Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-24-419

Reviewer A

Q1 Overall I am missing the discussion of the risk of operation without malignancy. How many people in the same time period underwent unnecessary surgery.
You mention the risk of TNB numerous times, but the risk of surgery is much higher and we ned to take the unnecessary surgery in mind.

A1
Thank you for your feedback. We agree that the risks of surgical resection for benign tumors should be discussed in the manuscript. We have added a section discussing this.
Regarding unnecessary surgery, a study by Li *et al.* investigated PET/CT's ability to predict lung nodule malignancy. They reported sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of 88% (95%CI: 0.86-0.91), 78% (95%CI: 0.71-0.85), 4.10 (95%CI: 2.98-5.64), and 0.15 (95%CI: 0.12-0.19), respectively.(1) At our institution, we combine preoperative CT, PET/CT, and tumor markers to guide surgical decisions. A retrospective review of 2022 data revealed that 11 out of 423 suspected lung cancer surgeries resulted in benign pathology (2.6%). As diagnostic technology advances, non-invasive methods are expected to become even more accurate.
Regarding postoperative complications, Luca *et al.*'s meta-analysis reported complication rates of 26.7% (135/507) for segmentectomy and 23.2% (255/1100) for lobectomy.(2) Ma *et al.*'s meta-analysis compared robotic-assisted thoracoscopic surgery (RATS) and video-assisted thoracoscopic surgery (VATS), finding complication rates of 30.1% (1510/4890) for RATS and 39.2% (2244/5729) for VATS.(3) Additionally, Li *et al.*'s study compared complications with and without enhanced recovery after surgery (ERAS) following pulmonary resection, reporting rates of 6.5-42.1% in the ERAS group and 13.3-83.3% without ERAS.(4)
These findings suggest that surgical and transthoracic needle biopsy (TNB) complication rates might be comparable, based on existing studies. (19-21) However, patient heterogeneity across studies is likely, and further research is needed to directly compare complication rates between surgery and TNB.

Line 278: These findings suggest that surgical and TNB complication rates might be comparable, based on existing studies. (19-21)

Line 244: Third, this study lacks a controlled comparison of postoperative complication rates for pulmonary resection surgery and TNB procedures. We believe follow-up studies are necessary to address this.

1. Li Y, Shi YB, Hu CF. (18)F-FDG PET/CT based model for predicting

malignancy in pulmonary nodules: a meta-analysis. J Cardiothorac Surg 2024;19:148.
2. Bertolaccini L, Prisciandaro E, Bardoni C, et al. Minimally Invasive Anatomical Segmentectomy versus Lobectomy in Stage IA Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel) 2022;14.
3. Ma J, Li X, Zhao S, et al. Robot-assisted thoracic surgery versus video-assisted thoracic surgery for lung lobectomy or segmentectomy in patients with non-small cell lung cancer: a meta-analysis. BMC Cancer 2021;21:498.
4. Li R, Wang K, Qu C, et al. The effect of the enhanced recovery after surgery program on lung cancer surgery: a systematic review and meta-analysis. J Thorac Dis 2021;13:3566-86.

Q2 You mention that direct surgery can be a way of economic reward by sparing the TNB. Again, this should be held against the amount of surgery without malignant results. Incidental pulmonary nodules will become more and more frequent and the managing of these will become increasing. Studies in a real-world setting have shown that only half of the TNB is malignant. Therefore if all must have primary surgery it will be an ekstra cost and ekstra risk for the patient.

A2
That is a great point. The risk of false negatives is indeed a key limitation of TNB compared to surgery. The economic concern raised in the paper is that false negatives with TNB could lead to the need for surgery later. The rate of unnecessary surgeries for benign nodules is currently low (2.5%, 11/432 at our center), and this is likely to decline further as diagnostic technology improves.

Q3 Further more you mention patients with high risk of malignancy. How do you make this evaluation? Progression on CT? Brock module? Herder module? medical history?

A3.
Thank you for your comment. Imaging evaluation is crucial, and a patient's family history of cancer can also be a significant factor. At our institution, we routinely use PET scans on most suspected lung cancer patients. The metabolic activity on these scans is very helpful in assessing malignancy. Additionally, tumor markers in pleural effusion or blood samples aid in identifying patients at high risk. As mentioned earlier, the development of non-invasive examination technologies is likely to lead to even better prediction of malignancy in the future.

Q4 You have few patients over a 10 year period. How big an area does your hospital cover?
A4.

Thank you for your comment. Our lung cancer surgery volume has increased significantly. In 2010, the year of the study, we performed approximately 200 cases. This number grew to 300 cases in 2020, and by 2022, we had reached approximately 400 primary lung cancer surgeries.

Q5 line 35: Mortality is not increasing (in western country's) treatment is improving, recommend refraining.

