의학석사 학위논문

말초 폐병변에 대한 초음파 기관지내시경 검사에서 CT workstation 적용을 통한 진단률 개선에 대한 연구

Diagnosis of Peripheral Lung Lesion using Endobronchial Ultrasonography with Guided Sheath and CT Workstation

울산대학교대학원

의 학 과

배 수 현

말초 폐병변에 대한 초음파 기관지내시경 검사에서 CT workstation 적용을 통한 진단률 개선에 대한 연구

지도교수 이 태 훈

이 논문을 의학석사 학위 논문으로 제출함

2018년 8월

울산대학교 대학원

의 학 과

배 수 현

배수현의 의학석사학위 논문을 인준함

심사위원 안 종 준 인

심사위원 제갈양진 인

심사위원 이 태 훈 인

울 산 대 학 교 대 학 원

2018 년 08 월

국문요약

제목: 말초 폐병변에 대한 초음파 기관지내시경 검사에서 CT workstation 적용을 통한 진단률 개선에 대한 연구

연구 배경 및 목적: 기관지내시경은 폐결절 진단에 사용되는 유용한 방법이다. 하지만 말초 폐병변(PLL, peripheral lung lesion) 의 경우, 중심성 병변이나 중심과 말초 사이 위치한 병변들보다 기관지내시경으로 접근하기가 어려워 진단률이 낮고 이로 인해 내시경의 사용이 제한적으로 이루어졌다. 이러한 단점을 보완하기 위해 많은 새로운 방법들이 개발되었으며 그 중 하나가 초음파 기관지내시경과 가이드 시스를 이용한 경기관지 폐생검 검사이다 (EBUS-GS-TLBL, endobronchial ultrasound with guide-sheath transbronchial lung biopsy). 더 나아가 최근 많은 연구들에서는 새로운 기관지내시경 방법들을 조합하여 말초 폐병변에 대한 진단률 향상을 도모하고 있으며 그 중 초음파 기관지내시경 (rEBUS, radial EBUS)과 전자기유도 네비게이션 기관지내시경 (ENB, electro magnetic navigation) 의 조합, 초음파 기관지내시경과 가상 기관지내시경 네비게이션 (VBN, virtual bronchoscopy navigation) 의 조합이 좋은 효과를 보이고 있다. 그러나 이러한 방법들은 초기 시스템 도입에 상당히 많은 비용이 들어 재정적 부담을 야기하기 때문에 모든 병원에서 이와 같은 시스템을 도입할 수 없다. 따라서 본 저자들은 CT 기계 도입시 기본적으로 제공되는 CT workstation 으로 가상 기관지내시경 네비게이션과 유사한 효과를 거둘 수 있을 것으로 보고 CT workstation 을 가상 기관지내시경 네비게이션으로 활용하여 말초 폐병변에 대한 조직검사를 시행하고자 하였다.

연구 방법: 2017 년 2 월부터 2018 년 2 월까지 말초 폐병변에 대한 EBUS-GS-TBLB 검

사를 위해 내원한 환자를 대상으로 하였다. 환자들은 무작위로 VBN (Virtual bronchoscopy navigation) 군과 NVBN (Non virtual bronchoscopy navigation) 군으로 나뉘어졌다. VBN 군은 CT workstation 으로 생성된 이미지를 가상 기관지내시경 네비게이션으로 사용한 군이었으며 NVBN 군은 가상 기관지경 네비게이션 없이 시술자가 손으로 직접 말초 폐병변까지 도달하는 기관지를 추적하여 기관지 지도를 그린 뒤 이 지도를 참고하여 검사를 시행한 군이다. 조직검사 부위의 적절성은 초음파 기관지내시경 및 X- 선 형광투시법으로 확인하였다.

연구 결과: 각각 64 명의 환자가 등록되었다. 등록된 환자들 중 VBN 군에서 1 명이 기관지내 병변이 존재하여 검사에서 제외되었으며 5 명이 추적관찰 되지 않아 탈락되었고 NVBN 군에서는 3 명이 추적관찰 되지 않아 탈락되었다. 최종분석에는 VBN 군은 57 명, NVBN 군은 61 명이 등록되었다. 연구결과 두 군에서 등록된 환자들의 나이, 성별, 병변의 크기, 병변의 위치, CT 상에서 관찰된 병변의 특징 등 기본적인 특성은 차이가 나지 않았다. 진단률은 VBN 군은 41/57 (72%) 였으며, NVBN 군은 49/61 (80%)로 두 군간의 유의한 차이는 관찰되지 않았다. 또한 총시술시간이나 병변까지 도달하는 시간 등에 있어서도 VBN 군과 NVBN 군에서 차이는 나지 않았고 합병증도 두 군에서 통계학적으로 유의한 차이는 관찰되지 않았다.

