



Tissue Adequacy and Safety of Percutaneous Transthoracic Needle Biopsy for Molecular Analysis in Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis

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Objective: We conducted a systematic review and meta-analysis of the tissue adequacy and complication rates of percutaneous transthoracic needle biopsy (PTNB) for molecular analysis in patients with non-small cell lung cancer (NSCLC).

Materials and Methods: We performed a literature search of the OVID-MEDLINE and Embase databases to identify original studies on the tissue adequacy and complication rates of PTNB for molecular analysis in patients with NSCLC published between January 2005 and January 2020. Inverse variance and random-effects models were used to evaluate and acquire meta-analytic estimates of the outcomes. To explore heterogeneity across the studies, univariable and multivariable meta-regression analyses were performed.

Results: A total of 21 studies with 2232 biopsies (initial biopsy, 8 studies; rebiopsy after therapy, 13 studies) were included. The pooled rates of tissue adequacy and complications were 89.3% (95% confidence interval [CI]: 85.6%–92.6%; $I^2 = 0.81$) and 17.3% (95% CI: 12.1%–23.1%; $I^2 = 0.89$), respectively. These rates were 93.5% and 22.2% for the initial biopsies and 86.2% and 16.8% for the rebiopsies, respectively. Severe complications, including pneumothorax requiring chest tube placement and massive hemoptysis, occurred in 0.7% of the cases (95% CI: 0%–2.2%; $I^2 = 0.67$). Multivariable meta-regression analysis showed that the tissue adequacy rate was not significantly lower in studies on rebiopsies ($p = 0.058$). The complication rate was significantly higher in studies that preferentially included older adults ($p = 0.001$).

Conclusion: PTNB demonstrated an average tissue adequacy rate of 89.3% for molecular analysis in patients with NSCLC, with a complication rate of 17.3%. PTNB is a generally safe and effective diagnostic procedure for obtaining tissue samples for molecular analysis in NSCLC. Rebiopsy may be performed actively with an acceptable risk of complications if clinically required.

Keywords: Biopsy; Carcinoma, non-small-cell lung; Epidermal growth factor receptor; Tomography, X-ray computed

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers, and most patients with NSCLC

have locally advanced or metastatic disease at diagnosis. In advanced NSCLC, it is typically necessary to determine whether standard chemotherapy or therapy targeting actionable mutations should be applied in the current era

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of personalized medicine [1,2]. Consequently, molecular testing of NSCLC has gained importance since the advent of targeted cancer therapy [3]. The era of precision medicine in lung cancer began with the discovery of epidermal growth factor receptor (EGFR) mutations in NSCLC and the use of tyrosine kinase inhibitors (TKIs) to target these mutations successfully [4]. Several other actionable mutations, including anaplastic lymphoma kinase (ALK) rearrangement and c-ros oncogene 1 (ROS1) mutation, have been subsequently identified, and the corresponding targeted therapies have improved the prognosis of lung cancer [4,5]. Accordingly, molecular analysis to identify actionable mutations is a necessary step in the diagnosis of NSCLC [2,6].

Percutaneous transthoracic needle biopsy (PTNB) has been traditionally used to diagnose lung parenchymal lesions, particularly in peripheral locations, which are difficult to approach using bronchoscopy [7]. PTNB under various types of imaging guidance is a reliable and safe procedure that provides a diagnostic sensitivity of 90% or more for the histopathologic diagnosis of NSCLC [1,8-10]. One of the major indications of PTNB for NSCLC is to obtain tumor tissue for molecular analysis to identify targetable mutations, and the need for such biopsies is growing [11,12]. However, the diagnostic adequacy of PTNB for molecular analysis has not been established, especially with regard to the likelihood of obtaining a sufficient tissue sample and the complication rate, and no comprehensive review has been conducted on these issues. Therefore, we conducted a systematic review and meta-analysis of the tissue adequacy and complication rates of PTNB for molecular analysis in patients with NSCLC.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [13] after registration of the study protocol in the PROSPERO database (registration number: CRD42020166405).

Search Strategy

A search of the OVID-MEDLINE and Embase databases was conducted for publications published between January 2005 and January 2020 on the tissue adequacy and complication rate of PTNB for molecular analysis in patients with NSCLC, since advanced molecular analysis began to receive attention in precision medicine for lung cancer [14]. The

following keywords were used in different combinations: (“non-small cell lung cancer,” OR “lung adenocarcinoma”) AND (“rebiopsy,” OR “research biopsy”) AND (“molecular analysis” and “mutation”). The search was restricted to human participants and English language studies. This search was supplemented by screening the bibliographies of the retrieved articles and review articles.

Selection of Studies

We reviewed articles for the following components to determine eligibility: 1) studies with a population consisting of at least 10 patients with NSCLC who underwent PTNB, 2) studies fully or partially addressing tissue adequacy with or without complications for molecular analysis of PTNB, 3) studies analyzing PTNB performed under radiological guidance, including fluoroscopy, computed tomography (CT), cone-beam CT, CT fluoroscopy, or ultrasonography, and 4) studies with a sufficient description of the data for outcomes to be extracted.

The exclusion criteria were as follows: 1) case reports, review articles, editorials, letters, comments, and conference proceedings and 2) studies dealing with only bronchoscopy or endobronchial ultrasound (EBUS)-guided procedure. The titles and abstracts of the searched publications were screened. The full texts of the articles were reviewed after selecting potentially eligible abstracts. Two reviewers independently performed both steps and finally included articles that were eligible based on consensus.

