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Efficacy and Cost-effectiveness of Surgical Biopsy for Histologic Diagnosis of Indeterminate Nodules Suspected for Early Stage Lung Cancer: Comparison with Percutaneous Needle Biopsy

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ABSTRACT

Background: Indeterminate pulmonary nodules (IPN) suspected for early stage lung cancer mandate accurate diagnosis. Both percutaneous needle biopsy (PCNB) and surgical biopsy (SB) are valuable options. The present study aimed to compare the efficacy and cost-effectiveness between PCNB and SB for IPN suspected for early stage lung cancer.

Methods: During January–November 2018, patients who underwent operation for IPN suspected for early stage lung cancer (SB group, n = 245) or operation after PCNB (PCNB group, n = 113) were included. Patient-level cost data were extracted from medical bills from the institution. Propensity score matching was performed between the two groups from a retrospectively-collected database.

Results: Fifteen patients (11.5%) had complications after PCNB; thirteen (11.5%) were not confirmed to have lung cancer through PCNB but underwent operation for IPN. In SB group, 172 (70.2%) and 7 (2.9%) patients underwent wedge resection and segmentectomy for SB, respectively; 66 patients (26.9%) underwent direct lobectomy without SB. After propensity score matching, 58 paired samples were produced. Most patients in PCNB group were admitted twice (n = 55, 94.8%). The average hospital stay was longer in PCNB group (12.9 ± 5.3 vs. 7.3 ± 3.0, *P* < 0.001). Though the cost of the operation was comparable (USD 12,509 ± 2,909 vs. 12,669 ± 3,334; *P* = 0.782), the total cost was higher for PCNB group (USD 14,403 ± 3,085 vs. 12,669 ± 3,334; *P* = 0.006). The average subcategory cost, which increases proportional to hospital stay, was higher in PCNB group, whereas the cost of operation and surgical materials were comparable between the two groups.

Conclusion: Lung cancer operation following SB for IPN was associated with lesser cost, shorter hospital stays, and lesser admission time than lung cancer operation after PCNB. The increased cost and longer hospital stay appear largely related to the admission for PCNB.

Keywords: Percutaneous Needle Biopsy; Surgical Biopsy; Lung Cancer; Cost-effectiveness

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Na KJ, Park IK. Data curation: Na KJ. Formal analysis: Na KJ, Park IK. Methodology: Na KJ, Park IK. Software: Na KJ. Validation: Park IK, Park S, Kang CH, Kim YT. Investigation: Na KJ, Park IK, Park S, Kang CH, Kim YT. Writing - original draft: Na KJ, Park IK. Writing - review & editing: Na KJ, Park IK, Park S, Kang CH, Kim YT.

INTRODUCTION

With the recent technological advances and widespread use of computed tomography (CT) in clinical settings, indeterminate pulmonary nodules (IPN), especially ground-glass opacity nodules (GGN), have become increasingly detectable. Reportedly, up to 40% of IPNs are malignant, particularly in high-risk populations.¹⁻³ Moreover, persistent partly solid GGNs have a much higher probability of malignancy than solid IPNs do,^{4,5} especially when the partly solid GGNs have a solid component larger than 5 mm.⁶ Thus, one of the most important steps in managing IPN is to determine the probability of the IPN being malignant and decide the management plan for the lesion.

As the detection rate of IPNs has increased recently, several guidelines regarding the management of IPNs have been published and updated during the last two decades.⁷⁻⁹ The most current guidelines recommend nonsurgical and/or surgical biopsy (SB) for IPNs with a high probability of malignancy. Percutaneous needle biopsy (PCNB) is a traditional method for pathological confirmation of IPN and is still considered the first choice in several medical institutions.¹⁰ Nonetheless, SB followed by curative lung cancer operation has been one of the most valuable options for management of IPNs. This is because of the significantly decreased morbidity rate through adoption of minimally invasive thoracic surgery and improved diagnostic accuracy of CT-based assessment of IPN.^{6-9,11,12}

Given the worsening financial challenges in the medical field, the cost-effectiveness and efficacy of diagnosis and treatment procedures are the focus of increasing interest. Investigating the economic effect of procedures is important for helping patients as well as doctors in choosing appropriate treatment and/or diagnostic procedures and for providing necessary information for framing health policies and resource allocation. Several previous studies have investigated the diagnostic accuracy and peri-procedural or peri-operative outcome of PCNB and SB. However, studies comparing the cost-effectiveness between the two methods for diagnosis and treatment of IPN suspected for early stage lung cancer are rare.