결론: CT workstation 으로도 VBN 과 유사한 기관지의 3 차원적인 구성이 가능하지만, 손으로 그린 지도만으로 검사를 시행한 NVBN 군과 비교하여 볼 때, VBN 군에서 진단률의 향상이나 시술시간의 차이, 합병증의 차이 등은 관찰되지 않았다. 따라서 말초 폐병변을 진단하는데 있어, 숙련된 기관지내시경 시술자의 경우, 병변까지 도달할 수 있

는 자세한 기관지 지도를 그릴 수만 있다면 3 차원적인 영상이 있는 VBN 과 유사한 효과를 거둘 수 있을 것으로 생각된다.

중심단어: 말초 폐병변, 가상 기관지내시경 네비게이션, 기관지 지도, CT workstation,

차 례

그림목차

표 목차

Background

With recent developments in computed tomography (CT) technology, especially the introduction of low dose CT for lung cancer screening, the detection rate of peripheral lung lesion (PLL) has been increased (1). Causes of PLL are various, including both benign and malignant diseases. The incidence of malignancy in such lesion ranges from 10 to 70% (2, 3). To establish a tissue diagnosis, multiple approaches including surgical resection, CT-guided percutaneous transthoracic needle biopsy (TTNB) and bronchoscopy could be undertaken. In case of high probability of malignancy, surgical resection might be a considerable option. However, indeterminate probability of malignancy, less invasive way such as TTNB or bronchoscopy could be considered as diagnostic options (4). Of the two, TTNB is currently preferred because of its very high diagnostic yield (about 90%) (5, 6). However, complication of TTNB is relatively common and the rate of pneumothorax and hemoptysis have been reported to be 15-20% and 1-5%, respectively (4, 7).

Although the diagnostic yield of conventional bronchoscopy is not good for PLL (~30%) (4), it could be much improved with recently developed additional bronchoscopic techniques such as radial endobronchial ultrasound (EBUS), virtual bronchoscopic navigation (VBN), or electromagnetic navigation (EMN). According to recent studies (8, 9), combined methods such as “EBUS” plus “EMN” or “EBUS” plus “VBN” further improved the diagnostic yield of PLL without compromising safety.

The problem is medical expenses. While EBUS is available at relatively low cost, VBN

and EMN are very expensive. For EBUS, although training to identify the route to the PLL (hand drawing of bronchial map based on CT images) are needed (10, 11), mini probe and driving unit for EBUS cost 7 million won and 25 million won (in Korean currency) respectively. In contrast, in case of EMN, two systems are commercially available (Veran and superDimension), and they cost over 200 million won. In case of VBN system, Lungpoint and Directpath are commercially available and they cost over 100 million won (12). Compared to the price of EBUS, latter two systems impose a high cost burden to hospital.

As an alternative and adaptive way, we used a CT workstation that was widely used in coronary artery reconstruction (13) and virtual colonoscopy (14-16). The CT workstation has a capability to reconstruct three-dimensional (3D) image and could make virtual bronchosopy. Previous two retrospective studies showed that "VBN by CT workstation" improved diagnostic yield for PLL (17, 18). In addition, CT workstation was offered as default program, so additional costs would not be charged (19). We used CT workstation called "Aquarius iNtuition Viewer" to make VBN (Figure 1). In the present study, endobronchial ultrasound guide-sheath transbronchial lung biopsy (EBUS GS TBLB) was done at PLL with or without assist of VBN by CT workstation. We performed a prospective randomized controlled trial to investigate whether VBN by CT workstation could improve diagnosis yield of PLL.