A5.
Thank you for your comment. The text was revised as follows.

Line 83: Lung cancer reigns as the world's most common cancer, striking both men and women, and it remains the leading cause of cancer death (1, 2).

Q6 line 46: the risks mentioned are higher with surgery. This point needs recognition.

A6.
Thank you for your comment. Our focus on TNB limitations might have minimized the potential risks of surgery. As mentioned earlier, a key question remains: how do complication rates between TNB and surgery truly compare? To address this, we've added a new point to the discussion section highlighting the need for further research comparing these complication rates in a controlled setting.

Line 278: These findings suggest that surgical and TNB complication rates might be comparable, based on existing studies. (19-21)

Line 244: Third, this study lacks a controlled comparison of postoperative complication rates for pulmonary resection surgery and TNB procedures. We believe follow-up studies are necessary to address this.

Q7 Do you the location of the recurrence?

A7.
Thank you for your comment. In patients with confirmed local recurrence, the table below details the distribution of recurrence sites. We counted all locations for patients with recurrence in multiple areas.
Eleven patients in the no-TNB group experienced confirmed local recurrence of the cancer. This number increased to 18 patients in the TNB group.

Location of local recurrence	No TNB(N=380)	TNB(N=190)
1. Bronchial stump	1	2
2. Parenchymal margin	1	2
3.Ipsilateral mediastinum/lymph node	7	10
4.Ipsilateral pleura	6	4
5.Ipsilateral chest wall	2	2

Q8 The TBN group have lager nodules and more non-adenocarcinoma. both risk factors of recurrence. This needs to be discussed more clearly.

A8.
Thank you for your comment. I agree that this is a crucial aspect of the study. To minimize bias, I implemented 1:2 propensity score matching. This approach ensured well-balanced distributions of cell type and tumor size between the two groups, as shown in Table 2.

19. Bertolaccini L, Prisciandaro E, Bardoni C, et al. Minimally Invasive Anatomical Segmentectomy versus Lobectomy in Stage IA Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel) 2022;14.
20. Ma J, Li X, Zhao S, et al. Robot-assisted thoracic surgery versus video-assisted thoracic surgery for lung lobectomy or segmentectomy in patients with non-small cell lung cancer: a meta-analysis. BMC Cancer 2021;21:498.
21. Li R, Wang K, Qu C, et al. The effect of the enhanced recovery after surgery program on lung cancer surgery: a systematic review and meta-analysis. J Thorac Dis 2021;13:3566-86.

Reviewer B

1. The ethical statement below should be added to the Methods section.
This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Catholic University College of Medicine (No. KC22RISI0761), and individual consent for this retrospective analysis was waived.
A: We added the ethical statement in method section like below.
(Line 193-197)

2.5 Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Catholic University College of Medicine (No. KC22RISI0761), and individual consent for this retrospective analysis was waived.

2. Figures & Tables
1) Figure 1: please define the abbreviation 'Hx' in the figure legend.
A: The word was revied as follows. (Hx, -> History)
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2) Tables 1 and 2: please add a heading to the top left cell.

A: We added the word characteristics and changed the variable in the other table to characteristics

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3) Table 5, please check the value to see if any adjustments should be made.

Table 5. TNB procedure-related complications

Complications	Number	Rate (%)
Pneumothorax (requiring drainage)	41 (9)	21.6 (5.0)
Hemoptysis	6	3.2

229 3.3 TNB-related complications

230 The proportion of patients who developed pneumothorax in the TNB group was 21.6%

231 (N=41), of which 22% (N=9) required air drainage and others required conservative care,

232 such as oxygen supplementation. Hemoptysis was observed in 3.2% (N=6) of patients, and

A: The two numbers have different denominators.
The number in table 5 represents 9/190 (190=PCNB patients), while the number in the text represents 9/41 (41=pneumothorax patients). To reduce misunderstandings, we've added fraction in the main text. In addition, the complication rate that required drainage in Table 5 was revised from 5.0% to 4.7% (4.7%=9/190).

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4) Table 5: please also check the summarized percentages.

Death	0	0
Total	50	26.3

TNB, transthoracic needle biopsy

A: This number represents the percentage of patients who suffered a complication in patients who underwent PCNB. (50/190 = 26.3%)

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3. As authors mention previous studies, please check if any reference should be cited to this sentence.

109 The degree of visceral pleural invasion was an important factor mentioned numerous times in

110 previous studies that compared oncologic outcomes due to TNB. According to the Modified

111 Hammar Classification of visceral pleural invasion, a PL0 tumor is one within the subpleural

A: As shown below, the reference was updated
(Line102-104)
The degree of visceral pleural invasion was an important factor mentioned numerous

times in previous studies that compared oncologic outcomes due to TNB (10-12).