This study aimed to compare the efficacy and cost-effectiveness of lung cancer operation after PCNB and SB for IPNs suspected for early stage lung cancer. Propensity-score matched analysis was performed to minimize selection bias and account for heterogeneity between the groups.

METHODS**Patients**

A retrospective review of the prospectively collected database was performed for 622 patients who had undergone lung resection operation for pathologically-confirmed lung cancer or a pulmonary nodule or mass suspected for lung cancer between January and November 2018 in our institution, Seoul National University Hospital. We excluded patients who had undergone PCNB at another hospital (n = 61), transbronchial biopsy for pulmonary nodules (n = 31), robotic lung operation (n = 22), combined operation for other diseases with lung resection operation (n = 9), PCNB during treatment for other diseases (n = 8), other previous treatment for lung cancer (n = 2), and patients who had lymph node metastasis and required an extensive lung operation (n = 32). We also excluded 9 patients who did not have available cost data for analysis. Among them, we included the patients who had IPN equal to or less than

30 mm in preoperative CT. As a result, 358 patients were included in the analysis: 113 patients in the PCNB group and 245 patients in the SB group. PCNB group is defined as patients who underwent lung cancer surgery after PCNB for IPN and SB group is defined as patients who underwent SB followed by lung cancer surgery for IPN without PCNB.

Cost data acquisition

The cost based on patient-level data was collected, and the average cost of each group was calculated. The medical cost data were extracted from the medical bills from our institution. The medical bills were classified into the Korea National Health Insurance covered payment and Korea National Health Insurance non-covered payment on specific items, such as physician service, hospitalization, injection, medication, anesthesia, procedure and operation, imaging studies, and laboratory test. We excluded the cost of imaging studies for lung cancer staging work up, such as brain magnetic resonance imaging and 18-Fluoro-deoxyglucose-positron emission tomography, as those studies were not performed identically in all the patients. We compared the total amount of Korea National Health Insurance covered and Korea National Health Insurance non-covered medical costs for the analysis.

Propensity score matching

For propensity score matching, we excluded 66 patients from the SB group who had undergone direct lobectomy without SB for various reasons. As these patients underwent direct lung cancer surgery without biopsy, we excluded them as the purpose of this study was to compare two different biopsy methods for IPN suspected for early stage lung cancer. Propensity scores were calculated using logistic regression modeling, including the following variables that were considered as determinant factors in selecting the methods for tissue diagnosis and operative strategies: age, sex, tumor size on CT, consolidation/tumor ratio, clinical T stage, history of redo-operation, and extent of the operation. We matched propensity scores one-to-one using the nearest neighbor methods without replacement, using a 0.15 caliper width. After the matching procedure, 58 patients were selected from each group for the analysis.

Statistical analysis

All statistical analyses were performed using the R software package, version 3.5.0 (<http://www.R-project.org>). Student's *t*-test and Wilcoxon rank-sum test were used to compare continuous variables, and χ^2 test and Fischer's exact test were used to compare nominal variables for unmatched data. McNemar test and paired *t*-test were used for comparison between matched data. All statistical analyses were performed using the two-sided method. *P* values less than 0.05 were considered statistically significant.

Ethics statement

The study protocol was reviewed by the Institutional Review Board of Seoul National University Hospital and was approved as a minimal-risk retrospective study (approval No. H-1902-044-1008) that did not require individual informed consent according to the institutional guidelines for consent waivers.

RESULTS

Baseline characteristics

The demographic and clinical characteristics of the study population are summarized in **Table 1**. The PCNB group included the patients with a significantly large-sized tumor, high

Table 1. Demographic and clinical characteristics of the study population

Variables	Unmatched groups			Matched groups		
	PCNB group (n = 113)	SB group (n = 245)	P value	PCNB group (n = 58)	SB group (n = 58)	P value
Age, yr	65.6 ± 10.0	62.9 ± 10.1	0.019	64.7 ± 10.3	65.0 ± 8.7	0.833
Sex, male	46 (40.7)	96 (39.2)	0.784	19 (32.8)	18 (31.0)	0.827
Smoking			0.974			0.722
Never	77 (68.1)	168 (68.6)		43 (74.1)	45 (77.6)	
Ex	28 (24.8)	60 (24.5)		13 (22.4)	10 (17.2)	
Current	8 (7.1)	15 (6.1)		2 (3.5)	3 (5.2)	
FEV ₁ , %	106.8 ± 17.6	108.2 ± 16.9	0.485	107.0 ± 19.1	108.3 ± 14.9	0.685
D _{lco} , %	92.0 ± 16.2	94.8 ± 17.7	0.153	91.4 ± 15.3	93.7 ± 15.3	0.546
Size of tumor, mm	20.0 ± 6.0	17.2 ± 6.3	< 0.001	17.9 ± 5.9	17.4 ± 6.4	0.580
C/T ratio	0.95 ± 0.13	0.60 ± 0.33	< 0.001	0.90 ± 0.17	0.89 ± 0.18	0.621
Clinical T stage			< 0.001			0.706
cT1	93 (82.3)	230 (93.9)		52 (89.7)	53 (91.4)	
cT2	18 (15.9)	15 (6.1)		6 (10.3)	5 (8.6)	
cT3	2 (1.8)	0		0	0	
Clinical N stage			NA			NA
cN0	113 (100.0)	245 (100.0)		58 (100.0)	58 (100.0)	