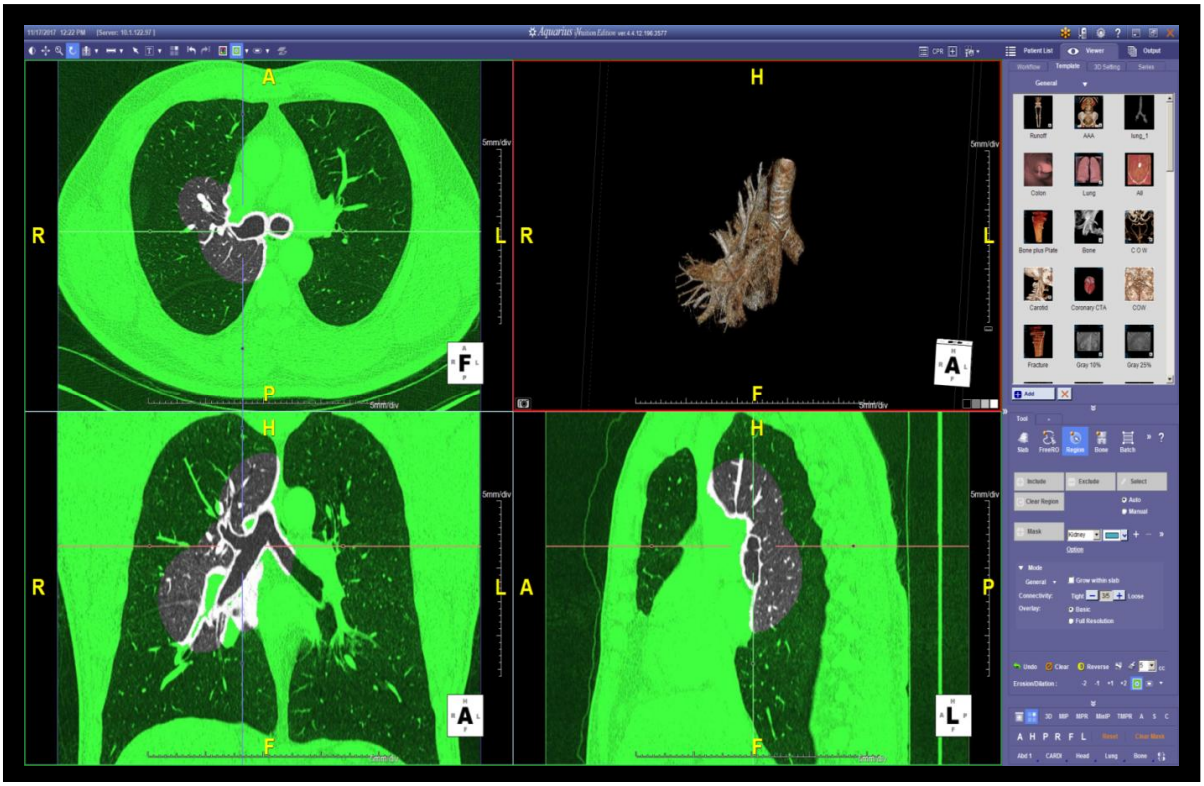

Figure 1. VBN by CT workstation (Aquaris iNtuition, TeraRecon).

Materials and methods

Patients: VBN group and non-VBN (NVBN) group

Between February 2017 and February 2018, 128 patients with PLLs on chest CT who visited Ulsan University Hospital were enrolled in this study (Figure 2). Eligible patients were adults (≥ 20 years) with PLL. PLL were defined as lesions that are surrounded by normal lung parenchyma without any CT evidence of endobronchial abnormality and unlikely to be visualized by bronchoscopy (8, 20). The exclusion criteria were as follows: evidence of endobrochial disease revealed by chest CT, percutaneous oxygen saturation < 90%, a range known severe co-morbid conditions (unstable angina, acute myocardial infarction with the past 3months, severe asthma or uncontrolled pulmonary infection), pregnancy and unable to proceed without anticoagulant or antiplatelet medication (8, 20). Eligible patients were randomly divided into the VBN group and non-VBN (NVBN) group. Informed consent was obtained from all patients and the study protocol had been approved by the institutional review board of Ulsan University Hospital (IRB number UUH-2017-01-013).

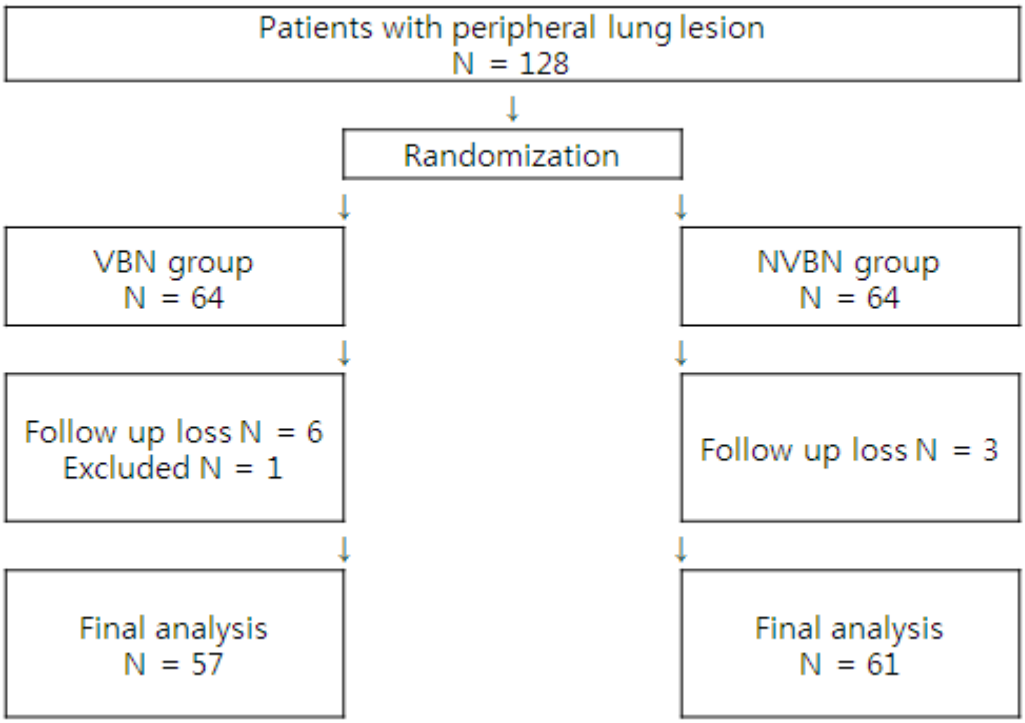

Figure 2. Flow diagram of EBUS-GS TBLB protocol .

