

Efficacy of Percutaneous Direct Puncture Biopsy of Malignant Lung Tumors Contacting to the Pleura

HIROSHI KODAMA, HARUYUKI TAKAKI, JUNICHI TANIGUCHI, ATSUSHI OGASAWARA,
YASUKAZU KAKO, KAORU KOBAYASHI and KOICHIRO YAMAKADO

Department of Radiology, Hyogo Medical University, Nishinomiya, Japan

Abstract. *Background/Aim: This is a retrospective evaluation of whether percutaneous direct puncture biopsy of lung lesions contacting to the pleura is justified. Patients and Methods: Between August 2016 and July 2021, 163 consecutive patients (100 males, 63 females with a median age of 73 years) who had malignant lung tumors measuring 0.6-12.4 cm (median, 2.9 cm) that contacted to the pleura and underwent percutaneous lung biopsy under computed tomography fluoroscopic guidance using an 18-gauge end-cut needle were examined. The trajectory was direct puncture in 80 patients (49.1%, 80/163), and trans-lung in 83 patients (50.9%, 83/163). Diagnostic yield and major adverse event rates of direct and trans-lung puncture biopsies were compared. Results: No difference was found in diagnostic yield between direct puncture and trans-lung biopsies (93.8% vs. 98.8%, $p=0.11$). Major adverse events were major pneumothorax ($n=13/163$, 8.0%), pleural dissemination ($n=18/163$, 11.0%), and hemothorax requiring arterial embolization ($n=1/163$, 1.0%). Direct puncture caused major pneumothorax significantly less than trans-lung puncture did (0%, 0/80 vs. 15.7%, 13/83, $p<0.001$). No significant difference was found between the two biopsy methods regarding the incidence of pleural dissemination (11.0%, 11/80 vs. 8.4%, 7/83, $p=0.32$). Conclusion: Direct puncture biopsy of malignant lung tumors contacting to the pleura is justified.*

Correspondence to: Hiroshi Kodama, MD, Department of Radiology, Hyogo Medical University, Mukogawa 1-1, Nishinomiya, Hyogo, Japan. Tel: +81 798456362, Fax: +81 798456361, e-mail: hi-kodama@hyo-med.ac.jp

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As a reliable and safe procedure for the diagnosis of lung lesions, computed tomography (CT)-guided lung biopsy is widely accepted. The most frequent adverse event (AE) is pneumothorax. Pneumothorax requiring chest tube placement develops in approximately 7% of patients (1-3). Although rare, severe AEs including hemothorax, air embolism and tumor seeding might occur (2). Several reported risk factors related to major pneumothorax are the presence of emphysema, no pleural contact of the target tumor, and longer needle passage within the aerated lung tissue (1, 4, 5). Therefore, direct puncture through the pleura without passing the lung might mitigate the risk of pneumothorax. Direct puncture of malignant tumors might increase the risk of pleural tumor dissemination because subcapsular location has been reported as a risk factor of tumor dissemination when radiofrequency ablation is applied to liver tumors (6). Nevertheless, no consensus has been reached on whether direct puncture of malignant tumors contacting the pleura decreases the risk of pneumothorax and increases the risk of tumor dissemination.

This retrospective study was conducted to evaluate whether percutaneous direct puncture biopsy is justified in malignant lung tumors contacting to the pleura.

Patients and Methods

Study design. This single center retrospective study was approved by our institutional review board. A waiver of written informed consent of enrollment in the study was obtained. All patients provided informed consent to percutaneous lung biopsy.

Patients. Between August 2016 and July 2021, 279 consecutive patients underwent CT-guided percutaneous lung biopsy. A total of 116 patients were excluded because target lesions did not contact to the pleura in 81 patients (29.0%, 81/279), lesions were benign in 30 patients (10.8%, 30/279), and 5 patients (1.8%, 5/279) had pleural tumor dissemination at the time of biopsy.