Definition of Outcomes

The primary outcome of this meta-analysis was the tissue adequacy rate of PTNB for molecular analysis in patients with NSCLC. The tissue adequacy rate was defined as the proportion of procedures that yielded an adequate amount of tumor tissue for molecular testing of at least one kind, including EGFR, ALK, ROS1, Kirsten rat sarcoma viral oncogene homolog (KRAS), and rearranged during transfection (RET). Articles on the assessment of programmed cell death ligand-1 expression were not included in this study. The secondary outcomes were the rates of complications and severe complications related to PTNB for molecular analysis. Severe complications included pneumothorax requiring chest tube placement, massive hemoptysis, air embolism, and death.

Data Extraction and Quality Assessment

Two of the authors with 9 and 16 years of clinical

experience independently extracted the data using a standardized Excel file. The extracted data included patient characteristics (mean age, sex distribution, underlying disease, and type of lung cancer), study characteristics (authors, journal, affiliation, country, and publication year), procedural characteristics (number of procedures, needle type and gauge, imaging guidance, biopsy position, specimen length, and target lesion characteristics), and outcomes (proportion of procedures with sufficient tissue specimens for molecular diagnosis and frequency and types of complications). Any conflicts were resolved through consensus. We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool for quality assessment [15].

Statistical Analysis

A DerSimonian–Laird random-effects model was used to estimate the pooled proportions of tissue adequacy and complications overall, depending on whether the biopsy was an initial biopsy or rebiopsy after chemotherapy. For the meta-analysis, the inverse variance method was used to calculate the weights. Heterogeneity across the included studies was evaluated using I^2 statistics and forest plots. I^2 was derived from the Cochrane Q statistic using the following equation: $I^2 = 100\% \times (Q-df)/Q$. An I^2 statistic of $> 50\%$ indicated substantial heterogeneity [16]. The potential for publication bias was evaluated visually using funnel plots. Subgroup analysis was conducted for the biopsy timing (initial biopsy versus rebiopsy) and complication rates (higher versus lower complication rates). The criterion for dividing the subgroups was the value of the pooled incidence. Subgroup analysis for severe complications was performed with arcsine transformation due to the low sample numbers. To explore the reasons for inter-study heterogeneity, univariable and multivariable meta-regression analyses were performed, and the significant factors ($p < 0.05$) on univariable analysis and the timing of the biopsy (initial biopsy versus rebiopsy) were used in the multivariable model. R version 3.6.2 (The R Foundation for Statistical Computing), with the ‘meta’ and ‘metafor’ packages, was used for the analyses.

RESULTS

Literature Search

The literature search process is shown in Figure 1. In total, 325 articles were screened after removing duplicates. Of these 325 articles, 268 were excluded based on their

titles and abstracts. Thirty-eight additional articles were excluded after reviewing their full texts, and two articles were further added by screening the bibliographies. Finally, 21 articles involving 2232 patients met the eligibility criteria and were included [1,2,7,17-34].

Baseline Characteristics and Quality Assessment

The study population in the included studies ranged from 17 to 560 (median, 112; interquartile range [IQR], 66–236), and the number of total biopsy procedures ranged from 5 to 577 (median, 90; IQR, 23–134) (Table 1, Supplementary Table 1). Two-thirds of the studies were conducted in Asia (67%, 14/21), followed by the United States (29%, 6/21). PTNB was performed for rebiopsy after chemotherapy or targeted therapy in 62% of the studies (13/21) and for initial biopsy in the rest (38%, 8/21). CT was the most frequent guidance modality for PTNB (17 studies), followed by ultrasonography ($n = 5$), cone-beam CT ($n = 3$), and fluoroscopy ($n = 2$). Seven studies used two or more modalities for needle guidance.

When assessed using the QUADAS-2 tool, the included studies appeared to have a relatively low risk of bias in the patient selection and index test domains. However, the risk of bias was mostly unclear in the reference standard, as well as in the flow and timing, as the study population itself was used as a reference standard in several studies (Supplementary Fig. 1).

Tissue Adequacy Rate for Molecular Analysis

The pooled overall tissue adequacy rate of PTNB for molecular analysis was 89.3% (95% CI, 85.6%–92.6%; $I^2 = 0.81$; 2232 biopsies in 21 studies) (Fig. 2A) [1,2,7,17-34]. In the subgroup analysis, the pooled tissue adequacy rate for the initial biopsies was 93.5% (95% CI, 86.0%–98.6%; $I^2 = 0.89$; 715 biopsies in 8 studies) [1,2,7,21,28,30,31,34], and the pooled tissue adequacy rate for the rebiopsies was 86.2% (95% CI, 83.1%–89.0%; $I^2 = 0.47$; 1517 biopsies in 13 studies) (Fig. 2B) [17-20,22-27,29,32,33]. The pooled tissue adequacy rate of PTNB in the groups with higher and lower complication rates was 92.5% (95% CI, 87.8%–96.2%; $I^2 = 0.77$; 1135 biopsies in 9 studies) [7,18,19,22,25,30-32,34] and 86.8% (95% CI, 83.1%–90.2%; $I^2 = 0.35$; 711 biopsies in 7 studies), respectively [1,17,20,23,26,27,33], with a significant difference ($p = 0.030$) (Supplementary Fig. 2). Figure 3 shows the representative cases with differences in radiologic features between the initial biopsy and rebiopsy.