Hand-drawn bronchial map and virtual bronchoscopy image (VBI)

All patients underwent CT scan prior to bronchoscopy (256-MDCT scanner: Somatom Definition AS+ and Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). Images were reconstructed twice with the slice thickness 1.0 mm and 2.0 mm with a high spatial-frequency-reconstruction kernel (B40) without interval. In NVBN group, EBUS GS TBLB was performed with the hand-drawn bronchial map based on the above CT images (Figure 3) (10, 11). VBN group underwent EBUS GS TBLB with the use of VBI in addition to the hand-drawn bronchial map (Figure 4). Two experienced radiologist (S. Lim and W.-J. Kwon) processed CT acquisition data to VBI by using a high-performance workstation (TeraRecon Aquarius iNtuition, Foster City, CA).

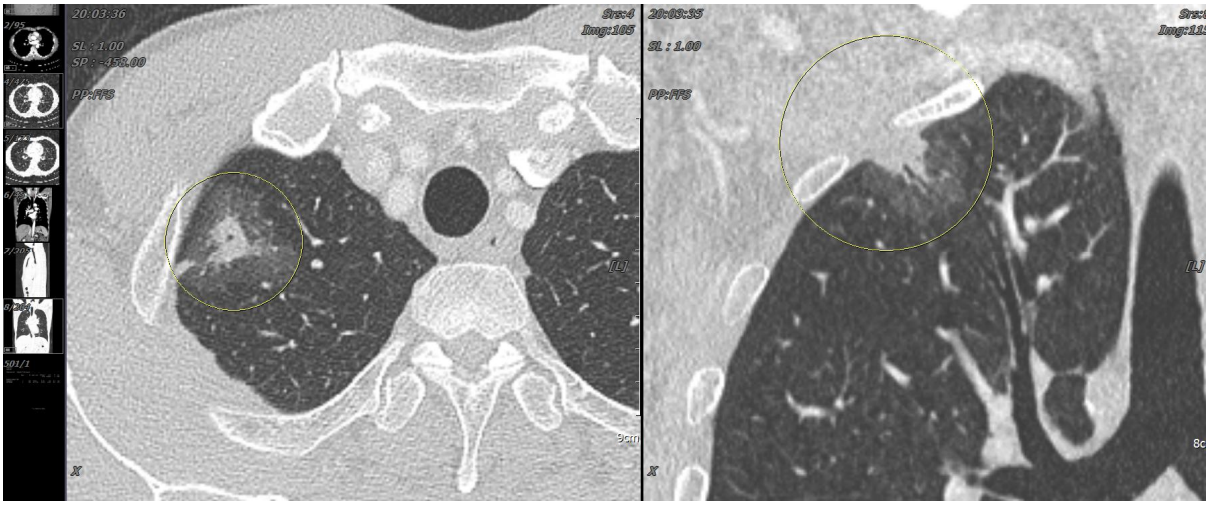

Figure 3. A example case of the NVBN group.

(A). Irregular shaped PLL was examined in LUL on Chest CT.