This study included 163 patients (58.4%, 163/279) with malignant tumors contacting the pleura (Figure 1): 100 men (61.3%, 100/163) and 63 women (38.7%, 63/163). Their median age was 73 years (range=32-91 years). Diagnosis of malignancy was established



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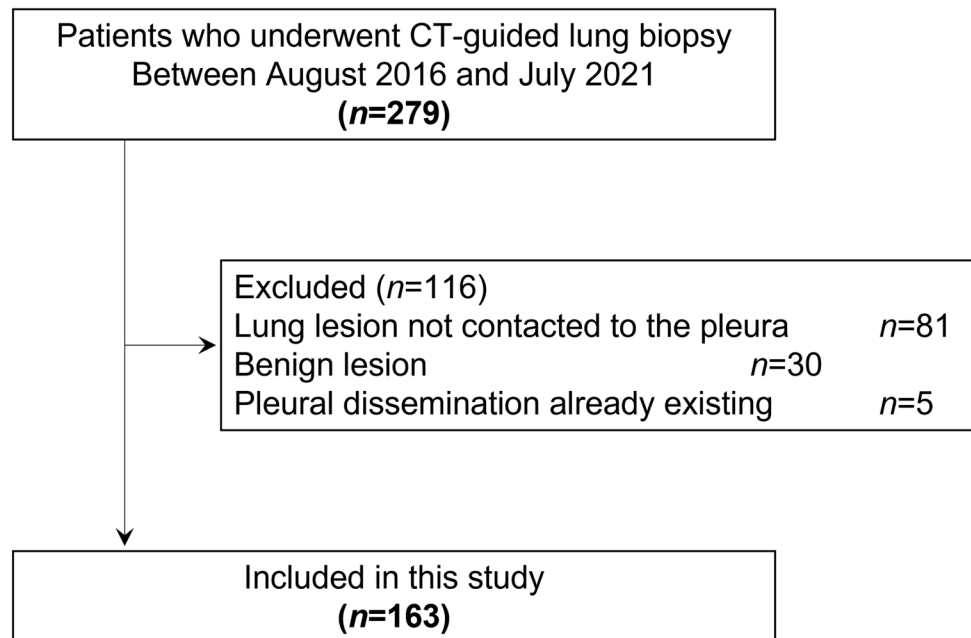


Figure 1. Flowchart of patient inclusion.

by biopsy in 158 patients (96.9%) and by follow-up image findings in 5 patients (3.1%). Even when the biopsy result was benign, when the target lung lesion became larger on serial CT images, the final diagnosis was “malignant”.

The tumor diameters were 0.6–12.4 cm (median, 2.9 cm). The lengths of contact to the pleura were 0.4–15.5 cm (median, 2.4 cm).

CT-guided lung biopsy. All CT-guided biopsies were performed under local anesthesia by six interventional radiologists (blinded for review) using CT fluoroscopic guidance. An 18-gauge end-cut full core biopsy needle (Biopince; Argon Medical Devices Inc., Plano, TX, USA) was used. The patient position during the procedure, the biopsy trajectory, and the number of punctures were decided by the operator based on the tumor location or gross evaluation of obtained tissue. The patient position during biopsy was supine in 84 patients (51.5%, 84/163). Most patients (86.5%, 141/163) underwent biopsy with multiple puncture numbers of 2–9. Immediately after the biopsy, CT scanning was performed. Adverse events including pneumothorax, bleeding, and air embolism were evaluated.

Patients were divided into two groups based on the biopsy trajectory. Biopsy was performed by puncturing the tumor from the contacting pleura in 80 patients (direct puncture group), and by passing the normal lung in 83 patients (trans-lung group). The median trajectory length through the aerated lung was 1.6 cm (range=0.2–6.8 cm) in the trans-lung group. Patients’ backgrounds are presented in Table I. The tumor diameter (4.1 cm vs. 2.4 cm, $p<0.001$) and pleural contact length (3.9 cm vs. 1.8 cm, $p<0.001$) were significantly longer in the direct puncture group. Biopsy was performed in the prone position more frequently (57.5%, 46/80 vs. 39.8%, 33/83, $p=0.03$). More patients of the direct puncture group underwent multiple punctures than patients of the trans-lung group (93.7%, 75/80 vs. 80.5%, 66/83, $p=0.01$).

Follow-up. Patients were followed up with chest X-ray 3 h after biopsy, then routine physical examination, laboratory tests, and chest CT were performed every 1–6 months thereafter. The median follow-up period was 17.2 months (range=1–65 months).

Assessment. The diagnostic sensitivities of direct puncture and trans-lung biopsy were calculated and then compared. AEs that increased the level of care, or which resulted in hospital admission, or which markedly lengthened the hospital stay were classified as major AEs (Society of Interventional Radiology classifications C–E) (7). The AEs were evaluated using medical records. Then the rates of AEs of the two groups were also compared.

