Peer Review File

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Reviewer A

1.- injection into perilesional tumor can distort real optimal resection margins when intraoperative ring-shaped forceps are used. How could the authors overcome this drawback?

Reply 1: We agree with the reviewer that injection directly into or too close to the tumor could potentially distort the actual tumor–margin relationship when using intraoperative ring-shaped forceps. In our protocol, lipiodol is injected adjacent to the lesion while avoiding direct injection into the tumor itself, as confirmed on CT images. We also take care to select an injection pathway that allows adequate grasping of the marked area without compressing or displacing the tumor during stapling. We have now clarified this strategy in the Marking Technique section.

Changes in the text: We have added an explanation in the Marking Technique section describing how we avoid distortion by carefully placing the injection site adjacent to but not within the tumor (see Page 7, lines 1–2, Page7, lines5–7).

2.-in pathological analysis: "fully inflated lung with staples removed" in a pulmonary wedge resection: authors should explain how they do it (usually when stapling to remove a pulmonary nodule the lung remains collapsed with no inflated lobes)

Reply 2: We appreciate the reviewer's request for clarification. In our institution, immediately after resection, the specimen is inflated with formalin through the bronchus to achieve near-complete inflation, after which the staples are removed for margin measurement. This method allows accurate measurement of the margin in an inflated state. We have now detailed this process in the Pathological Analysis section.

Changes in the text: Additional explanation of lung inflation and staple removal before measurement has been added to the Pathological Analysis section (see Page 7, lines 25–Page 8, lines 3).

3.-long term follow-up to verify local relapse related to pulmonary wedge resection specially in the deeper required resection group would be interesting

Reply 3: We agree with the reviewer that long-term follow-up data would be valuable to clarify the risk of local relapse, especially in patients who required deeper wedge resection. Unfortunately, our current retrospective study design did not include uniform long-term follow-up for all cases, particularly those with metastatic lesions. However, we recognize the importance of this issue and are currently planning a prospective study that will incorporate long-term outcomes to specifically address this question.

4.-could the authors make any comment about the low sensitivity and specificity they got in their AUC results and weather they consider a useful cutoff for daily clinical practice?
Reply 4: We acknowledge that the AUC value of 0.68 indicates only moderate predictive performance, with sensitivity of 57.5% and specificity of 73.0%. While this level may not be sufficient as a sole determinant in daily practice, we believe the identified cut-off for required resection depth can serve as a supportive preoperative risk assessment tool in combination with other clinical factors. We have added this interpretation to the Discussion.
Changes in the text: A paragraph discussing the clinical utility and limitations of the cut-off value has been added to the Discussion (see Page 12, lines 3–8).

Reviewer B

1. Clarification of surgical indication for wedge resection
The most critical issue is the lack of a clear description of the indication for wedge resection. Since the study focuses on the adequacy of surgical margins, it is essential that the criteria for selecting wedge resection (as opposed to segmentectomy or lobectomy) be explicitly stated in the Methods section. This is particularly important given that the cohort includes invasive adenocarcinomas, for which wedge resection may not be oncologically appropriate in all clinical contexts. Without this information, it is difficult to assess the clinical relevance of the reported failure rate or the applicability of the findings to real-world practice.
Reply 1: We thank the reviewer for this insightful comment. We agree that clarification of the surgical indications for wedge resection is essential for interpreting the adequacy of surgical margins. In our institution, the indication for pulmonary localization and subsequent wedge resection was determined by thoracic surgeons. Nodules that were considered difficult to localize during thoracoscopy, such as GGO lesions, nodules located at a considerable depth from the pleural surface, and nodules less than 10 mm in size, were candidates for this technique.
We have now added this description to the Methods section to provide greater clarity on the clinical rationale for performing wedge resection in this study cohort.

Changes in the text: Details on surgical indications have been added to the Patients section in Methods (see Page 6, lines 3–7).

2. Interpretation of the 28.6% failure rate
While a 71.4% resection success rate is reported, it is important to briefly comment on the clinical implications of the 28.6% failure rate. For example, is this considered acceptable for wedge resection in current practice? If not, could this influence surgical decision-making or raise the need for alternative strategies in high-risk cases?

Reply 2: We agree that the clinical relevance of this rate should be discussed. In our view, a 28.6% failure rate suggests that in nearly one-third of cases, wedge resection with lipiodol marking may not achieve oncologically adequate margins, especially for deeper lesions. This highlights the need for careful patient selection and consideration of segmentectomy in high-risk cases. We have added this perspective to the Discussion.
Changes in the text: Discussion section updated to include interpretation of the failure rate and its implications (see Page 10, lines 21–25, Page 11, lines 1–2,Page 12, lines 23–25).

3. Segment-based variation in success rates
Figure 4 shows not only segment 6, but also segments such as right S1 and left S8–S9, had relatively low success rates. These findings may reflect anatomical challenges or limitations in stapler access. It would be helpful to include your interpretation of these findings and potential anatomical reasons in the Discussion section.
Reply 3: We appreciate this comment. In addition to segment 6, some apical (right S1) and basal segments (left S8–S9) had lower success rates. These may be due to challenging stapler access angles, deeper lesion location, and proximity to segmental bronchi or vessels. We have incorporated this explanation into the Discussion.
Changes in the text: Discussion section expanded to include anatomical considerations for segment-based variation (see Page 11, lines 18–24).