Data are presented as mean ± standard deviation or number (%).

PCNB = percutaneous needle biopsy, SB = surgical biopsy, FEV₁ = forced expiratory volume in one second, D_{lco} = diffusing capacity of carbon monoxide, C/T ratio = consolidation/tumor ratio.

consolidation/tumor ratio, and advanced clinical T stage. The differences of baseline and clinical characteristics between the two groups were adjusted after the propensity score matching process. Fifteen patients (13.3%) developed complications after PCNB: multiple PCNBs for IPNs (n = 5), hemoptysis or pulmonary hemorrhage (n = 5), pneumothorax requiring supportive care (n = 5) and intervention (n = 3). Lung cancer was confirmed in 100 patients (88.5%) and 13 patients (11.5%) were not confirmed to have lung cancer but they underwent lung resection operation as the IPN was strongly suspected for early stage lung cancer.

Operative and pathologic detail

In the SB group, 172 (70.2%) and 7 patients (2.9%) underwent wedge resection and segmentectomy for SB, respectively. Sixty-six patients (26.9%) underwent direct lobectomy for the IPN without SB. The proportion of patients who underwent limited resection was significantly higher in the SB group. Moreover, the SB group included more patients who underwent minimally invasive operation or redo-operation. Mediastinal lymph node dissection was performed more on patients in the PCNB group. After the matching process, the differences between the two groups were comparable. However, the number of cartridges used for the operation was higher in the SB group in the matched analysis (Table 2).

Table 2. Operative details

Variables	Unmatched groups			Matched groups		
	PCNB group (n = 113)	SB group (n = 245)	P value	PCNB group (n = 58)	SB group (n = 58)	P value
Extent of operation			< 0.001			0.298
Wedge resection	9 (8.0)	62 (25.3)		13 (22.4)	9 (15.5)	
Segmentectomy	11 (9.7)	48 (19.6)		7 (12.1)	6 (10.3)	
Lobectomy	93 (82.3)	135 (55.1)		38 (65.5)	43 (74.1)	
VATS	105 (92.9)	241 (98.4)	0.022	57 (98.3)	57 (98.3)	1.000
Redo-operation	1 (0.9)	24 (9.8)	0.001	1 (1.7)	1 (1.7)	1.000
Mediastinal LN dissection	105 (92.9)	193 (78.8)	< 0.001	48 (82.8)	50 (86.2)	0.593
No. of cartridges	6.4 ± 2.1	7.5 ± 3.1	< 0.001	6.3 ± 2.2	7.4 ± 3.0	0.030

Data are presented as mean ± standard deviation or number (%).

PCNB = percutaneous needle biopsy, SB = surgical biopsy, VATS = video-assisted thoracic surgery, LN = lymph node.

Table 3. Length of stays and admission times

Variables	Unmatched groups			Matched groups		
	PCNB group (n = 113)	SB group (n = 245)	P value	PCNB group (n = 58)	SB group (n = 58)	P value
Length of stay, day	13.0 ± 4.6	6.9 ± 2.4	< 0.001	12.9 ± 5.3	7.3 ± 3.0	< 0.001
Admission for PCNB	5.1 ± 2.0	NA	NA	4.8 ± 1.7	NA	NA
Admission for operation	7.9 ± 4.2	6.9 ± 2.4	0.004	8.0 ± 5.1	7.3 ± 3.0	0.379
Admission			< 0.001			< 0.001
Once	6 (5.3)	245 (100.0)		3 (5.2)	58 (100.0)	
Twice	107 (94.7)	0		55 (94.8)	0	

Data are presented as mean ± standard deviation or number (%).

PCNB = percutaneous needle biopsy, SB = surgical biopsy, NA = not applicable.