Statistical analysis. Univariate analysis was performed using the Mann–Whitney *U*-test for continuous variables and Fisher’s exact test for nominal variables. For multivariate analysis, multiple linear regression analysis was used. Factors that might affect major AEs, including patient background, tumor characteristics and procedural details, as presented in Table I, were assessed using multivariate analysis. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (8). A *p*-value of less than 0.05 was inferred as a statistically significant result.

Results

Diagnostic sensitivity. Malignancy was found in 75 out of 80 tumors (93.8%) using direct puncture biopsy and in 82 out of 83 (98.8%) using trans-lung biopsy. No significant difference in sensitivity was found between the two biopsy methods ($p=0.11$).

Table I. Patient background, tumor characteristics, and procedure details.

	Direct puncture	Trans-lung	<i>p</i> -Value
Patient background			
Patient number	80	83	
Age (years)			0.83
Median	73	73	
Range	32-90	32-91	
Sex			0.26
Male	53 (66.3%)	47 (56.6%)	
Female	27 (33.7%)	36 (43.4%)	
Emphysema			0.002
Yes	45 (56.3%)	26 (31.3%)	
No	35 (43.7%)	57 (68.7%)	
Tumor characteristics			
Lesion diameter (cm)			<0.001
Median	4.1	2.4	
Range	(0.9-12.4)	(0.6-6.7)	
Pleural contact length (cm)			<0.001
Median	3.9	1.8	
Range	(0.6-15.5)	(3.7-10.5)	
Laterality			0.64
Left	46 (57.5%)	45 (54.2%)	
Right	34 (42.5%)	38 (45.8%)	
Procedure details			
Patient position			0.03
Supine	34 (42.5%)	50 (60.2%)	
Prone	46 (57.5%)	33 (39.8%)	
Puncture number			0.007
Median	2	2	
Range	(1-9)	(1-5)	
Single	5 (6.3%)	17 (20.5%)	0.01
Multiple	75 (93.7%)	66 (80.5%)	

Safety. Major AEs were pneumothorax requiring chest tube placement in 13 patients (8.0%, 13/163) (Figure 2), pleural tumor dissemination in 18 patients (11.0%, 18/163) (Figure 3), and hemothorax requiring arterial embolization in one patient (0.6%, 1/163) (Table II). Tumor dissemination developed 2.3-37.0 months (median, 6.7 months) after biopsy.

All occurrences of major pneumothorax developed after trans-lung biopsy (13.8%, 13/83). A significant difference was found in the incidences of major pneumothorax between the direct puncture (0%, 0/80) and trans-lung (13.8%, 13/83, $p<0.001$) groups (Table II). Multivariate analysis also indicated that trans-lung approach was the only significant risk factor affecting major pneumothorax ($p=0.004$).

Regarding the frequency of pleural tumor dissemination, no significant difference was found between the direct puncture group (13.6%, 11/83) and the trans-lung group (8.4%, 7/80, $p=0.33$) (Table II). No significant factor was identified from multivariate analysis as affecting pleural tumor dissemination.

Incidences of major hemothorax were not significantly different between direct puncture (1.3%, 1/80) and trans-lung (0%, 0/83, $p=0.49$).

Discussion

Results of this study indicate that direct puncture biopsy through the pleura provides no different diagnostic sensitivity from that provided by trans-lung biopsy. Earlier studies have demonstrated the diagnostic sensitivities of CT-guide lung biopsy as 71%-100% (pooled sensitivity, 92%) (9), which is comparable to our results. One earlier study with a small sample size indicated the sensitivity of direct puncture biopsy (4/8, 50.0%) as significantly lower than that of trans-lung biopsy (8/8, 100%) (10). In other studies, short needle trajectory length in the aerated lung (<1.0 cm), which is similar to direct puncture, was also reported as a significant factor associated with low diagnostic accuracy in patients with subpleural lesions (11,