4. Clarification of margin measurement methods
Although the manuscript states that margins were measured in a "fully inflated lung with staples removed," it would be helpful to specify whether the lung was inflated by formalin fixation or other methods, and whether the measurement was performed on fresh or fixed specimens. This clarification would improve reproducibility and transparency.
Reply 4: We have clarified that the lung specimens were inflated using formalin and the measurements were performed on fixed specimens after staple removal. This has been explicitly described in the Pathological Analysis section.
Changes in the text: Method of lung inflation and specimen handling before margin measurement added to Pathological Analysis section (see Page 7, lines 25–Page 8, lines 3).

5. Suggestions for future directions
The study would benefit from a richer discussion on how these findings could be applied in clinical practice. For instance, could this depth-based risk assessment guide case selection for wedge versus segmentectomy?
Reply 5: We agree and have added a paragraph discussing how required resection depth could be used in preoperative planning to decide between wedge resection and segmentectomy, as well as in developing new localization strategies for deep lesions.

Changes in the text: Future research and clinical application paragraph added to Discussion (see Page 12, lines 10–14, see Page 13, lines 1–4).

Reviewer C

Major Comment

1. The indications for this procedure at the authors' institution should be described. Are there criteria for tumor size, distance from the pleura to the lesion, and the presence or absence of ground-glass lesions?

Reply 1: We have now clearly stated the selection criteria for lipiodol marking and wedge resection, including tumor size, pleural distance, and radiological appearance.

Changes in the text: See Page 6, lines 3–7.

2. Ten patients who underwent anatomical pulmonary resection were excluded. Were these patients' surgical procedures changed due to insufficient margins in the wedge resection after marking? Please explain the reason for this exclusion.

Reply 2: We appreciate the reviewer's important comment. The 10 excluded cases were all diagnosed intraoperatively as primary lung cancer based on frozen-section examination. In accordance with patient preference, these patients subsequently underwent lobectomy as a curative procedure. The reason for exclusion was not related to inadequate surgical margins after wedge resection. We have clarified this point in the Methods section of the manuscript.

Changes in the text: See Page 6, lines 8–10.

3. Related to the above, do the authors not check the resection margins intraoperatively, even for non-palpable lesions? If the margins are insufficient, do they not perform additional resections?

Reply 3: Thank you for this valuable comment. For non-palpable lesions, we generally do not submit parenchymal margins for frozen-section analysis. The main reasons are the risk of specimen distortion and crush artifact, possible loss of orientation for definitive pathology, and time constraints when multiple small or deep nodules are involved.

4. It is necessary to describe whether pulmonary embolism and central nervous system disorder are caused by lipiodol injection. If not, it would be better to explain the rationale.

Reply 4: Thank you for pointing out this important issue. In our cohort, no cases of pulmonary embolism or central nervous system (CNS) complications attributable to lipiodol injection were observed. This finding is consistent with previous reports (*J Thorac Dis*. PMID:299997960), including our earlier series, which demonstrated that lipiodol marking is generally safe, with only minor complications such as pneumothorax or localized hemorrhage being reported.

The rationale is that only a very small volume (0.2 mL) of lipiodol is carefully injected into the perilesional lung parenchyma , with confirmation that no blood reflux occurs before injection. This precaution minimizes the risk of inadvertent intravascular administration, which could otherwise lead to systemic embolism. Furthermore, in our protocol, the subsequent resection is performed immediately after marking under general anesthesia in a hybrid operating room, which further reduces the time window for migration or systemic distribution of lipiodol.

Therefore, while systemic embolic complications such as pulmonary embolism or CNS disorders are theoretically possible, we believe they are highly unlikely with the careful technique and workflow employed in this study.

Minor Comment

1. Does the tumor diameter on CT refer to the whole tumor diameter? Is the required resection depth also calculated based on the whole tumor diameter?

Reply 1: Yes, the tumor diameter on CT refers to the maximum whole tumor diameter, including both solid and ground-glass components if present. The required resection depth was also calculated based on the whole tumor diameter.

2. The marking method states that the absence of air reflux was confirmed, but is it possible for a needle to be inserted into the lung parenchyma without air reflux?

Reply 2: Yes, it is possible. In some cases, when the needle tip is positioned in the alveolar region without direct communication to larger airways, air reflux may not occur even if the needle is correctly placed in the lung parenchyma.

3. Did the authors inject Lipiodol centrally or peripherally around the tumor margin?

Reply 3: Lipiodol was injected peripherally adjacent to the tumor margin while avoiding direct injection into the tumor, to minimize distortion of the tumor–margin relationship and to facilitate accurate localization.

Changes in the text: Injection site details have been clarified in the Marking Technique section (see Page 7, lines 5–7).

4. How are specimens cut when preparing pathological sections?

Reply 4: Specimens were serially sectioned at 5–10 mm intervals along the plane that best included the tumor and the resection margin, in accordance with our institutional pathology protocol.

5. The authors stated that they performed a logistic analysis for factors with a p-value of less than 0.01 in univariate analysis, but isn't this an error of 0.1?

Reply 5: We thank the reviewer for pointing out this error. The correct threshold for inclusion in the multivariate logistic regression analysis was $p < 0.1$, not $p < 0.01$. This has been corrected in the text.

Changes in the text: The p-value threshold has been corrected in the Statistical Analysis section (see Page 8, line 19).

6. The text states that the rate of open thoracotomy was 2.9%, but this is incorrect - it should be 7.9%.

Reply 6: We appreciate the reviewer for catching this error. The correct rate of open thoracotomy was indeed 7.9%, and the manuscript has been revised accordingly.

Changes in the text: The open thoracotomy rate has been corrected in the Results section (see Page 9, line 15).