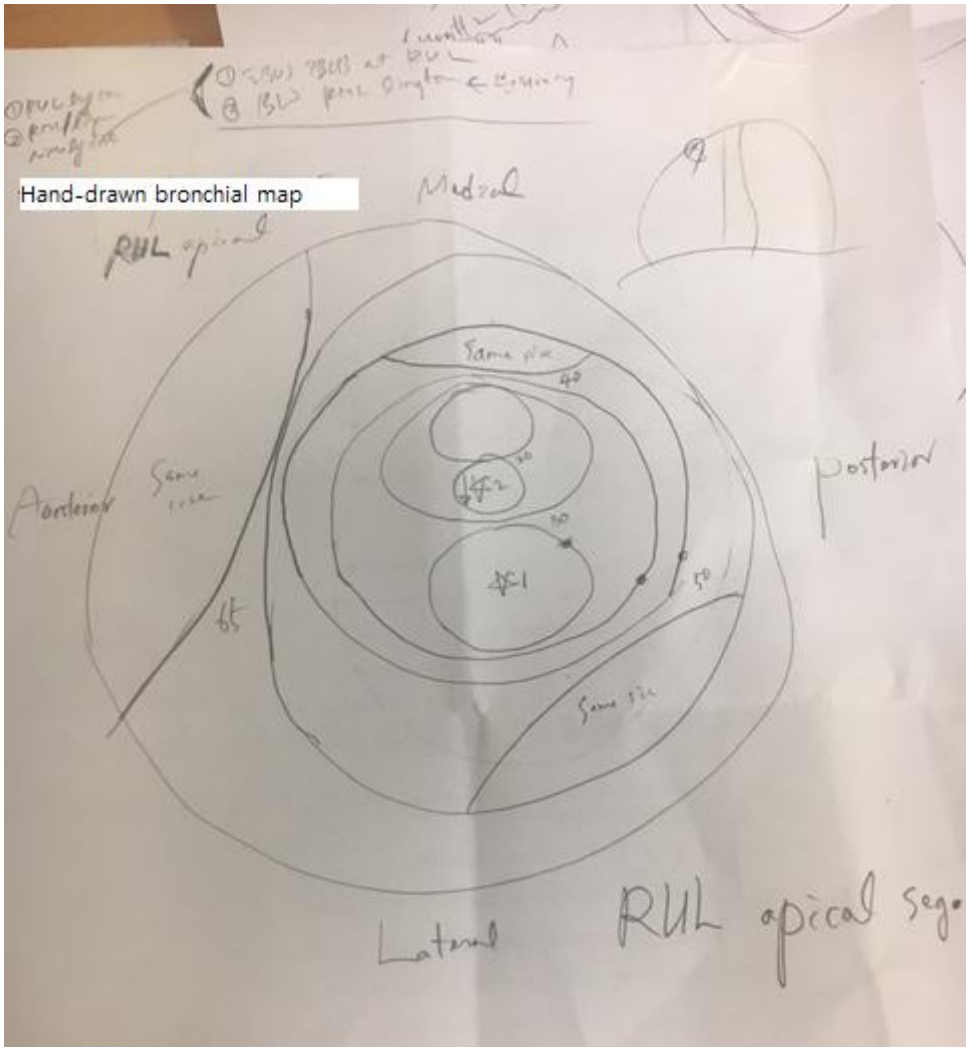

Figure 3. A example case of the NVBN group.

(B). With detailed examination of chest CT, manual bronchial map was drawn.

