment and loss of lung function.

Changes in the text: Please check second paragraph of discussion part, we added some sentence before and after this part to help understanding the purpose of showing these data (line 277 to 278, line284).

I really would question using this since the survival curves for the 8th edition for pathologic stage 1 lung cancers are between 77 and 92% or greater depending on substage. Comparing surgical resection to ablation as equivalent is a statement that I do not think is appropriate to make. "A meta-analysis showed no significant difference in 1-year to 5-year overall survival between surgery and pulmonary ablation for stage I NSCLC, with a 5-year overall survival rate of 41% after ablation."

Reply 2: Thanks for your comment and that's an inspiring point. Eight studies (total 792 patients: 460 resection and 332 ablation) were included in this meta-analysis which we cited (Chan MV, Huo YR, Cao C, Ridley L. Survival outcomes for surgical resection versus CT-guided percutaneous ablation for stage I non-small cell lung cancer (NSCLC): a systematic review and meta-analysis. *European radiology*. 2021;31(7):5421-5433.) and we reread the original citation and double check the data. The 5-year overall survival rate of 41% after ablation was cited correctly based on the result of the paper. Meanwhile, this research also give conclusion that there were no significant differences in 1- to 5-year OS or CSS between surgery versus ablation. And in two of eight studies which only included patients with stage 1a NSCLC, there is no significant differences in 1- to 3-year OS or DFS between surgery versus ablation. And we also cited other 5 papers which published between 2018 to 2022 with 5-year OS of ablation from 16%-68%.

However, the 8th edition for pathologic stage of 1A1 to 1A3 lung cancers are about 80% to 90%, and 1B are about 73%. The discrepancies in data present in these literatures may be due to a variety of reasons such as bias due to sample selection (not all patients with stage I lung cancer need immediate treatment, especially with stage IA), poor control of ablation indications, and inaccurate staging. However, at least part of the literature suggests that there is no difference in the long-term efficacy of ablation and lung resection surgery in the treatment of stage I lung cancer. Of course, certain controversial data remain to be confirmed by studies with larger samples.

Changes in the text: We add some points in discussion part to explain the possible reasons for

the deviation in literature data, please check line 319 to 325.

Given the recent Altorki data that has been confirmed about the value of sub lobar resections, why were these patients not just candidates for wedge resections of the lesions?

Reply 3: Thank you very much for your precious suggestion. Firstly, for major lesions in our cases, we believe that lymph node dissection in segmental resection and lobectomy is more radical, which is conducive to improving the long-term prognosis and reducing the possibility of recurrence. However, we are aware of the controversy over the need for systematic lymph node dissection in early-stage lung cancer, especially in sub-centimeter ground-glass nodules, which means that wedge resection for some suitable nodules is also a viable option. Secondly, intraoperative accurate location issues, for not only major lesions, but also non-major lesions, such as nodule 1 in our cases 1 and 2, these lesions are deeper in location and are not suitable for wedge resection.

No changes in the text.

DLCO is not provided for the patients and DLCO is considered to be more predictive of post operative complications and functional status than FEV1.

Reply 4: Thank you for your good suggestion. We check the original data of DLCO in our cases and add them into table 1. We will continue to monitor the long-term prognosis of patients who undergo hybrid surgery at our center, and we will pay more attention to the collection of this data in subsequent follow-up visits.

Changes in text: Please check table 1.

Imaging of the lesions to help explain why the hybrid approach was chosen.

Reply 5 : Thanks for your comment. We add some figures to help understanding our procedure. In figure1a and 1b, we show the hybridization operating room used in our center and the C-arm real-time X-ray machine used intraoperatively. And in figure 1c and 1d we show real-time CT images of the percutaneous ablation and our intraoperative localization approach. Furthermore, we add some typical images of case 1 and 2 as figure 2 and figure 3 to help explaining why we choose the hybrid approach for these patients. In figure 2 as an example, we show the CT images of all the suspicious nodules of this patient in 2a, and we show the intraoperative real-time images of the proposed radiofrequency ablation of the nodules in 2b. In 2c, we show the post-surgery CT images of the patient to demonstrate the effects of treatment. These images will help readers better understanding our intention in choosing hybrid surgery.

No changes in the text.

Give the relatively high complication rate of a the BPF after ablation in 1/4 patients, why should programs adopt that if surgical resection for all the lesions may be possible?

Reply 6: That's a good point, thank you. The technique of ablation is still relatively new in our center and we are still on the learning curve, so we encountered this serious complication of bronchopleural fistula during hybrid surgery. Fortunately, this problem was detected in time during thoracoscopic surgery, and the patient recovered well after suturing the pleural fistula, without further postoperative complications. We provide this group of cases only as our center's experience, but according to the currently published literatures, the incidence of bronchopleural fistula during pulmonary ablation is very low, about 0.5% to 1 %. More data on the safety and feasibility of this hybridization procedure are awaited.

At the same time, our hybrid surgical protocol has advantages in monitoring and managing intraoperative bronchopleural fistula. For patients with ipsilateral multiple primary pulmonary nodules, we can explore and repair possible bronchopleural fistula in time by thoracoscopic exploration of the ablation site after pulmonary ablation, which will effectively reduce the occurrence of this complication.

Changes in text: We add data from published papers to show the incidence of bronchopleural fistula, please check line 330 to 333.

With multiple sub centimeter nodules it would be good to know their growth over time and were they becoming more solid. The authors suggest that earlier intervention prevents metastatic spread, however, the risk of spread for sub centimeter GGOs is rather small if not negligible. This approach of combined surgery may lead to intervention on nodules of ultimately minimal significance. Furthermore, the post operative length of stay was significantly longer than what would have been expected from wedge resections and lymph node dissections alone.