Among 13 patients in the PCNB group who were not confirmed as having lung cancer by PCNB, 8 (61.5%) were diagnosed with cancer, and 5 (38.5%) were diagnosed with benign lesions. In the SB group, 19 patients (7.8%) were diagnosed with benign diseases after SB, and the other 226 patients (92.2%) were confirmed as having cancer. Most patients were diagnosed with lung adenocarcinoma in both groups (87.5% in the PCNB group, 90.2% in the SB group).

Hospital stays, admission, medical costs

The lengths of hospital stay for the operation were comparable between the two groups. However, the total length of hospital stays was significantly longer in the PCNB group, and this difference was mostly because of the hospital stays for PCNB (Table 3). The patients in the PCNB group were mostly admitted twice for PCNB and the operation (n = 55, 94.8%), whereas all patients in the SB group were admitted once for the operation.

The medical costs for the operation were comparable between the two groups. The total medical cost was significantly higher in the PCNB group, as the medical cost of PCNB was added to the medical cost of operation (Table 4). We analyzed the total medical cost between the two groups through subcategories. The medical costs related to the operation (costs for procedures and operation, surgical materials, and anesthesia) were comparable between the two groups. However, the medical costs which increase proportionally to the length of hospital stays (costs for laboratory test, injection, medication, hospitalization, doctor's fee, and others) were significantly higher in the PCNB group (Table 4).

Table 4. Comparison of the medical costs

Variables	Unmatched groups			Matched groups		
	PCNB group (n = 113)	SB group (n = 245)	P value	PCNB group (n = 58)	SB group (n = 58)	P value
Cost attributable to PCNB, USD	2,086.5 ± 1,220.6	NA	NA	1,894.1 ± 952.4	NA	NA
Cost attributable to operation, USD	12,778.2 ± 2,817.4	12,380.7 ± 3,137.6	0.247	12,509.4 ± 2,909.4	12,669.3 ± 3,334.1	0.782
Total cost, USD	14,864.6 ± 3,171.6	12,380.7 ± 3,137.6	< 0.001	14,403.5 ± 3,085.9	12,669.3 ± 3,334.1	0.006
Laboratory test	2,407.0 ± 893.7	1,265.2 ± 408.2	< 0.001	2,226.6 ± 705.7	1,266.3 ± 392.4	< 0.001
Surgical materials	3,899.3 ± 823.9	4,176.3 ± 1,310.0	0.040	3,768.4 ± 864.6	4,110.5 ± 1,151.8	0.094
Procedures and surgery	5,062.7 ± 1,145.7	4,283.2 ± 1,517.3	< 0.001	4,814.8 ± 1,391.7	4,558.0 ± 1,654.6	0.328
Anesthesia	722.0 ± 135.6	687.1 ± 128.0	0.019	699.8 ± 148.3	704.9 ± 135.9	0.843
Injection	402.0 ± 107.3	353.2 ± 107.2	< 0.001	405.8 ± 116.7	350.5 ± 61.9	< 0.001
Medication	145.5 ± 103.2	92.9 ± 76.1	< 0.001	145.8 ± 104.8	93.1 ± 70.8	0.001
Hospitalization	1,803.4 ± 1,115.5	1,215.9 ± 963.1	< 0.001	1,778.0 ± 1,205.5	1,261.4 ± 1,072.8	0.024
Doctor's fee	392.0 ± 161.5	214.1 ± 76.8	< 0.001	401.8 ± 182.8	225.6 ± 102.3	< 0.001
Others	163.2 ± 92.2	94.0 ± 55.3	< 0.001	162.5 ± 107.5	98.9 ± 61.5	< 0.001

Data are presented as mean ± standard deviation or number (%).

PCNB = percutaneous needle biopsy, SB = surgical biopsy, NA = not applicable, USD = the United States dollar.

DISCUSSION

According to the results of our study, SB is a more cost-effective strategy for diagnosis and treatment of IPN suspected for early stage lung cancer than PCNB. The total medical cost was significantly higher in the PCNB group because of the additional costs attributable to PCNB, whereas the cost of the operation was comparable between the two groups. The subcategory medical cost which increases proportionally to hospital stays were significantly higher in the PCNB group than in the SB group, whereas subcategory costs related to surgical procedures were comparable between the two groups. Conclusively, the difference of the cost between the two groups were mostly because of multiple admissions and longer hospital stays in the PCNB group. Though there have been many previous literature which reported the diagnostic accuracy of PCNB or SB for IPN suspected for lung cancer, our study is the first study that compared the cost-effectiveness of both procedures for the diagnosis and treatment of IPN.