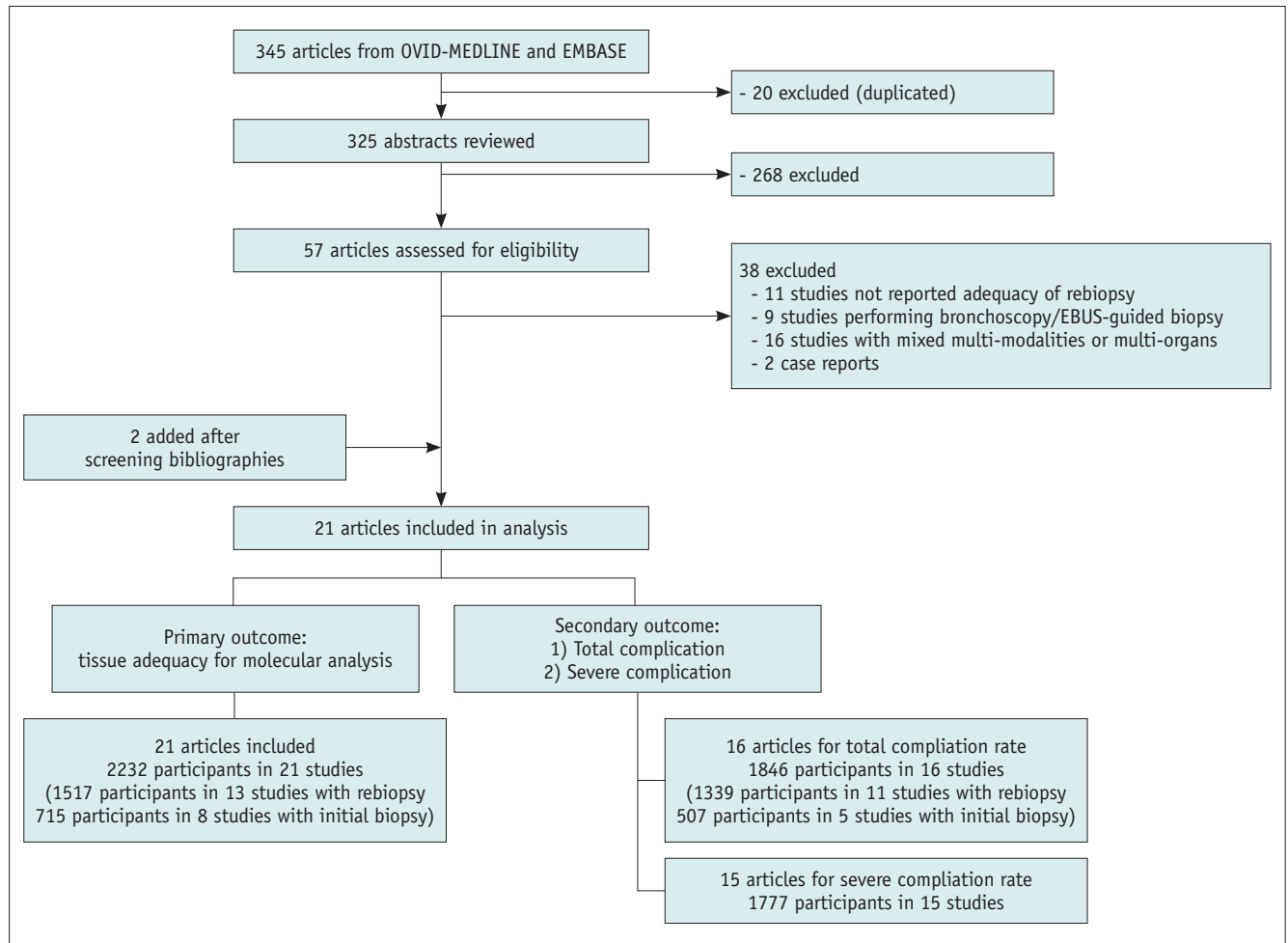


Fig. 1. PRISMA flow diagram outlining the article selection process. EBUS = endobronchial ultrasound

Complications

The pooled total complication rate for PTNB was 17.3% (95% CI, 12.1%–23.1%; $I^2 = 0.89$; 2326 biopsies in 16 studies) (Fig. 4A) [1,7,17-20,22,23,25-27,30-34]. The pooled severe complication rate for PTNB was 0.7% (95% CI, 0%–2.2%; $I^2 = 0.67$; 2016 biopsies in 13 studies) (Fig. 4B) [1,7,18-20,23,25,26,30-34]. The most common complication was pneumothorax, with a pooled incidence of 9.2% (95% CI, 4.0%–15.7%; $I^2 = 0.92$; 2263 biopsies in 15 studies) [1,7,17-20,23,25-27,30-34]. In the initial biopsy group, pneumothorax occurred in 135 participants, with a total of 1121 biopsies, and pneumothorax in the rebiopsy group was reported in 201 participants, with a total of 1142 biopsies. Hemoptysis was reported in 6 studies [7,18,19,26,31,32], with an incidence ranging from 0.5% to 21%.

