Diagnostic Factors of Standard Bronchoscopy for Small (≤ 15 mm) Peripheral Pulmonary Lesions: A Multivariate Analysis

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Abstract

Background The aim of this study was to evaluate the factors contributing to an accurate diagnosis of small (≤ 15 mm) peripheral pulmonary lesions (PPLs) by standard bronchoscopy and to determine the most suitable technology for such a diagnosis.

Objective Bronchoscopy was performed for 115 PPLs (≤ 15 mm diameter) on chest computed tomography (CT) between August 2003 and December 2006.

Methods Univariate and multivariate analyses were conducted retrospectively with the R software.

Results The diagnostic yield of the 115 PPLs was 65.2%; the yield was 61.9% and 69.2% for the malignant and benign lesions, respectively. In the univariate analysis, the approach to the lesion contributed the most to successful diagnosis, followed by skill and the use of hemostasis. In the multivariate analysis, the most important factor was approach, followed by lower lobe lesion and the use of hemostasis. Although it was better to use a sedative, operator skill was not a contributing factor.

Conclusion The approach to the lesion is the most important factor for a successful diagnosis of PPLs by bronchoscopy. Bronchoscopy is time consuming and painful; therefore, it is very important to establish an accurate diagnosis as soon as possible. Further, endobronchial ultrasonography with a guide sheath (EBUS-GS) and navigation systems are useful tools for the diagnosis of small PPLs.

Key words: small peripheral pulmonary lesions, PPLs, bronchoscopy, diagnostic factor

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Introduction

Lung cancer, one of the most frequently occurring malignant neoplasms, is the leading cause of cancer-related death among both men and women in developed countries (1). Following the recent advances in computed tomography (CT) equipment and their widespread use, particularly with the introduction of low-dose helical CT to examine lung

cancer, the detection rate of peripheral pulmonary lesions (PPLs) is increasing (2). Especially, with the increasingly successful outcomes of lung adenocarcinoma treated with epithelial growth factor receptor-tyrosine kinase inhibitor (3, 4), bronchoscopy is becoming important for the early diagnosis of lung cancer.

Flexible fiberoptic bronchoscopy (FFB) has been used for more than three decades to diagnose PPLs. In general, PPLs with a diameter of less than 20 mm are categorized as small

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Table 1. The Characteristics of 115 PPLs

Median age (range)		64:(19-86)
Sex	Male/Female	73/42
Lesion location	Upper	64 (55.6%)
	Middle + Lingular	10 (8.7%)
	Lower	41 (35.7%)
Diagnoses	Malignant	63 (54.8%)
	Benign	52 (45.2%)
Approach	Easy	24 (20.9%)
	Difficult	91 (79.1%)
Bronchoscope	Standard	102 (88.7%)
	Thin	13 (11.3%)
Devices	Standard forceps	85 (74.0%)
	STAF	45 (39.1%)
	Brushing, Curettage	76 (66.1%)
	TBAC	11 (9.7%)
Median times of TBB (range)		3 (0-10)
Use of hemostatic agent		8 (7.0%)
Under sedation		23 (20.0%)
Skill	Excellent	59 (51.3%)
	Other	56 (48.7%)

TBB: Transbronchial biopsy, STAF: Sasada transbronchial angled forceps, TBAC: Transbronchial needle aspiration cytology

lesions (5). Most PPLs with a diameter of 15-20 mm can be easily visualized by fluoroscopy and are considered relatively easy to diagnose through new technology such as endobronchial ultrasonography with a guide sheath (EBUS-GS) or its combination with a virtual bronchoscopic navigation (VBN) system (6-10). EBUS enables the detection of PPLs, thus possibly improving the diagnostic rate (8, 9); furthermore, by using a VBN system, chest physicians can presume the location of PPLs and insert the bronchoscope into the affected bronchus with great certainty (6, 7). However, the accuracy for detecting PPLs smaller than 15 mm has not been evaluated; it can be influenced by bronchoscopic factors such as lesion area, angle of approach, kind of device, or operator skill.

To evaluate the accuracy of new diagnostic technology, the data obtained by the advanced technique should be compared with that obtained by the conventional diagnostic procedures (CDPs). The purpose of this study was to assess the accuracy of the CDPs for detecting PPLs smaller than 15 mm and to evaluate the factors contributing to a successful diagnosis.

Methods

Bronchoscopy was performed for the first time on 115 consecutive patients with a PPL of ≤ 15 mm diameter through chest CT between August 2003 and December 2006 at the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Japan. In some cases, the final diagnosis decision was made by operation and re-examination using bronchoscope. The institutional review committee approved the study protocol, conducted in accordance with the tenets of the Declaration of Helsinki, and all the patients gave written informed consent before bronchoscopy.

