Implications of Preoperative Transbronchial Lung Biopsy for Non-small Cell Lung Cancer Less than 3-cm

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Abstract. *Background/Aim: Transbronchial lung biopsy (TBLB) has been recommended for patients with suspected lung cancer. However, its diagnostic value is limited to small lesions, and some studies have indicated that biopsy might be related to metastasis and/or dissemination. This study aimed to evaluate the outcomes after preoperative TBLB for non-small cell lung cancer (NSCLC) patients. Patients and Methods: Data were reviewed from 371 patients with resected pN0 NSCLC less than 3-cm. Patients were divided into two groups: TBLB and Non-TBLB. Recurrence-free survival (RFS) curves were plotted using the Kaplan-Meier method. Cox regression analyses were used to evaluate the hazard ratio (HR) with the endpoint RFS. Results: The 5-year RFS rates were 75.5% in the TBLB group and 91.4% in the Non-TBLB group (p<0.001). Poor RFS was independently associated with TBLB (HR=2.491, 95%CI=1.337-4.640; p=0.004). Conclusion: Preoperative TBLB may adversely affect RFS among NSCLC patients with small size tumours.*

Lung cancer remains the leading cause of cancer and its related mortality worldwide, and early diagnosis and surgical resection are essential for improving outcomes (1, 2). For example, the 5-year overall survival rates are 66-82% among patients with early-stage non-small cell lung cancer (NSCLC) (3). Lung cancer screening programs using low-dose computed tomography (CT) can help detect small lung nodules (4), although it can be difficult to accurately diagnose these small lesions using medical imaging techniques, such as positron emission tomography/CT. Therefore, biopsy is important for identifying lung cancer and confirming the diagnosis.

Transbronchial lung biopsy (TBLB) using flexible fibreoptic bronchoscopy (FFB) has been recommended for all patients with suspected lung cancer (5). TBLB is useful for visible endobronchial and central lesions, with an overall sensitivity of approximately 85% (5, 6). However, its diagnostic performance for small peripheral lesions is limited (sensitivity of 60-70%) (7, 8), and its sensitivity may even be as low as 56% for nodules that have a diameter of <20 mm (9). Furthermore, because of misdiagnosis due to unsuccessful biopsy, treatment delays can be associated with disease progression and poorer survival outcomes (10, 11). On the other hand, several studies have indicated that biopsy may even be related to metastasis and/or dissemination (12, 13). In general, nodules that harbour cancerous potential should undergo biopsy or surgical removal (14). Recently, the video-assisted thoracoscopic surgery (VATS) technique has provided a minimally invasive strategy for the diagnosis or therapeutic excision of small pulmonary nodules (15, 16). Our clinical question is whether omitting preoperative TBLB is appropriate for patients suspected of NSCLC, especially with a pulmonary nodule of less than 3-cm. This study evaluated the outcomes after preoperative TBLB among patients with pN0 NSCLC less than 3-cm.

Patients and Methods

This retrospective study evaluated data from 891 consecutive patients who underwent resection of NSCLC at Nara Medical University Hospital, Nara, Japan, between January 2010 and December 2016. We ultimately identified 371 patients with pathologically diagnosed N0 NSCLC with a less than 3-cm tumour infiltration diameter, which had been treated using complete resection (lobectomy). The T classifications were assigned based on the eighth edition of the TNM staging system (17). The exclusion criteria were: presence of other concomitant malignant diseases and

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Table I. *The patients' clinicopathological characteristics.*