In the subgroup analysis, the pooled complication rate for the initial biopsies was 22.2% (95% CI, 15.1%–30.1%; $I^2 = 0.83$; 987 biopsies in 5 studies) [1,7,30,31,34],

and the pooled complication rate for the rebiopsies was 16.8 (95% CI, 10.3%–24.5%; $I^2 = 0.90$; 1339 biopsies in 11 studies [17-20,22,23,25-27,32,33], with no statistically significant difference ($p = 0.26$) (Fig. 4C). The pooled severe complication rate for the initial biopsies was 2.41% (95% CI, 0.24%–6.74%; $I^2 = 0.80$; 507 biopsies in 5 studies) [1,7,30,31,34], and the pooled complication rate for the rebiopsies was 0.82% (95% CI, 0.28%–1.63%; $I^2 = 0.19$; 1136 biopsies in 9 studies) [17-20,23,25,26,32,33], with no statistically significant difference ($p = 0.259$) (Supplementary Fig. 3). The pooled complication rate was 28.4% in preferential older adult patients (95% CI, 22.4%–34.6%; $I^2 = 0.50$; 927 biopsies in 7 studies) [7,18,19,23,25,30,32] and 12.5% in the younger patients (95% CI, 7.5%–18.5%; $I^2 = 0.88$; 1399 biopsies in 9 studies) ($p < 0.001$) (Supplementary Fig. 4) [1,17,20,22,26,27,31,33,34]. The criterion was defined as an average age of 65 years.

Table 1. Baseline Characteristics of the Included Studies

Study	Study Population							Total PTNB No. for Molecular Analysis	Complications			
	Total No.	Age, Year (Range)	Male (%)	Adenocarcinoma (%)	Needle Guide	Needle Size (G)	Tissue Sampling No. Mean (Range)		Tissue Adequacy (%)	Total Complication No. (%)	Pneumothorax No. (%)	Hemoptysis No. (%)
Solomon et al. 2010 [30]	18	Mean, 68 (51-84)	6/18 (33)	17/18 (94)	CT, F	18, 20	NS	NS	3/18 (17)	3/18 (17)	0	0
Zhuang et al. 2011 [34]	43	Mean, 62 (38-80)	16/43 (37)	32/43 (74)	CT	18, 20	NS	18	8/43 (19)	8/43 (19)	0	0
Yoon et al. 2012 [33]	94	Mean, 57 (33-85)	31/94 (33)	83/94 (88)	CBT	18	NS	43	6/94 (6)	13/94 (14)	6/94 (6)	2/94 (2)
Hsiao et al. 2013 [21]	332	Mean, 65 (24-95)	199/332 (60)	261/332 (79)	CT	18, 20	3.9 (0-6)	94	8/134 (6)	NS	8/134 (6)	NS
Tam et al. 2013 [1]	151	Mean, 61 (34-81)	86/151 (57)	91/151 (60)	CT	20	NS	134	26/170 (15)	27/170 (16)	26/170 (15)	16/170 (9)
Schneider et al. 2015 [28]	52	NS	NS	52/52 (100)	CT	18, 20, 22	NS	170	NS	NS	NS	NS
Florentine et al. 2015 [2]	216	Mean, 70	103/216 (48)	NS	CT	20	NS	52	NS	NS	NS	NS
Nosaki et al. 2016 [27]	395	Mean, 63 (27-84)	154/395 (39)	380/395 (96)	CT, US	NS	NS	22	3/113 (3)	10/113 (9)	3/113 (3)	NS
Tokaca et al. 2018 [32]	66	Mean, 67 (60-71)	35/66 (53)	62/66 (94)	CT, US	NS	NS	113	12/66 (18)	17/66 (26)	12/66 (18)	5/66 (8)
Hata et al. 2017 [19]	81	Mean, 81 (26-84)	37/81 (46)	71/81 (88)	CT	NS	NS	66	16/55 (29)	25/55 (45)	16/55 (29)	1/55 (2)
Tian et al. 2017 [31]	560	Mean, 52 (11-83)	323/560 (58)	353/560 (63)	CT, F	NS	2.6 (1-4)	55	58/560 (10)	128/560 (23)	58/560 (10)	4/560 (1)
Matsumoto et al. 2018 [25]	17	Mean, 72 (44-83)	11/17 (65)	17/17 (100)	CT	18	2 (1-5)	176	0/10 (0)	3/10 (30)	0/10 (0)	0
Komiya et al. 2018 [23]	22	Mean, 66 (43-87)	11/22 (50)	22/22 (100)	CT, US	NS	NS	10	0	0	0	0
Seto et al. 2018 [29]	236	Mean, 73 (40-93)	77/236 (33)	232/236 (98)	CT	NS	NS	5	NS	NS	NS	NS
Nam et al. 2019 [26]	199	Mean, 60 (32-84)	76/199 (38)	199/199 (100)	CT, CBT, US	18, 20	1 (1-4)	16	7/199 (4)	8/199 (4)	7/199 (4)	3/199 (2)
Gill et al. 2018 [18]	577	Mean, 67 (20-95)	229/577 (40)	571/577 (99)	18, 20, 22	NS	3 (1-10)	199	156/577 (27)	158/577 (27)	156/577 (27)	3/577 (0.5)
Kim et al. 2018 [22]	90	Mean, 61 (34-88)	28/90 (31)	80/90 (89)	CBT	18, 20	NS	577	NS	18/90 (20)	NS	NS
Fintelmann et al. 2019 [17]	107	Mean, 60 (54-67)	41/107 (38)	NS	CT	20, 22	NS	90	4/107 (4)	9/107 (8)	4/107 (4)	5/107 (5)
Hong et al. 2019 [20]	112	Mean, 61 (31-85)	34/112 (30)	112/112 (100)	CT, US	NS	NS	107	1/23 (4)	1/23 (4)	1/23 (4)	0
Lee et al. 2019 [24]	338	Mean, 63	139/338 (41)	338/338 (100)	NS	NS	NS	23	NS	NS	NS	NS
Beck et al. 2019 [7]	196	Mean, 68 (31-92)	124/196 (63)	131/196 (67)	CT	NS	4.1 (1-9)	162	40/196 (20)	61/196 (31)	40/196 (20)	4/196 (2)