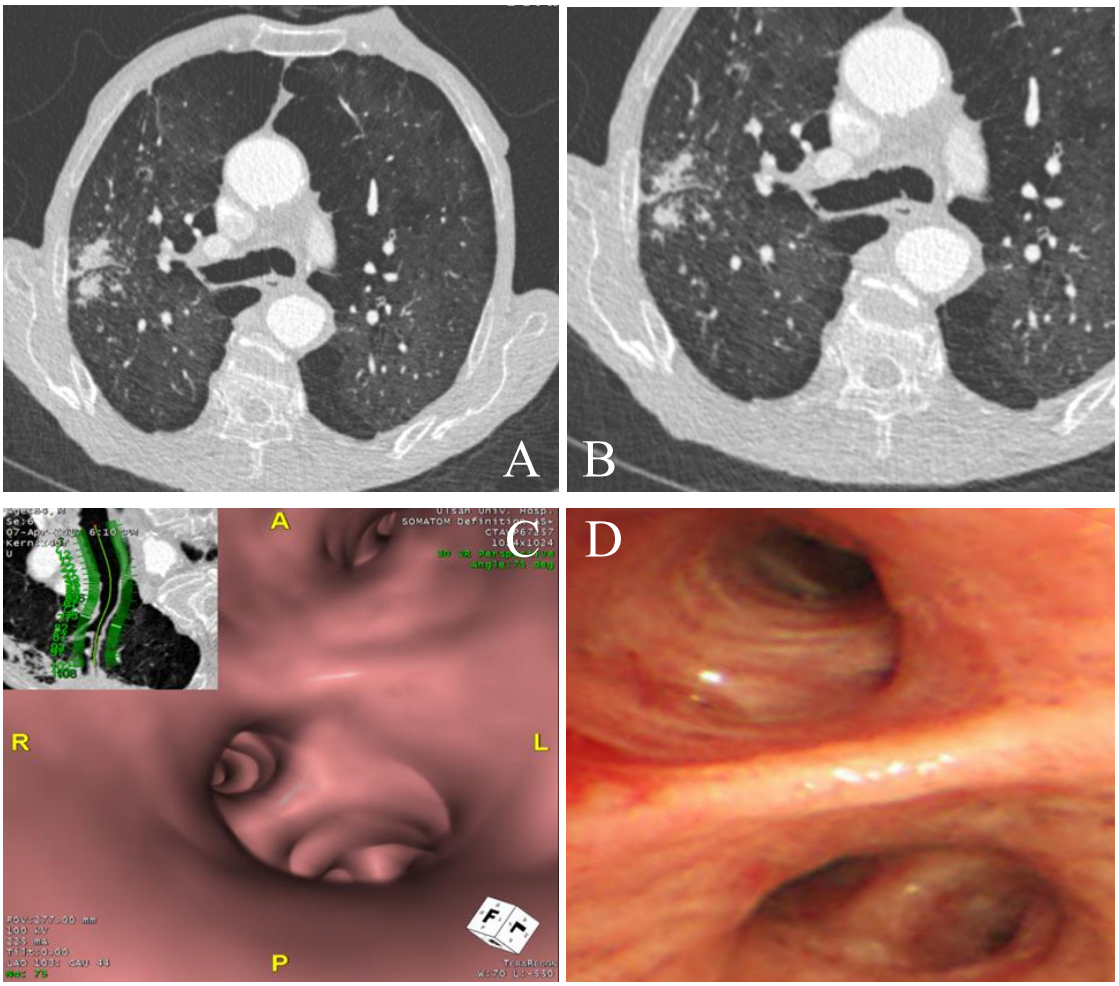

Figure 4. A representative case of the VBN group.

(A). Irregular shaped PLL was examined in RUL on Chest CT.

(B). The PLL had bronchus sign.

(C, D) Virtual bronchoscopy using the CT workstation.

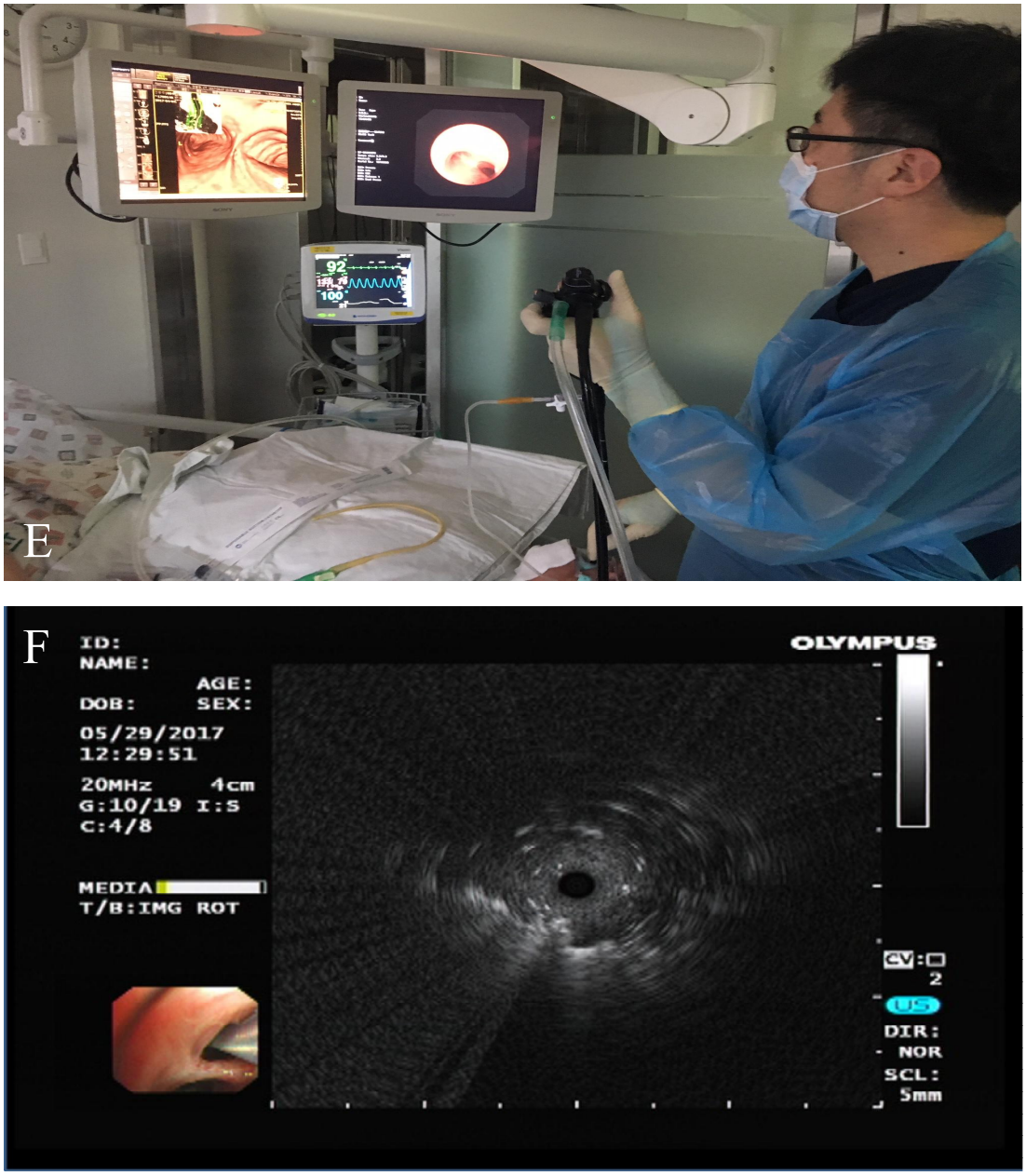

Figure 4. A representative case of the VBN group.