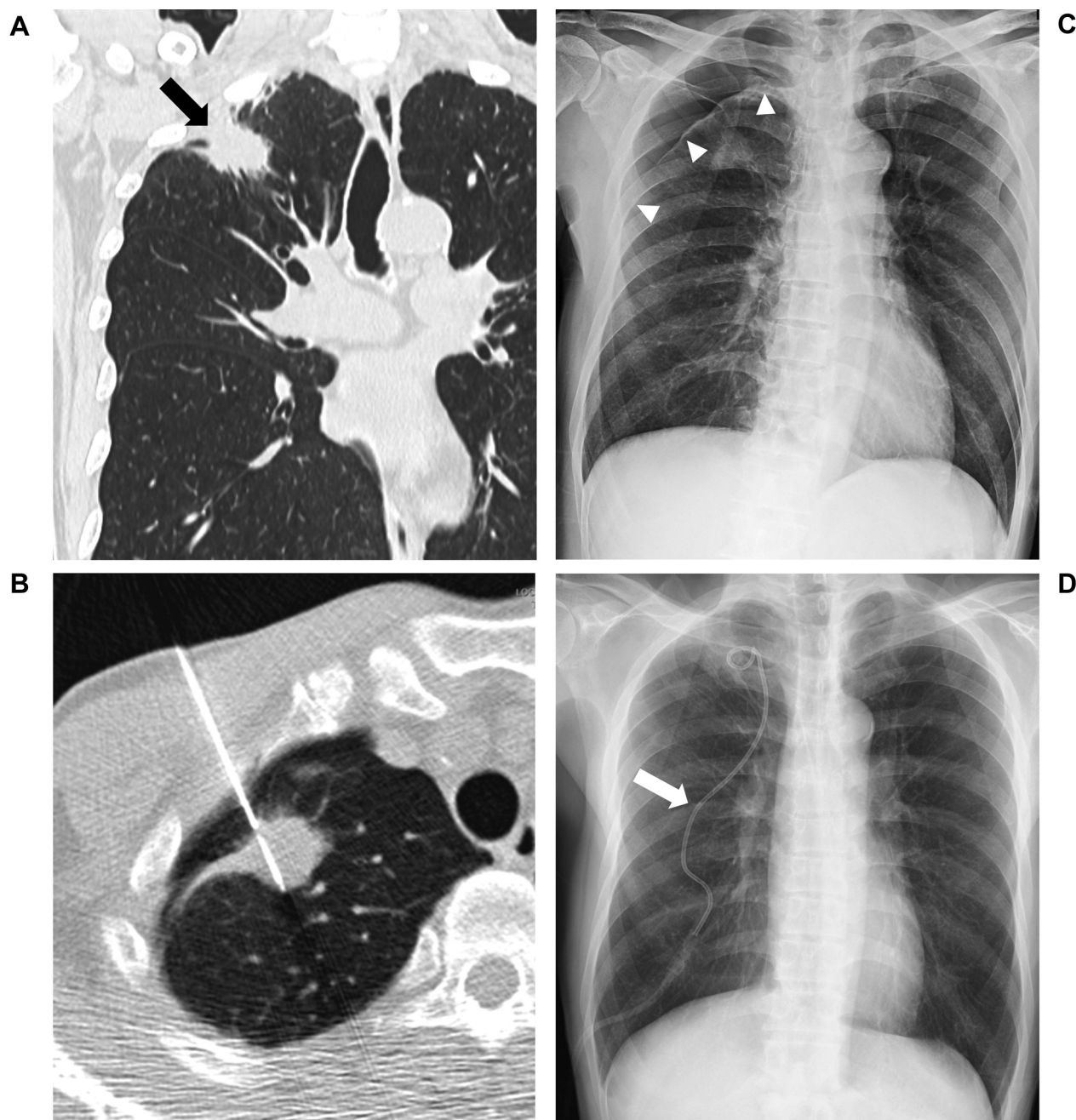


Figure 2. Major complication of pneumothorax. (A) Coronal CT image shows a 2.8 cm spiculated nodule contacting the pleura with 1.2 cm length (black arrow). (B) CT-guided biopsy was performed through the aerated lung parenchyma. (C) Chest X-ray 3 h after biopsy revealed pneumothorax (white arrowheads). (D) Pneumothorax was treated by using chest tube placement (white arrow).

12). In contrast to those earlier reports, no significant difference was found in diagnostic sensitivity in our study. Similar results were also reported by Iguchi *et al.* with relatively smaller sample size compared to this study (13). Earlier studies have attributed low diagnostic sensitivity of short trajectory biopsy to easier dislocation of a guiding

needle because needle movement in the short trajectory is influenced more by breathing and pneumothorax than needle movement in the long trajectory. We performed all procedures under real-time CT fluoroscopy and obtained tissue samples after confirming that the biopsy needle tip is in the target tumor.