	TBLB (n=104)	Non-TBLB (n=267)	*p*-Value
Age: <70/≥70 years	46/58	137/130	0.248
Gender: Male/Female	63/41	147/120	0.353
CT findings: Pure GGN/Others	7/97	84/183	<0.001*
Location: Peripheral/Others	82/22	218/49	0.558
pT descriptor: Tmin/T1a/T1b/T1c/T2 or more	0/5/27/49/23	13/27/121/75/31	<0.001*
Invasive size of the tumour (cm)	2.22±0.55	1.82±0.67	
≤2 cm/>2 cm	38/66	176/91	<0.001*
Histology:			0.005*
Adenocarcinoma	73	224	
Squamous cell carcinoma	20	34	
Others	11	9	
EGFR mutation:			
Yes/No/Unknown	24/56/24	15/168/84	<0.001*
Histological grade:			0.001
1	23	110	
2 or more	81	157	
PL: Present/Absent	23/81	31/236	0.014*
LY: Present/Absent	49/55	58/209	<0.001*
V: Present/Absent	43/61	53/214	<0.001*
Adjuvant chemotherapy: Yes/No	27/77	32/235	0.001*
Preoperative CEA			0.484
<5 ng/ml/≥5 ng/ml	79/25	212/55	
Time from point out to surgery			0.741
<60 days/≥60 days	16/79	35/191	
Death	10	12	0.084
Recurrence	25	18	<0.001*

TBLB: Transbronchial lung biopsy; CT: computed tomography; GGN: ground glass nodule; PL: pleural invasion; LY: lymphatic vessel invasion; V: vascular invasion; EGFR: epidermal growth factor receptor; CEA: carcinoembryonic antigen. *statistically significant.

determination of NSCLC based on intraoperative needle biopsy or preoperative percutaneous needle biopsy (*e.g.*, computed tomography-guided lung biopsy). The 371 patients were categorized according to whether preoperative TBLB using FFB was done (104 patients) or not done (267 patients). The study's retrospective protocol was approved by our institutional review board (no. 1634), which waived the requirement for informed consent based on the retrospective analysis of de-identified patient data.

The 3-port VATS technique was used to resect the lung cancers. Follow-up examinations were symptom-oriented, although all patients completed medical check-ups and chest radiography at least twice per year and whole-body CT scans at least once per year. The observation period began on the day of the operation and was terminated on December 31, 2018 for surviving patients.

Differences between the TBLB and non-TBLB groups were evaluated using the chi-squared test or Fisher's exact test, as appropriate. The Kaplan-Meier method and log-rank test were used to compare the curves for overall survival and recurrence-free survival. Univariate and multivariate Cox regression analyses were also used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the survival outcomes. Multivariate analysis was performed using the backward stepwise method with all of the entry factors. All *p*-values were two-sided and differences were considered statistically significant at *p*-values of <0.05. All analyses were performed using the EZR plugin for R commander (version 1.33; Saitama, Japan).

Results

The present study included 104 patients in the TBLB group and 267 patients in the non-TBLB group. The median follow-up period was 49 months (range=1-102 months). Table I shows the patients' clinicopathological characteristics. The TBLB group had significantly higher values for pT classification, epidermal growth factor receptor (*EGFR*) mutation, high-grade cancers, and non-pure ground-glass nodules (GGNs) on CT.

During the observation period, NSCLC recurrence was identified in 25 patients from the TBLB group and 18 patients from the non-TBLB group. Death was identified for 10 patients from the TBLB group and 12 patients from the non-TBLB group. The 5-year overall survival rates were 88.5% in the TBLB group (95%CI=79.4-93.7%) and 94.7% in the non-TBLB group (95%CI=90.1-97.2%) (*p*=0.056) (Figure 1). The 5-year recurrence-free survival rates were 75.5% in the TBLB group (95%CI=63.8-83.9%) and 91.54 in the non-TBLB group (95%CI=85.6-94.9%) (*p*<0.001) (Figure 2).