Currently, both PCNB and SB are recommended for the diagnosis of IPN suspected for early stage lung cancer.⁷⁻⁹ Though the clinical significance of SB has increased during recent decades, PCNB is still regarded the primary option for the diagnosis of IPN. PCNB is an established diagnostic technique for IPN with high diagnostic yield.^{13,14} However, PCNB is not always feasible for IPN in clinical settings for its controversial role in the diagnosis of GGN, low sensitivity for small nodules, or difficult location of IPN.^{15,16} Moreover, PCNB could result in post-procedural complications, such as pneumothorax, hemothorax, and hemoptysis which have been reported to be as high as 38% in previous studies.¹⁷ SB is regarded a valuable option for the diagnosis of IPN and recommended by several guidelines from international societies.⁷⁻⁹ The evidence for these guidelines is: 1) The radiological characteristics of IPN, especially in GGN, are closely correlated with the pathological finding of IPN with the recent technological advancement of CT. Therefore, SB without preoperative tissue diagnosis is regarded a reasonable strategy for the evaluation of IPN suspected for early stage lung cancer. 2) SB could be used for both the diagnosis and treatment of IPN without unnecessary procedures and hospital admission. 3) The accurate pathological diagnosis of small nodules and GGNs is possible as the specimen including entire tumor lesion can be obtained using SB and it could lead to thorough histological evaluation of IPN.

In the National Lung Screening Trial, low-dose chest CT screening resulted in 20% decrease in lung cancer-specific mortality and 6.7% decrease in the overall mortality in high-risk patients compared with those resulting from conventional chest radiography.¹⁸ A Korean multi-society collaborative committee provided guidelines for lung cancer screening, which recommended annual, low-dose CT screening for high-risk patients and the pilot study demonstrated significant positive results.^{19,20} As thin-section, multi-detector CT raised the sensitivity for lung nodules detection, the requirement for evaluation of IPN has been increased in clinical settings.²¹ Therefore, it is important to analyze the cost-effectiveness of both PCNB and SB for evaluating IPNs to help doctors as well as patients choose appropriate diagnostic methods and allocate healthcare resources. According to the result of our study, the PCNB group showed significantly higher total medical costs than the SB group. Though the number of cartridges used for the operation was significantly higher in the SB group, the cost of the lung cancer operation was not different between the two groups. The largest driver of increased cost in the PCNB group is the price of admission for PCNB, and not for the PCNB procedure itself. Specifically, subcategory costs which increased proportionally to hospital stays were significantly higher in the PCNB group than in the SB group, and it largely contributed to the difference in medical costs between the two groups. Furthermore, the

complications developed after PCNB result in prolonged health care system contact and can lead to a substantial increase in medical cost through longer hospital stays and procedures for treating complications.

Some recent studies demonstrated that CT-based assessment of IPN showed a high correlation with pathological findings and could even predict for histopathological invasiveness to differentiate lung adenocarcinoma subtypes.^{6,22,23} Lee et al.⁶ reported that CT-based resection of GGN with a solid component > 5 mm had 86.4% accuracy for lung cancer. They proposed that CT-based resection without biopsy could be a reasonable option in routine practice. In our study, the accuracy of the CT-based assessment of IPNs in the SB group was 92.2%. Moreover, thirteen patients (11.5%) in the PCNB group who were not confirmed as having lung cancer after PCNB eventually received operation, and 8 patients were diagnosed with lung cancer by SB. The result of our study was consistent with those of previous studies and demonstrated that approximately 10% of patients in the PCNB group underwent SB as clinicians could not exclude malignancy using radiological and clinical findings. Thus, our results also support that SB without preoperative tissue diagnosis for IPN is a reasonable option.

There are several limitations of this study that must be acknowledged. First, there might be a selection bias because this study was retrospective in nature and not randomized. Second, the cost data of both the groups only included cost incurred during admission, so the cost incurred at the outpatient clinic and the social cost were not included. Third, our study could not reflect the diversity of health care systems worldwide as we only included the cost data incurred in Korea. However, we think that our result can be universally applicable in other countries, as we revealed that the largest driver of the cost increase in the PCNB group was longer hospital stays because of multiple admissions.

Conclusively, we demonstrated that SB is associated with lower cost, shorter hospital stays, and lesser admission time. Moreover, increased cost and longer hospital stay appear largely related to the admission for PCNB. Given that CT-based assessment of IPN provides high accuracy in the diagnosis of malignancy, we suggest that direct SB is a cost-effective strategy for diagnosis and treatment of IPN suspected for early stage lung cancer.

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