*Severe complications included pneumothorax requiring chest tube placement, massive hemoptysis, air embolism, or death. CBCT = cone-beam CT, F = fluoroscopy, NS = not specified, US = ultrasonography

Meta-Regression Analysis

The results of the meta-regression analysis for tissue adequacy and complication rates are summarized in Table 2. In the univariable meta-regression analysis, the rate of tissue adequacy for molecular analysis was significantly higher in the studies on the initial biopsies (versus rebiopsies; $p = 0.033$) and those that reported higher total complication rates (versus lower complication rates; $p = 0.046$). No statistically significant relationships were found in the univariable meta-regression analysis for the number of patients included in the studies or the procedure-related

factors, such as the imaging guidance method, needle guide type, or needle size. The multivariable meta-regression analysis showed that the initial biopsies were associated with a higher diagnostic yield of PTNB than the rebiopsies, but this was not statistically significant ($p = 0.058$). The complication rate was not significantly related to the tissue adequacy rate for PTNB in the multivariable analysis ($p = 0.120$).

Both of the univariable and multivariable meta-regression analyses showed a significantly higher complication rate of PTNB in the older patients ($p = 0.001$).

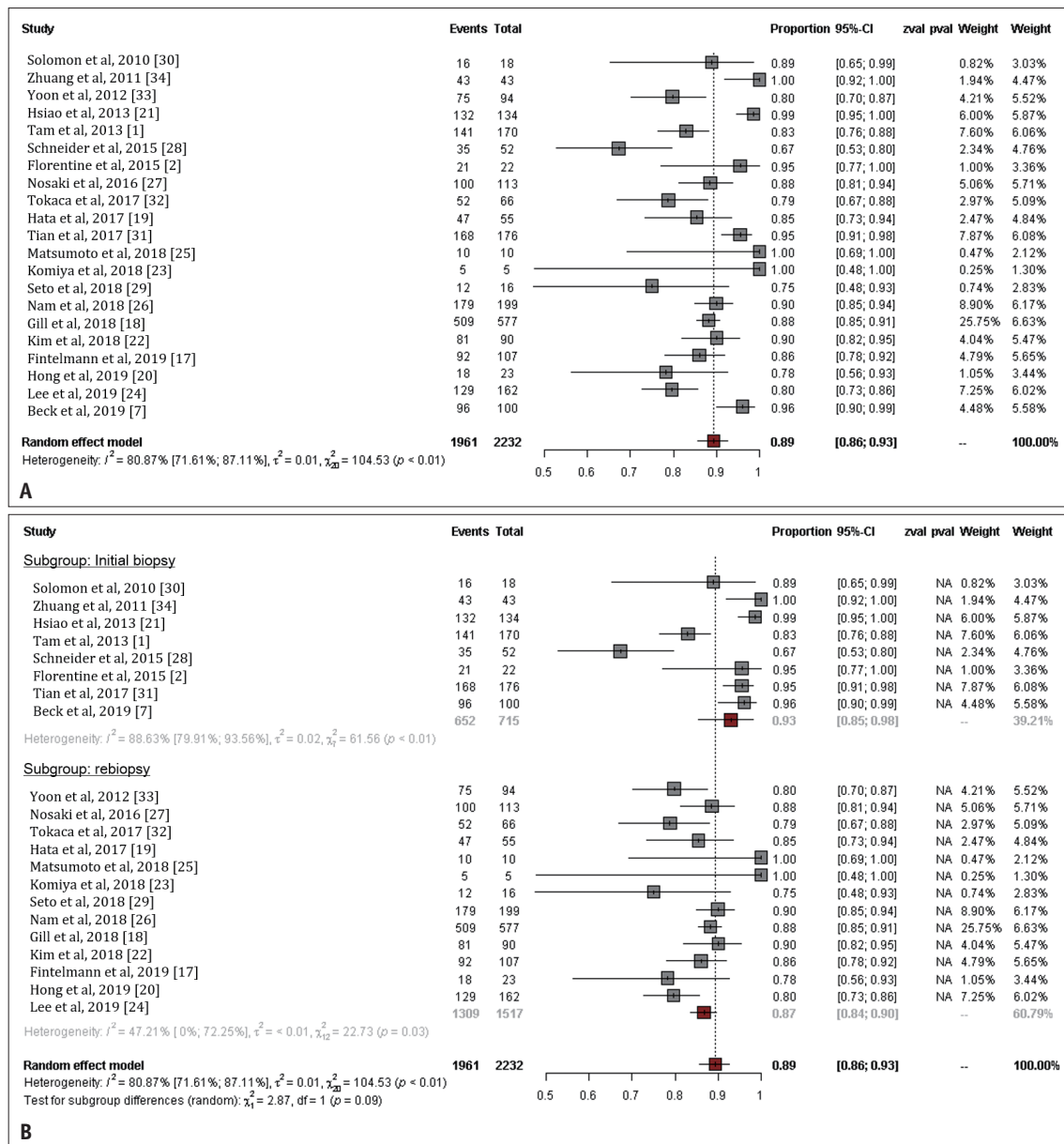


Fig. 2. Forest plot of the tissue adequacy rate of percutaneous transthoracic needle biopsy for molecular analysis in non-small cell lung cancer.