The longest diameters of all lesions revealed by chest CT were recorded. "Difficult" approach was defined as follows:

standard forceps (FB-21C-1; Olympus, Tokyo, Japan) of a bronchoscope could not reach the lesions or could hardly reach them in two or more directions by X-ray fluoroscopy (not C-arm).

The PPLs confirmed by X-ray fluoroscopy were approached with a standard bronchoscope (1T260, 1T240, 1T200, 1T40, 6-mm outer diameter; Olympus). If a PPL could be easily approached with standard forceps, biopsy and cytological brushing (BC-202D-3010; Olympus) were performed. If any difficulty was encountered in the standard method, Sasada transbronchial angled forceps (STAF) (HBF-2010SH; Machida Endoscope Co., Ltd., Tokyo, Japan) (14) and a thin bronchoscope (P260F, 4-mm outer diameter; Olympus) were used for transbronchial needle aspiration cytology (TBAC) (NA-1C-1; Olympus) and curettage (CC-4 CR-1; Olympus) rather than routinely performing biopsy with standard forceps. These techniques are defined as CDPs. Each specimen was preserved separately and compared for pathological diagnosis. If the standard bronchoscope could not be inserted in the affected bronchus, a thin bronchoscope was used. If extensive bleeding occurred and was uncontrollable with pressure application for five minutes or more, hemostatic agents (carbazochrome and tranexamic acid) were administered intravenously. To control the cough reflex and uneasiness, a sedative (diazepam) was administered.

Bronchoscopy was performed by one of twenty physicians (including residents and endoscopic specialists), and was preferentially performed by a younger doctor. Some specialists evaluated the operator skill on the basis of years of experience, interest in bronchoscopy, and diligence. Excellent operator skill was defined in terms of a specialist qualification in bronchoscopy and weekly participation in bronchoscopic procedures for five years or more.

Positive diagnostic criteria were as follows:

- Malignant lesion: class IV/V lesion by cytology, except for lesions outside the lung; metastatic lesion; negative case which diagnosis did not attach in a lung field but by cytology or biopsy of lymph gland; malignancy by pathology.
- Benign lesion: nonspecific inflammation for more than six months followed by a reduction in lesion size, except for cases under observation.

The analyzed variables were age, gender, lesion area, tissue number, bronchoscope diameter, kind of device, approach, diagnosis, hemostasis, sedation, and operator skill. The R software was used for univariate and multivariate analyses by logistic regression. Only those variables with a p-value less than 0.15 in the univariate analysis were included in the multiple logistic regression analysis (with lesion area, approach, skill, and hemostasis as factors). A p-value less than 0.05 was considered statistically significant.

Results

Table 1 shows the patient characteristics. The study in-

Table 2. Clinical Diagnosis and Diagnostic Yield of 115 PPLs

Disease	Number of lesions with Positive findings	Total number of patients	%
Primary lung cancer	39/59		66.1%
Metastatic lung cancer	0/4		0%
Malignant lesions total	39/63		61.9%
Pulmonary tuberculosis	10/14		71.4%
NTM	4/6		66.7%
Nonspecific inflammation	17/20		85.0%
Hamartoma	2/4		50%
Pneumoconiosis	2/2		100%
Fungus infection	1/4		33%
Others (Amyloidosis)	0/2		0%
Benign lesions total	36/52		69.2%
All lesions total	75/115		65.2%

NTM: Nontuberculous mycobacterial infection

Table 3a. Diagnostic Factors for Small (≤ 15 Mm) PPLs: An Univariate Analysis of 115 PPLs

Variables		Success (n=75)	Failure (n=40)	p value
Age	≤ 64	42	18	0.262
	> 64	33	22	
Sex	Male	51	22	0.170
	Female	24	18	
Lesion location	Upper	45	19	0.128
	Middle+Lingular	7	3	
	Lower	23	18	
Diagnoses	Malignant	39	24	0.412
	Benign	36	16	
Approach	Ease	21	3	0.016
	Difficult	54	37	

cluded 73 men and 42 women. Their median age was 64 years (range, 19-86 years). The median longest diameter of the PPLs was 13 mm (range, 5-15 mm). The lesions were mostly located in the upper lobes (55.6%), and 54.8% of the PPLs were malignant. The approach to the PPLs was difficult in almost 80% of the cases, because of the very small lesions. A thin bronchoscope was used in only 11.3% of the cases. STAF and TBAC were applied in 39.1% and 9.7% of the cases, respectively. Transbronchial biopsy (TBB) was generally performed thrice (range, 0-10). The hemostatic agents and sedative were administered in 7% and 20% of the cases, respectively. About 59 PPLs were retrieved under excellent operator skill.

Table 2 shows the pathological findings and diagnostic yields in the study. The overall diagnostic yield was 65.2%, and the yields of the malignant and benign lesions were 61.9% and 69.2%, respectively. Especially, the diagnostic yield of primary lung cancer was 66.1% but that of metastatic lung cancer was 0%.