In the univariate analyses, recurrence was associated with male gender, Non-pure GGN, histological grade 2 or 3 disease (non-lepidic adenocarcinoma), pathological tumour invasion (>2 cm), pleural invasion, vascular invasion, lymphatic vessel
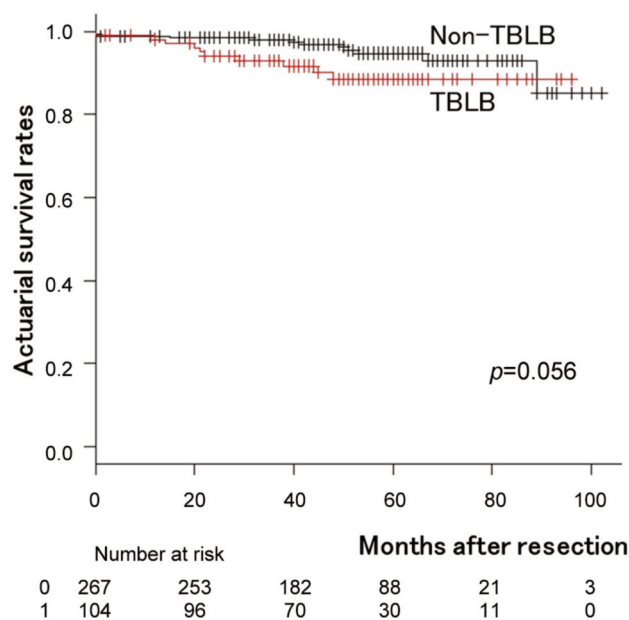
Figure 1. *Overall survival curves for all patients according to transbronchial lung biopsy (TBLB). The 5-year overall survival rates were 88.5% in the TBLB group and 94.7% in the Non-TBLB group (p=0.056).*
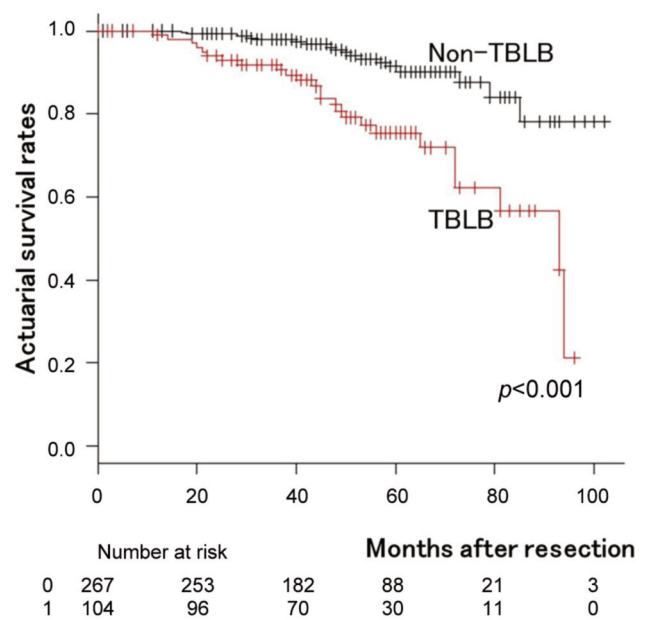

Figure 2. *Recurrence-free survival curves for all patients according to transbronchial lung biopsy (TBLB). The 5-year recurrence-free survival rates were 75.5% in the TBLB group and 91.4% in the Non-TBLB group (p<0.001).*

invasion, and preoperative TBLB. In the multivariate analyses, recurrence was independently predicted by TBLB (HR=2.491, 95%CI=1.337-4.640; *p*=0.004) (Tables II and III).

Discussion

The present study revealed that preoperative TBLB was associated with significantly poorer RFS among patients with small (<3 cm) pN0 NSCLC. Furthermore, preoperative TBLB independently predicted recurrence. We have previously reported similar results after complete resection of all-stage NSCLC (13). The present study focused on pN0 NSCLC less than 3-cm diameter. Among patients with small lung nodules, TBLB tents to be unsuccessful in diagnosis and delay treatment, which may lead to an unfavourable prognosis.

Furthermore, several studies have demonstrated that preoperative TBLB might be related to poorer survival outcomes, relative to patients who do not receive TBLB before undergoing resection of NSCLC. That is the reason why TBLB can relate to the high incidence of spreading of tumour cells (18). Several reports have indicated that TBLB can lead to needle tract seeding (12). Additionally, previously studies have reported that acute infection can also be associated with tumorigenesis due to TBLB using FFB (13, 19, 20). This present study revealed that preoperative TBLB is associated with an increased risk of recurrence after surgical intervention treatment of NSCLC less than 3-cm.

