

Peer Review File

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Reviewer A

The authors report a retrospective study on 221 patients undergoing CT-guided biopsy of "tumor-like" lung lesions with a focus on complication rates and prognostic factors. This is a well-done study that should be a general interest to the JTD readership. There are a number of minor grammatic/stylistic errors appropriate for editorial modification, but I have not changes to the substance of the manuscript.

Thank you for your time to review and give feedback to our study. We appreciate it.

Reviewer B

The topic of the paper is interesting and relevant.

The text is written in good English.

The paper is well structured, the aims and purposes are clearly explained.

The authors also acknowledge the limitations of this study (retrospective, no control group)

The results are in line with other previously published studies. Therefore, the study data confirm what we know about this issue

Thank you for your input, your time to review and briefly summarize our study. We appreciate it.

Reviewer C

This study retrospectively evaluated the risk factors for major complications associated with CT-TTNB. In this study, the authors have demonstrated that the tumors with a distance from chest wall to tumor edge of more than 20mm and skin to tumor edge of more than 40mm, and the tumors with a diameter less than 2cm were associated with a higher risk of pneumothorax complication. The knowledge on the risk factors of pneumothorax during CT-TTNB is indispensable for clinicians. The results are easy to understand but I found some limitations. My comments are as follows:

Major:

1. So far, many investigators have indicated the risk factor of pneumothorax, such as a smaller and deeper target, the presence of emphysema, the presence of smoking history, lesions without pleural contact, the angle of trajectory to the pleura and the use of large-bore biopsy needles. The large limitation of this study is that the findings were resulted from univariate but not multivariate analysis.

We've tried to perform the multivariate analysis, please see the following text and table.

The results of multivariate logistic regression analysis in Table 5 showed that the most

important prognostic factor of pneumothorax was the Skin-Tumor Edge Distance (CI95% Coef: 0.127 – 0.289; $p < 0.0001$). Another factor that was significant in the multivariate model was tumor size ($p = 0.039$). These factors were further analyzed by the Area under the ROC curve to determine a specific cutoff in predicting complications.

Table 5 Multivariate regression of prognostic factors for pneumothorax complications

Distances	Coef. [95% CI]	z	p-value
Skin - chest wall distance	-0.071 [-0.141 – (-0.000)]	-1.99	0.05
Skin - tumor edge distance	0.208 [0.127 – 0.289]	5.09	<0.0001
Skin - tumor center distance	0.168 [-0.018 – 0.355]	1.77	0.078
Chest wall - tumor center distance	-0.109 [-0.297 – 0.077]	-1.16	0.249
Tumor size	-0.075 [-0.148 – (-0.003)]	-2.07	0.039

We have modified our text as advised (please see page 13, line 218 to line 223)

2. Please describe the details of CT-TTNB procedures (which needles, which CT, operators, use of ROSE, specimen handlings, number of punctures, etc.).

CT-guided transthoracic needle biopsy procedure:

All biopsies were performed by using our 32-slide conventional CT machine (Siemens). Operators (T.B.N and T.N.A.T) were both qualified for the procedures. To enable the shortest path for lung biopsy, patients were positioned either prone or supine, depending on the location of the lesion. CT images were acquired from the apex of the lungs to the diaphragm in order to identify the pulmonary lesion at the end of inspiration. The center of the lesion was determined at the CT landmark by placement of a radiopaque skin grid onto the patient's skin. A second set of CT images were acquired, and the location of the puncture point was identified by measuring the distance between the skin surface and the pleura, the length of the needle path, and the minimum angle formed by the vertical line and the needle. Routine disinfection and draping was carried out after marking the body surface puncture site, with the puncture site positioned at the center. Subsequently, the chest wall was anesthetized layer by layer using 2% lidocaine. After local anesthesia, all biopsies were performed with a 18- or 20-gauge semi-automatic biopsy needle with coaxial (GSN1815/GSN2015, Geotek Medical, Figure 1). An initial puncture was done without piercing the pleura. After this, CT scans were acquired to locate the exact position of the biopsy needle tip, and biopsies were performed while trying to avoid piercing the ribs, bullae, blood vessels, and fissures. If the lesion was located along the extended path of the needle track, the biopsy procedure was continued; otherwise, the site of puncture point was changed. Prior to rapidly advancing the needle towards the identified lesion, the patient was instructed to hold the breath. Subsequently, a CT scan was done immediately to verify that the

needle tip has successfully reached the intended lesion. Then, sampling using the aforementioned semi-automatic biopsy gun was performed. Because our institution were a sub-urban hospital, we did not have Rapid Onsite Evaluation (ROSE) available in our institution, so around 4 to 8 tissue cores were obtained during the biopsy to facilitate further histopathologic diagnosis, molecular and immunohistochemistry analyses. Specimens were immediately immersed in 10% formalin solution and were sent to the pathologist for examination. Routine CT scan was performed right after the procedure to promptly identify any possible complications, such as pneumothorax, hemothorax...

We have modified our text as advised (please see page 10/line 148 to page 11/line 172)

3. Inclusion and exclusion criteria: Are the inclusion and exclusion criteria for CT-TTNB in your institution, or for this study?

This is the inclusion and exclusion criteria for CT-TTNB in our institution, mainly based on the Guidelines For Percutaneous Transthoracic Needle Biopsy from ATS, published in 1988.

We have modified our text as advised (please see page 9/line 132-133)

4. Line 108, "Bronchoscopy was the primary procedure for all patients."

Please describe the details of the indications of CT-TTNB related to the bronchoscopy results (How many patients underwent bronchoscopy? How many underwent biopsy? How many had non-diagnostic results, etc.). Please add the patient flow of the 221 patients.

Bronchoscopy was the primary procedure for all patients. All patients with pulmonary tumor lesions on CT will be indicated for bronchoscopy. Bronchoscopic biopsy procedures include intrabronchial biopsy if tumors are seen, or blind transbronchial biopsy. After bronchoscopy, if no visible lesions that can be biopsied, no sample were collected, or the pathological results after biopsy are not consistent with the clinical presentation, we will conduct a consultation for the indication for transthoracic needle biopsy. The patients and their family received a detailed explanation of the transthoracic biopsy procedure, as well as the potential complications that may happen, such as pneumothorax, chest tube drainage if needed, hemorrhage, hemoptysis, and air embolism. Subsequently, the patients were requested to provide their signature on a written consent form, reaffirming their well-informed decision regarding the procedure. From this, we retrospectively review 221 patients in this study.

We have clarified this details as advised (please see page 9/line 135 to page 10/line 147).

5. Lines 133-134, "The first-attempt sample collection rate is 95%, and 11 patients needed a second attempt at sample collecting."

Does it mean 95% of patients terminated the CT-TTNB procedure after the first pass? If not, please describe the mean puncture number per patient.

Yes, it means that 95% of patients terminated the CT-TTNB procedure after the first pass.

Minor:

1. Please confirm the location of “Tables” in the main document. For example. “Table 2” in line 134 seems to be “Table 1,” and Table 3” in line 139 seems to be “Table 2.”

We have modified our text as advised, please see

- Page 11, line 190, line 194, line 200 and line 207
- Page 12, line 217, line 223, line 226 and line 231
- Page 13, line 234, line 239, line 242, line 245, line 248 and line 251

2. Line 150-151, “Similarly, of the 93 patients in the more-than-40 mm group, the rate of pneumothorax is 54.8%; in the less-than-40 mm group, that rate is only 7.2% with $p < 0.0001$.” Please describe this is the data on the skin to tumor edge distance.

We have modified our text as advised (please see page 13, line 212)