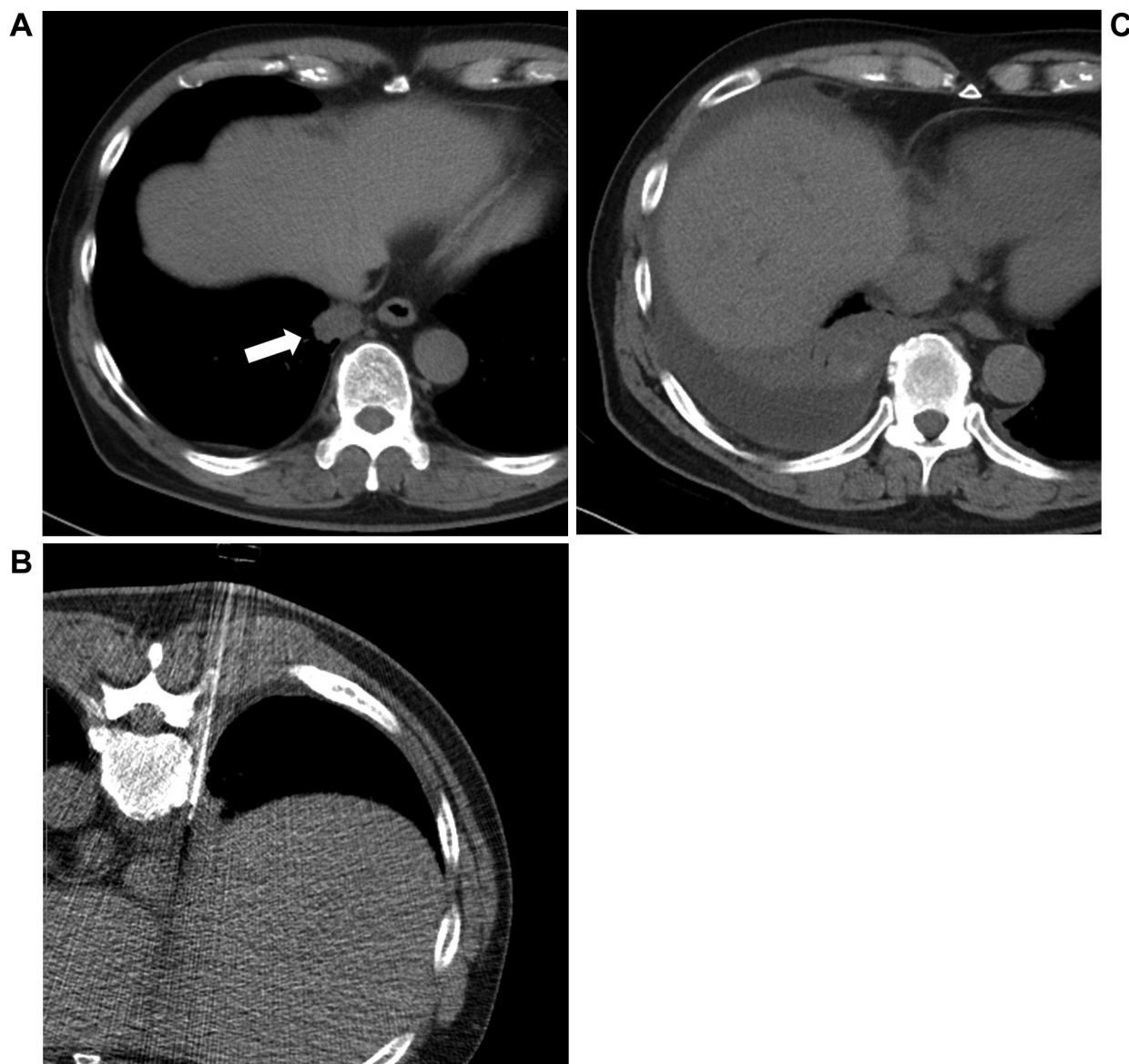


Figure 3. Major complication of pleural dissemination. (A) Axial CT image shows a 2.3 cm nodule contacting the pleura with 2.5 cm length (white arrow). (B) CT-guided biopsy was performed directly through pleura. The nodule was diagnosed histologically as lung adenocarcinoma. (C) Follow-up CT 6 months after biopsy showed emerging pleural effusion (white arrowheads). Adenocarcinoma cells were detected by pleural fluid cytology.