Preoperative imaging diagnosis is becoming increasingly common. However, with the CT criteria, it is hard to confidently differentiate small malignant pulmonary nodules from benign ones. Qi *et al*. (15) reported 5 misdiagnosed pulmonary nodules with the size of 20 mm or less among 34 nodules. Therefore, histopathological diagnoses have become the vital step in the management of pulmonary nodules. However, the reported diagnostic yield using TBLB is rather low. A small pulmonary nodule leads to this dilemma for clinicians. Deppen *et al*. (21) suggested that patients who have a greater than 65% likelihood of cancer should be recommended for a VATS biopsy. The present study's findings suggest that omitting preoperative TBLB may be appropriate for highly suspected NSCLC, especially when the suspected lesion is small (<3 cm). This strategy of omitting preoperative TBLB may help provide better outcomes not only through preventing dissemination of tumour cells due to biopsy, but also through preventing treatment delays. However, the present study's findings are limited by the retrospective single-centre design. Thus, a well-designed prospective study is needed to confirm the relationship between preoperative TBLB and NSCLC recurrence in this setting.

To the best of our knowledge, this is the first report to identify the possible advantage of omitting preoperative TBLB for small size (<3 cm) NSCLC. This is because operative TBLB was associated with significantly poorer

Table II. *Univariate analyses of factors influencing recurrence after complete resection of primary lung cancer.*

	Hazard ratio	95%CI	*p*-Value
Age ≥70 years	1.310	0.716-2.399	0.381
Gender: Male/Female	2.049	1.051-3.993	0.035*
TBLB	3.568	1.945-6.546	<0.001*
CT findings: Pure GGN	0.230	0.071-0.744	0.014*
Location: Peripheral	1.206	0.577-2.519	0.619
Histology: Adenocarcinoma	0.520	0.270-1.001	0.050
Histological grade:			
Grade 2 or 3/Grade 1	6.359	2.269-17.820	<0.001*
Invasive size of tumour >2 cm	2.920	1.571-5.430	<0.001*
PL: Present	3.679	1.986-6.814	<0.001*
LY: Present	2.768	1.514-5.060	<0.001*
V: Present	3.635	1.978-6.682	<0.001*
EGFR mutation: Yes	0.898	0.366-2.201	0.814
Adjuvant chemotherapy	1.792	0.877-3.660	0.109
Time from point out to surgery ≥60 days	0.898	0.377-2.139	0.807
Preoperative CEA of ≥5 ng/ml	1.604	0.843-3.051	0.150

CI: Confidence interval; TBLB: transbronchial lung biopsy; CT: computed tomography; GGN: ground glass nodule; PL: pleural invasion; LY: lymphatic vessel invasion; V: vascular invasion; EGFR: epidermal growth factor receptor; CEA: carcinoembryonic antigen. *statistically significant.

Table III. *Multivariate analyses of factors influencing recurrence after complete resection of primary lung cancer.*

	Hazard ratio	95%CI	*p*-Value
TBLB	2.491	1.337-4.640	0.004*
Histological grade 2 or 3	3.837	1.309-11.240	0.014*
PL present	2.236	1.183-4.226	0.013*

CI: Confidence interval; TBLB: transbronchial lung biopsy; PL: pleural invasion. *statistically significant.

RFS, and independently predicted recurrence in this setting. Thus, it may be a fair strategy to omit preoperative pathological diagnosis by TBLB for patients with NSCLC less than 3-cm, which might avoid delays in surgical intervention and improve outcomes in these patients.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

Study concept and design: M.Y.; Drafting of the manuscript: M.Y.; Critical revision of the manuscript: T.T., M.K. and T.K.; Study supervision: S.T.

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