(E) Actual procedure process.

(F) ByVBN with rEBUS, adequate EBUS image was obtained..

Endobronchial ultrasound guided-sheath transbronchial lung biopsy (EBUS GS TBLB)

Two experienced bronchoscopists (S. Bae and T. Lee) performed EBUS GS TBLB as previously described (11, 21, 22). Firstly, thin bronchoscope (outer diameter, 4.0mm~4.2mm, BF-P260F or BF-P290, Olympus, Japan) was inserted as much as possible into the bronchus nearest to the PLL. Secondly, radial EBUS probe (UM-S20-17S, Olympus, Japan) was inserted with GS (K-201, Olympus, Japan) through the working channel of bronchoscope. By EBUS imaging, it was confirmed to have reached to the target lesion. Biopsy and brush were performed only when a lesion was confirmed by EBUS visualization (within or adjacent). After the lesion was confirmed, lastly, the EBUS probe was removed but GS remained at the lesion. Brush and biopsy forcep were introduced via the GS to obtain cytology and pathologic sampling. Most of the procedures were carried out with the help of fluoroscopy. All cases were performed by conscious sedation under the guidance of anesthesiologists (S.E. Park and Y.J. Shin). Routine chest radiograph was done within 2 hours after the procedure.

Baseline data gathering and final diagnosis establishing

Baseline characteristics of all enrolled patients were collected: age, sex, PLL size, PLL distance from the pleura, lobar location of PLL, bronchus sign and nature of PLL on chest CT. The bronchus sign means that there is an open bronchus connected from proximal airway in the PLL (23). The PLLs were classified into three types depending on the chest

CT nature: a ground glass opacity, a mixed opacity, and a solid opacity. The ground glass opacity is defined as focal densities in which underlying lung morphology is preserved (4). A mixed opacity was defined when a lesion contains both solid and ground glass opacities but ground glass opacity is > 50% (4).

The final diagnosis was basically established according to pathological diagnostic results.

If not diagnosed by EBUS GS TBLB, further examination (TTNB or surgical resection) was performed. If the pathologic result was not malignant, decreasing or invariant lesions of 6 months in follow-up CT scan were regarded as a benign lesion (17, 24).

Outcome variables

The primary outcome of the present study is diagnostic yield, which is the fraction of people whose final diagnosis has been confirmed by EBUS GS TBLB (8, 9, 25). As secondary outcomes, various indicators related to EBUS GS TBLB procedure were investigated (8, 25, 26): success rate of EBUS visualization (EBUS probe within or adjacent to PLL) (26), total procedure time (from when the bronchoscopy passes through the vocal cords, until the end of the procedure), total EBUS time (from the start of EBUS, until the end of the procedure), navigation time (from the start of EBUS, until the lesion is found by EBUS), endoscopically inserted bronchial generation (a segmental bronchus was

defined as third generation), and fluoroscopy exposure time. Development of complication (bleeding/hemoptysis, pneumothorax) was also monitored and recorded.

Statistical analysis

Statistical analyses were performed using SPSS 21 (IBM Corporation, Armonk, New York). Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are presented as percentages. To explore the association, independent t-test was used for continuous variables and the chi-square test for dichotomous variables. Diagnostic yields were analyzed by the chi-square test. In order to identify factors that affect diagnosis yield regardless of VBN or NVBN, univariate and multivariate analyses were performed to all enrolled patients. Multivariate logistic regression analyses were performed using variables found to be significant (ie, $P < 0.05$) in the univariate analysis and those reported to be associated diagnostic yield in previous studies (lesion size [$\geq$ 20 mm vs < 20 mm], EBUS visualization type [within vs adjacent to], bronchus sign on CT [yes vs no], Chest CT nature [not solid vs solid])(25, 26), and basic demographic variables (age, gender). A P value less than 0.05 was considered statistically significant in all analyses.

