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 pN0 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
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 91.5% 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 invasion and vascular invasion. 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).

### Table I. The patients’ clinicopathological characteristics.

| Characteristic                          | TBLB (n=104) | Non-TBLB (n=267) | \( p \)-Value |
|----------------------------------------|-------------|-----------------|--------------|
| Age: <70/\( \geq 70 \) 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)       | 2.2±0.55    | 1.8±0.67        | <0.001*      |
| \( \leq 2 \) cm/\( >2 \) cm            | 38/66       | 176/91          | 0.005*       |
| Histology:                              |             |                 |              |
| 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: <5 ng/ml/\( \geq 5 \) ng/ml | 79/25       | 212/55          | 0.741        |
| Time from point out to surgery         | 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.
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. 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 | 1.026    | 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 | 0.200   |
| Time from point out to surgery ≥60 days | 0.898    | 0.377-2.139 | 0.087   |
| Preoperative CEA of ≥5 ng/ml | 1.604    | 0.843-3.051 | 0.130   |

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.
10 Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, O’Sullivan DE, Booth CM, Sullivan R and Aggarwal A: Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ 371: m4087, 2020. PMID: 33148535. DOI: 10.1136/bmj.m4087

11 Huang CS, Hsu PK, Chen CK, Yeh YC, Shih CC and Huang BS: Delayed surgery after histologic or radiologic-diagnosed clinical stage I lung adenocarcinoma. J Thorac Dis 12: 615-625, 2020. PMID: 32274127. DOI: 10.21037/jtd.2019.12.123

12 Nakajima J, Sato H and Takamoto S: Does preoperative transbronchial biopsy worsen the postsurgical prognosis of lung cancer? A propensity score-adjusted analysis. Chest 128: 3512-3518, 2015. PMID: 16304307. DOI: 10.1378/chest.128.5.3512

13 Yasukawa M, Sawabata N, Kawaguchi T, Kawai N and Taniguchi S: Clinical implications of transbronchial biopsy for surgically resected non-small cell lung cancer. In Vivo 32: 691-698, 2018. PMID: 29695580. DOI: 10.21873/invivo.11295.

14 MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, Mehta AC, Ohno Y, Powell CA, Prokop M, Rubin GD, Schaefer-Prokop CM, Travis WD, Van Schil PE and Bankier AA: Guidelines for the management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology 284: 228-243, 2017. PMID: 28240562. DOI: 10.1148/radiol.2017161659

15 Qi H, Wan C, Zhang L, Wang J, Song Z, Zhang R, Zhang Z and Fan W: Early effective treatment of small pulmonary nodules with video-assisted thoracoscopic surgery combined with CT-guided dual-barbed hookwire localization. Oncotarget 8: 38793-38801, 2017. PMID: 28455967. DOI: 10.18632/oncotarget.17044

16 Pang X, Xue L, Chen J and Ding J: A novel hybrid technique for localization of subcentimeter lung nodule. J Thorac Dis 9: 1107-1112, 2017. PMID: 28523166. DOI: 10.21037/jtd.2017.03.75

17 Geisinger K, Rami-Porta R, Moreira AL, Travis WD and Nicholson AG: Lung cancer staging and grading. In: World Health Organization Classification of Tumors. Pathology and Genetics of the Lung, Pleura, Thymus and Heart. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG (eds.). Lyon, IARC Press, pp. 14-15, 2015.

18 Bodendorf MO, Haas V, Laberke HG, Blumenstock G, Wex P and Graeter T: Prognostic value and therapeutic consequences of vascular invasion in non-small cell lung carcinoma. Lung Cancer 64: 71-78, 2009. PMID: 18790545. DOI: 10.1016/j.lungcan.2008.07.011

19 Krebs MG, Sloane R, Priest L, Lancashire L, Hou JM, Greystoke A, Ward TH, Ferraldeschi R, Hughes A, Clack G, Ranson M, Dive C and Blackhall FH: Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. J Clin Oncol 29: 1556-1563, 2011. PMID: 21422424. DOI: 10.1200/JCO.2010.28.7045

20 Alix-Panabières C and Pantel K: Challenges in circulating tumour cell research. Nat Rev Cancer 14: 623-631, 2014. PMID: 25154812. DOI: 10.1038/nrc3820

21 Deppen SA, Davis WT, Green EA, Rickman O, Aldrich MC, Fletcher S, Putnam JB Jr. and Grogan EL: Cost-effectiveness of initial diagnostic strategies for pulmonary nodules presenting to thoracic surgeons. Ann Thorac Surg 98: 1214-1222, 2014. PMID: 25087933. DOI: 10.1016/j.athoracsur.2014.05.025

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