A. Overall tissue adequacy rate. **B.** Tissue adequacy rates for the initial biopsies and rebiopsies. CI = confidence interval

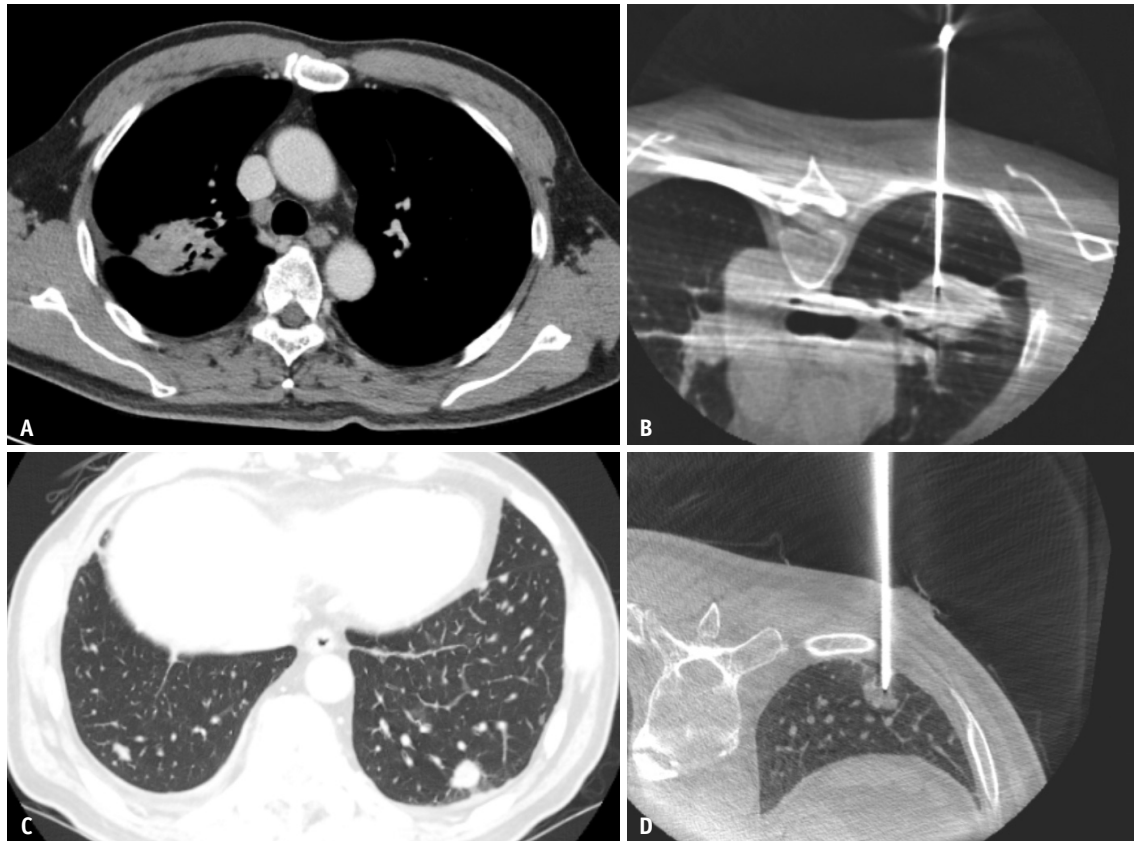


Fig. 3. Representative images of initial biopsy (A, B) and rebiopsy (C, D) for molecular testing in a 66-year-old male patient with primary lung adenocarcinoma. **A.** CT image shows a 5.9-cm mass in the left upper lobe with multiple N2 node enlargement. **B.** An initial percutaneous transthoracic needle biopsy of the mass was successfully performed under cone-beam CT guidance. A mild pneumothorax occurred after the biopsy. The biopsy specimen revealed a primary lung adenocarcinoma with a missense mutation of the EGFR gene exon 21 (L858R). The patient received concurrent chemoradiotherapy. **C.** Multiple metastatic lung nodules appear four years later with interlobular septal thickening, which is suggestive of lymphangitic metastasis in both lower lobes. **D.** Rebiopsy for molecular testing was successfully performed for the nodule in the left lower lobe to determine the eligibility of the clinical trial. No complication occurred after the rebiopsy. EGFR = epidermal growth factor receptor

Publication Bias

Funnel plot asymmetry was assessed for the tissue adequacy rate in 21 studies and the complication rate in 16 studies. The funnel plots were not asymmetric, and no obvious publication bias was identified for tissue adequacy (Egger's test, $p = 0.88$) (Supplementary Fig. 5) or complications (Egger's test, $p = 0.73$) (Supplementary Fig. 6).

DISCUSSION

Our meta-analysis revealed that the use of PTNB for molecular analysis in patients with NSCLC is effective and safe, even for rebiopsies. In this meta-analysis, PTNB showed a high tissue yield for molecular analysis, including for initial biopsies and rebiopsies (89.3%). Our meta-analysis demonstrated an acceptably low complication rate of PTNB (17.3%) and a very low rate of severe complications

(0.7%).