Reply 7 : Thank you for raising a good point. Follow-up observation remains a viable treatment strategy for sub-centimeter nodules, especially for pure ground-glass nodules, and overtreatment due to premature intervention is a concern in thoracic surgical management. Therefore the indications for intervention are very important, but consensus is still lacking. For the elderly and high-risk patients with poor organ function, it is important to individualize the surgical strategy with good long-term prognosis and low perioperative risk. This hybrid surgery was explored as a novel strategy for multiple pulmonary nodules, and all these patients with multiple lung nodules underwent preoperative multidisciplinary discussions to develop a Individualized treatment plan. we designed the hybridization surgical plan by considering the patient's age, nodule characteristics (solid nodule, mixed or pure ground-glass), organ function and possible postoperative complications individually, rather than directly treating all the lesions. However, the number of cases accumulated in this novel hybrid surgery strategy is still relatively small and in the exploratory stage. Therefore, further research and exploration is needed, and this is one of the key directions for future research in our center for this group of patients.

No changes in the text.

Reviewer B

This paper discusses the method of performing pulmonary resection combined with real-time image-guided percutaneous ablation for multiple pulmonary nodules, with the addition of a literature review for each decade. There are several issues that can be pointed out, and I would like you to address them.

1.The history of radiofrequency ablation for pulmonary nodules is long, with Dupuy DE, et al. presenting the first clinical case in 2000 in Am J Roentgenol. Since then, many presentations have been made. While not for primary lung cancer, in 2008, Sano Y, et al. published in J Thorac Oncol. regarding the usefulness of radiofrequency ablation in conjunction with surgery for multiple metastatic pulmonary tumors. Given this quarter-century history, please explain why you conducted a literature review only for the past 10 years and did not include earlier reviews.

Reply 1 : Thanks for your reminding. We redo the literature review and removed the 10-year filter in the search equation. We modified the search equation in order to search as comprehensively as possible for relevant literature, and as of March 25, 2024, there were 526 results, and we reviewed the titles and abstracts of each article and selected those that met the requirements. Eventually, the number of literatures that met the requirements was still very limited, as detailed in table 2.

Changes in text: Please check literature review part in result section and table 2.

2.When you perform simultaneous surgery with radiofrequency ablation, it is mentioned that a C-arm X-ray machine is used. However, this is considered to result in inferior image quality compared to CT-fluoroscopy commonly used for percutaneous ablation, and it may be disadvantageous compared to performing these procedures at different times. What is your perspective on this?

Reply 2 : Thanks for your comment. The full official name of our C-arm X-ray machine is actually called the Discovery IGS 7 angiography system (please check out the figure on the right which was downloaded from official website of our center). It not only generates real-time dynamic images,

but its C-arm can also be rotated 360 degrees to generate high-resolution thin-layer images. Its thin-layer scanning could reach 0.48 mm per level. In our practical use, its resolution is sufficient for localization and ablation of lung nodules that meet surgical indications.

No changes in the text.

3. In cases where nodules are present in both lungs, what do you do? What do you consider should be done?

Reply 3: That's an inspiring point, thank you. The management strategy for multiple primary nodules in both lungs is still in the exploratory stage, and a unified consensus has not yet been reached. Follow-up observation remains a viable treatment strategy for sub-centimeter nodules, especially for pure ground-glass nodules, and overtreatment due to premature intervention is a concern in thoracic surgical management. Therefore, the time point of surgical intervention is very important. The size, density, and doubling time of the nodule will determine whether the nodule requires surgical intervention, and the patient's age and concomitant diseases should also be taken into account to determine the appropriate timing of surgery, so as to avoid missing the best opportunity for treatment due to prolonged follow-up observation. For nodules requiring intervention, resection can be used for the major lesion and ablation can be used for the minor lesion in the contralateral lung. However, for very small nodules and sub-centimeter nodules with predominantly ground glass components, we need to individualize the approach and consider follow-up or surgery. Therefore, each patient requires an individualized surgical design, a set of multidisciplinary discussions to jointly decide on the surgical plan.

No changes in the text.

4. Considering the above, please reevaluate the significance of performing pulmonary resection and real-time image-guided percutaneous ablation simultaneously for multiple pulmonary nodules.

Reply 4 : As medical technology advances, the treatment options for lung nodules become more diverse. However, there has never been a uniform protocol on how to treat multiple primary lung nodules precisely. First, the surgical indications should be careful, and over-treatment of pure ground glass density nodules with sub-centimeter diameter is inappropriate. Meanwhile, the patient's relevant medical history and follow-up situation should be considered comprehensively to provide the necessary treatment with minimal trauma. For patients with surgical indications, lung ablation is a good choice to eliminate the hidden risk and protect the cardiopulmonary function of the patient at the same time. secondly, for the higher risk of mixed density and solid lung nodules, we believe that the traditional surgical treatment strategy including lobectomy, segmentectomy, sub-segmentectomy and wedge resection should still be used with a more definite long-term prognosis. Finally, the surgical plan should be individualized, and the patient's underlying physical condition should be taken into account fully while grasping the indications of the surgery. Surgery without indications and excessive surgical scope should be avoided. For patients with multiple primary lung nodules who has to be treated with surgery, our procedure has advantages compared with traditional strategy (simultaneous or staged multiple lung resections) in less loss of pulmonary function, good perioperative safety, less financial burden of hospitalization and the prospect of a favorable long-term prognosis.

Changes in the text: We realize that responses to this comment are useful in helping to understand our surgical protocol choices, so we have added this paragraph to the discussion section. Thank you very much for your enlightening comments. Please check line 358-377.