In the univariate analysis (Table 3a, b), the angle of approach showed a significant difference ($p=0.016$). Further, the use of a hemostatic agent during bronchoscopy ($p=0.10$) and operator skill ($p=0.078$) tended to influence the diagno-

sis. Although not significant, the lower lobe lesions had a lower diagnostic rate than the other areas.

Next, the factors considered to influence the diagnosis in the univariate analysis were included in the multivariate analysis (Table 4). Again, approach was statistically significant ($p=0.019$). The lower lobe lesions obviously had a lower diagnostic rate than the other areas. Operator skill and the use of a hemostatic agent were not important for a successful diagnosis in the multivariate analysis.

Discussion

TBB with FFB has been widely used since the 1970s and is now the most common method for retrieving lung tissue (11, 12). In difficult cases, CT-guided needle biopsy (CTGNB) or video-assisted thoracic surgery (VATS) is used (13, 14). However, CTGNB is more invasive than bronchoscopy and results in critical complications, including air embolism and pleural dissemination (15, 16), and VATS is generally not performed in patients with a poor performance status or in the elderly. Therefore, TBB with FFB is still the first choice to diagnose PPLs, and diagnostic procedures including bronchoscopy with STAF (17), broncho-

Table 3b. Diagnostic Factors for Small (≤ 15 Mm) PPLs: An Univariate Analysis of 115 PPLs

Variables		No. of positive samples		p value
		/Total No.	(%)	
Bronchoscope	Standard	68/102	(67)	0.365
	Thin	7/13	(54)	
Devices	TBB, B, C only	42/61	(69)	0.385
	With STAF, TBAC	33/54	(61)	
	STAF only	31/45	(69)	
Tissue Number	<3	30/49	(61)	0.439
	≥ 3	45/66	(68)	
Hemostasis	Yes	3/8	(36)	0.10
	No	72/107	(67)	
Sedation	Yes	16/23	(70)	0.625
	No	59/92	(64)	
Operator skill	Excellent	43/59	(73)	0.078
	Other	32/56	(57)	

TBB: Transbronchial biopsy, B: Brushing, C: Curettage

STAF: Sasada transbronchial angled forceps, TBAC: Transbronchial needle aspiration cytology

Table 4. Diagnostic Factors of Standard Bronchoscopy for Small (≤ 15 Mm) PPLs: A Multivariate Analysis of 115 PPLs

Variables		No. of positive samples		p value
		/Total No.	(%)	
Lesion location	not Lower	52/74	70.3	0.068
	Lower	23/41	59.1	
Approach	Easy	21/24	87.5	0.019
	Difficult	54/91	59.3	
Operator Skill	Excellent	43/59	72.9	0.117
	Other	32/56	57.1	
Hemostasis	No	72/107	67.3	0.154
	Yes	3/8	37.5	

scopy with an (ultra)thin bronchoscope coupled with a VBN system, and EBUS-GS (6-10) have been developed to complement this technique.

In particular, it is not easy to diagnose small PPLs by bronchoscopy. The *American College of Chest Physicians* does not recommend bronchoscopy for diagnosing PPLs with a diameter of 20 mm or less (5). However, PPLs smaller than 20 mm are being diagnosed comparatively more easily and often, possibly due to developments in technology; therefore, in the present study, the accuracy of bronchoscopic diagnosis of PPLs smaller than 15 mm was evaluated. The approach to the PPLs (≤ 15 mm) was the most important diagnostic factor; STAF and TBAC can improve the approach to PPLs, are inexpensive, and are easily introduced in institutions (17-19).

Fluoroscopic localization of lesions in the lower lobe basal segments or upper lobe apical segment was the most difficult in the past (20, 21). In the present study, the lower lobe lesions had a lower diagnostic rate than the other areas. PPLs of the lower lobe are difficult to diagnose under fluoroscopy because of overlap of the pericardium and diaphragm or respiratory fluctuation. In such cases, EBUS-GS

and a VBN system useful to improve the accuracy of diagnosis. On the other hand, although apical lesions are difficult to diagnose, the use of bronchoscopes with an outer diameter less than 4 mm could overcome the problem. In addition, thin bronchoscopes are preferred in the case of bronchial brushing or TBAC, which involve less bleeding, because the detection of small PPLs under fluoroscopy is difficult after repetitive forceps biopsy and the subsequent bleeding. Operator skill and use of a hemostatic agent tended to have a positive influence on the diagnosis in this study. These factors are essential for a successful diagnosis by reducing the diagnostic time and improving visibility.

In conclusion, the approach to the lesion is the most significant factor influencing the diagnostic accuracy of PPLs smaller than 15 mm. Although the diagnosis of small PPLs has long been a challenge for chest physicians, the introduction of navigable technology such as EBUS-GS or a VBN system may improve the diagnostic accuracy in bronchoscopy.

The authors state that they have no Conflict of Interest (COI).

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