The pooled tissue adequacy rate of rebiopsies was slightly lower than that of the initial biopsies (86.2% and 93.5%, respectively), and the pooled tissue adequacy rates of the patients with higher complication rates were higher than those with lower complication rates (92.5% and 86.8%, respectively). There are several plausible explanations for this result. Cytotoxic drugs or EGFR-TKIs may lead to post-treatment lung parenchymal changes with the shrinkage of the tumor burden, potentially increasing the risk of complications and decreasing the tissue adequacy rate for rebiopsies [35,36]. In addition, we presumed that rebiopsies would have a relatively low rate of tissue adequacy if the procedure was conservatively performed, assuming that patients are more vulnerable to complications due to prior treatment. The lower complication rate in the latter group may be associated with narrow indications and conservative

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procedures for preventing the risk of complications. In this study, a significant relationship was found between tissue adequacy and the complication rates in the meta-regression analyses, supporting the rationale for this hypothesis.

In our meta-analysis, old age was found to be a

statistically significant risk factor for the complications of PTNB in the univariable and multivariable meta-regression analyses, which is consistent with prior studies of initial PTNBs [37-40]. The higher incidence of pneumothorax in older patients results from reduced lung elasticity with aging

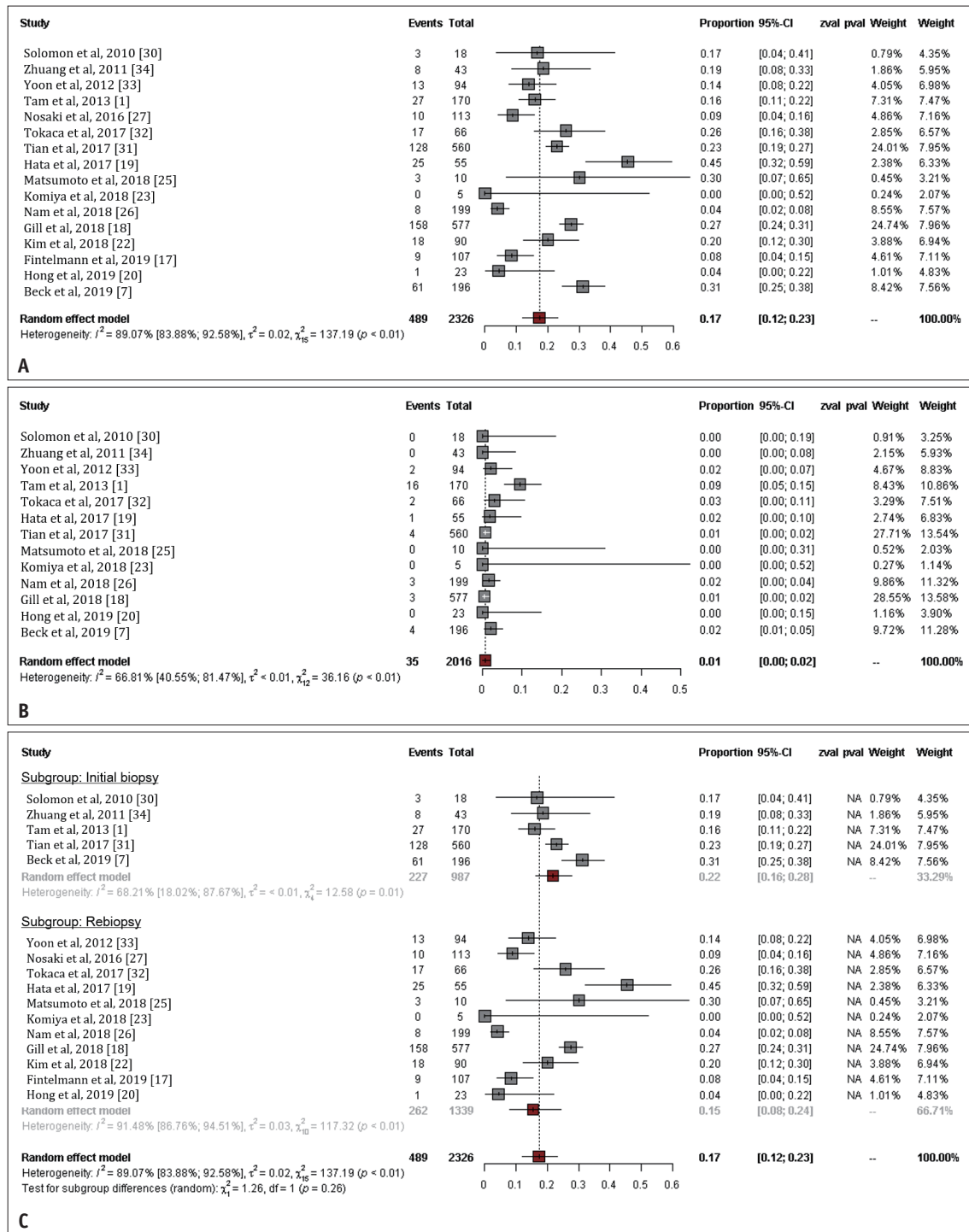


Fig. 4. Forest plot of the complication rates of percutaneous transthoracic needle biopsy for molecular analysis in non-small cell lung cancer.