Particularly for this study, it is noteworthy that direct puncture biopsy reduces the risk of major pneumothorax without increasing the risk of pleural tumor dissemination same as the previous reports (13). The incidence of major pneumothorax in this study was 8.0%, which is almost identical to findings of earlier studies (0%-15%, pooled incidence rate, 7%) (1). Several risk factors reported as affecting major pneumothorax after lung biopsy include lack of pleural contact to the lesion, the presence of emphysema, needles larger than 18-gauge, needle puncture crossing a fissure, and the patient's

position of puncture site up (1, 4, 5). Results of both univariate and multivariate analyses in this study showed only the trans-lung approach as a significant risk factor.

Management of pleural dissemination can be challenging. The patient's quality of life or survival might be affected strongly by the disease (14-16). Any technique that might increase the risk of pleural dissemination should be avoided if possible. Therefore, this study was conducted to ascertain whether percutaneous direct puncture biopsy increases the risk of pleural dissemination, or not.

Table II. Major adverse events after biopsy.

	Pneumothorax	Pleural dissemination	Hemothorax
Total (n=163)	13 (8.0%)	18 (11.0%)	1 (0.6%)
Direct puncture (n=80)	0 (0.0%)	11 (13.8%)	1 (1.3%)
Trans-lung (n=83)	13 (15.7%)	7 (8.4%)	0 (0.0%)
p-Value	<0.001	0.32	0.49

The incidence of pleural dissemination after percutaneous lung biopsy has been reported to be as low as less than 0.1% (2, 17). Compared to findings presented in earlier reports, the 11.0% finding of our study was quite high. Lung biopsy increases the risk of pleural recurrence after surgery. The 5-year pleural recurrence rate increased from 2.6% to 18.3% when patients underwent percutaneous lung biopsy before surgery (18). One meta-analysis has shown the pooled odds ratio of pleural recurrence after percutaneous lung biopsy to be as high as 10.76 for patients with sub-pleural lesions, and as high as 0.96 for patients without sub-pleural lesions (19). In addition to the influence of biopsy, there might be a latent pleural disease caused by the tumor itself. Malignant pleural disease has been found unexpectedly during thoracotomy in 0.9%-4.5% of patients with primary lung cancer (18-20). When lung cancer is adjacent to the visceral pleura, its incidence increases to 4.8% (21). Our study found that pleural tumor dissemination occurs either after trans-lung or direct puncture biopsy at the same frequency. Pleural tumors can disseminate from the lung biopsy because tumor cells are carried directly into the pleural space when the biopsy needle passes through the puncture route. The use of a small diameter needle with co-axial system might reduce the incidence of pleural tumor dissemination, even in patients with tumors contacting the pleura. When lung biopsy was performed using a 20-gauge or 19-gauge co-axial needle before surgery, no significant increase was found in the positive pleural lavage cytology rate during thoracotomy compared to that in patients who did not undergo biopsy (20).

Major hemothorax is also a rare complication after percutaneous lung biopsy. The rate was reported to be less than 0.1% (2, 21). Only one patient (0.6%, 1/163) in this study experienced major hemothorax after undergoing direct puncture biopsy. The main cause of hemothorax is usually injury by puncture of an intercostal artery or internal mammary artery. If the lung tumor invades the chest wall, then vessels of the chest wall, including the intercostal artery and internal mammary artery, might develop more than usual. Preprocedural CT images should be used to confirm the arteries in the planned biopsy trajectory. Also, care should be taken to avoid hemothorax.

This study has several noteworthy limitations. First, this is a retrospective single center study. Second, few patients

experienced an event of pleural dissemination and hemothorax. Third, no proof was found that pleural dissemination occurred because of the biopsy.

Conclusion

Direct puncture of the target lesion reduces the major pneumothorax rate significantly. Moreover, it does not increase the risk of tumor or bacterial pleural dissemination in lung lesions contacting to pleura.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Hiroshi Kodama, Haruyuki Takaki, and Koichiro Yamakado contributed substantially to the conception or design of the work. Hiroshi Kodama, Junichi Taniguchi, Atsushi Ogasawara, Yasukazu Kako and Kaoru Kobayashi contributed substantially to the acquisition, analysis, and interpretation of data. All Authors contributed to drafting the work or revising it critically for important intellectual content, and approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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