A. Total complication rate. B. Severe complication rate. C. Complication rates for the initial biopsies and rebiopsies. CI = confidence interval

Table 2. Univariable and Multivariable Random-Effects Meta-Regression of Tissue Adequacy Rate and Complication Rate

	Univariable Analysis			Multivariable Analysis*		
	Odds Ratio	95% Confidence Interval	<i>P</i>	Odds Ratio	95% Confidence Interval	<i>P</i>
Tissue adequacy						
Rebiopsy (vs. initial)	0.895	0.808–0.991	0.033	0.906	0.824–0.996	0.058
Age	1.090	0.974–1.219	0.132			
Number of patients	1.067	0.961–1.186	0.225			
Biopsy (vs. aspiration)	1.010	0.891–1.137	0.917			
Needle guide type	1.012	0.893–1.147	0.855			
Needle size	1.007	0.864–1.174	0.928			
Complication	1.102	1.002–1.211	0.046 [†]	1.086	0.993–1.187	0.120
Complication						
Rebiopsy (vs. initial)	0.937	0.801–1.096	0.415	0.924	0.834–1.024	0.132
Age	1.218	1.081–1.372	0.001 [†]	1.226	1.107–1.356	< 0.001 [†]
Number of patients	0.981	0.849–1.133	0.793			
Biopsy (vs. aspiration)	0.951	0.803–1.127	0.564			
Needle guide type	0.964	0.826–1.126	0.647			
Needle size	0.906	0.680–1.206	0.499			
Tissue adequacy	1.004	0.862–1.170	0.955			
Underlying disease	1.017	0.870–1.189	0.837			

*The findings that appeared to be significant factors ($p < 0.05$) in the univariable analysis and the timing of the biopsy (initial versus rebiopsy) were entered into the multivariable models, [†]Statistically significant results ($p < 0.05$).

[41]. Moreover, lung parenchymal changes caused by the use of chemotherapy, in addition to aging of the lungs, may increase the risk of complications such as pneumothorax or hemorrhage [35,42]. The pathogenesis of antineoplastic agent-induced lung injury is poorly understood, and several mechanisms have been proposed, including direct injury to pneumocytes or the alveolar capillary endothelium, the release of cytokines, and recruitment of inflammatory cells [42,43]. However, contrary to the reports of previous studies, the complication rates did not significantly differ for the initial biopsy and rebiopsy after prior chemotherapy or targeted therapy in our analysis (16.8% vs. 22.2%; $p = 0.26$). In contrast, we found a significant relationship between tissue yield and the complication rate. In the univariable meta-regression analysis, the rate of tissue adequacy for molecular analysis was significantly higher in the studies with higher overall complication rates than in those with lower overall complication rates ($p = 0.046$). In light of the concerns about the risks of complications and diagnostic yield, however, appropriate target lesion selection and careful planning of the trajectory may help explain this result.

The pooled incidence of severe complications, including pneumothorax requiring chest tube placement, massive hemothysis, air embolism, and death, was lower than

1%, which is similar to or lower than the corresponding rates reported by other meta-analyses or large cohort studies [37,44]. The incidence of severe complications was lower than 3% in all the included studies, except one [2]. This study primarily included patients from whom the chest tube was removed the next day, and only 1.8% of patients required prolonged chest tube drainage. Therefore, regardless of the initial biopsy or rebiopsy, PTNB can generally be considered a safe procedure for molecular analysis.

A bronchoscopic biopsy is an alternative procedure for the molecular analysis of intraparenchymal malignancies. For rebiopsies after chemotherapy, the adequacy rate of bronchoscopic biopsies for molecular analysis has been reported to be 73%–95% [45–50]. Recently, liquid biopsies, a set of methods that are used to enrich, detect, and analyze circulating tumor cells in cancer patients, have been used to diagnose and predict the prognosis of NSCLC patients [51–53]. Nevertheless, a comprehensive understanding of the comparative performance of various diagnostic methods for rebiopsies after chemotherapy is lacking. Therefore, further studies or systematic reviews are needed to compare the tissue adequacy rates for PTNB, bronchoscopic biopsy or radial EBUS-transbronchial lung biopsy, and liquid biopsy for molecular analysis in patients

with NSCLC.

This study has several limitations. First, the quality of the included studies in the initial biopsy and rebiopsy groups was not uniform because we focused on rebiopsies for molecular analysis in our study. Second, the reasons for statistical heterogeneity were not fully identified, despite the meta-regression analysis. Detailed information on lesion characteristics, technical factors of the biopsy procedure, or operator experience may help further identify the exact cause of heterogeneity, but this information was not extractable from most of the included studies because the aggregated data were pooled at the study level. Third, since we only analyzed published studies, the differences between the studies related to the censored participants and their effect on the results could not be fully explored. Fourth, the quality of the majority of included studies based on the flow, timing, and reference standard could not be established. Lastly, we excluded studies that demonstrated a difficulty in distinguishing NSCLC from cancers of other organs and secondary malignancies [54].

In conclusion, this meta-analysis of PTNB for molecular analysis in patients with NSCLC showed an overall pooled estimate of the tissue adequacy rate of 89.3% and an overall pooled estimate of the complication rate of 17.3% for initial biopsies and rebiopsies after chemotherapy or targeted therapy combined. PTNB is a generally safe and effective diagnostic procedure for obtaining tissue samples for molecular analysis to facilitate modern patient-tailored management of NSCLC. Rebiopsy may be performed actively with an acceptable risk of complications if required in a clinical setting.

Supplement

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Conflicts of Interest

Soon Ho Yoon works as a chief medical officer in MEDICALIP since Nov 2020, outside this work. Other authors report no conflicts of interest relevant to this article.

Author Contributions

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