RESULTS

Subjects and measured variables

Total 128 patients were recruited. The patients were randomly divided into two groups. Table 1 shows the baseline characteristics of the 128 patients. The mean age of total patients was 64.29±12.61 years (63.50±11.30 in VBN, 65.09±13.83 in NVBN). The proportion of male was 58% and 61% in VBN and NVBN, respectively. Lesion size was 28.43±18.20mm in VBN and 31.06±15.51 mm in NVBN. Distance of PLL from pleura was 10.28±10.79 mm in VBN and 8.39±9.80 mm in NVBN. PLL in VBN is relatively smaller and far from pleural than in NVBN, however there is no statistical difference. Location and nature of PLL is similar in both group. Almost PLL have bronchus sign. (60 cases, 94% in VBN vs 57 cases, 89% in NVBN). The proportion of malignancy and benign diseases were similar between the two groups. From the histological aspect of the PLL, malignant lesions were 80 (64%) and benign lesion were 38 (30%). The most common malignancy was adenocarcinoma. And the most common benign lesion were inflammatory lesion and tuberculosis (Table 2). Baseline characteristics were similar between the two groups.

Table 1. Clinical characteristics and final diagnosis

Variables	Total (n =128)	VBN (n =64)	NVBN (n =64)	p-value
Age, years, mean ± SD	64.29±12.61	63.50±11.30	65.09±13.83	0.477
Gender, male (%)	76 (56)	37 (58)	39 (61)	0.719
Lesion size (mm(SD))	29.75±16.91	28.43±18.20	31.06±15.51	0.381
Distribution of size				1.000
≤ 20mm, n (%)	42 (33)	21 (33)	21 (33)	
> 20mm, n (%)	86 (67)	43 (67)	43 (67)	
Distance from pleura	8.88±9.98	10.28±10.79	8.39±9.80	0.301
Location of PLL (%)				0.226
Right upper lobe	45 (35)	22 (34)	23 (36)	
Right middle lobe	11 (9)	7 (11)	4 (6)	
Right lower lobe	28 (22)	16 (25)	12 (19)	
Left upper lobe	23 (18)	13 (20)	10 (16)	
Left lower lobe	21 (16)	6 (9)	15 (23)	
Nature of PLL on chest CT (%)				0.515
Ground glass opacity	4 (3)	3 (5)	1 (2)	
Mixed	24 (19)	13 (20)	11 (17)	
Solid	100 (78)	48 (75)	52 (81)	
Bronchus sign on CT (%)				0.344
Absent	117 (91)	60 (94)	57 (89)	
Present	11 (9)	4 (6)	7 (11)	
Final diagnosis				0.273
Malignant	80 (63)	41 (64)	39 (61)	
Benign	38 (28)	16 (25)	22 (34)	
Undetermined	10 (9)	7 (11)	3 (5)	

Table 2. Diagnostic yield by histological diagnosis

Histologic diagnosis	N (%)	Yield (%)
Malignant lesions	80 (63)	
Adenocarcinoma	44 (34)	31(70)
Squamous cell carcinoma	8 (6)	5 (63)
Small cell lung cancer	6 (5)	5 (83)
Adenosquamous carcinoma	2 (2)	2 (100)
Metastasis	4 (3)	3 (75)
Neoplastic lesion	6 (5)	2 (33)
NSCLC	9 (7)	7 (78)
Lymphoma	1 (1)	1 (100)
Benign	38 (30)	
Hemangioma	1 (1)	0 (0)
NTM	1 (1)	1 (100)
Sarcoidosis	1 (1)	1 (100)
Pneumonia	1 (1)	1 (100)
Organizing pneumonia	3 (2)	2 (67)
Tuberculosis	10 (8)	8 (80)
Chronic inflammation	16 (12)	16 (100)
Aspergillosis	5 (4)	5 (100)
Undetermined	10 (7)	
Total	128 (100)	

After randomization, one patient in VBN group had a visible endobronchial lesion. Five and one patients in the VBN and NVBN group, respectively, patients were follow up loss. Therefore we excluded these 7 patients from the initial patient population, total 121 patients were included and finally analyzed. The study flow was shown in Figure 2.

Secondary outcome was shown in Table 2. Total procedure time was 26.53±10.24 min in VBN and 25.81 ±9.22 min in NVBN (p=0.932). It was not significantly different in the VBN versus the NVBN group. Total EBUS time, navigation time and fluoroscopy time were rather similar in both groups. No severe adverse events were occurred during procedure except 3 case of mild pneumothorax which did not require chest tube insertion in 2 patients from VBN and 1 patient from NVBN. small amount blood tinged sputum was found in a patients from the NVBN and it was disappeared without any medication.

Table 3. Bronchoscopic result in analyzed patient

Variables	Total (n = 117)	VBN (n = 57)	NVBN (n = 61)	P value
Duration (min)				
Total procedure time	25.33±10.82	26.53±10.24	25.81±9.22	0.932
Total EBUS time	21.00±9.70	22.10±9.30	22.28±9.51	0.565
Navigation time	9.57±7.20	10.02±7.30	8.67±7.02	0.917
Fluoroscopy	2.21±2.42	2.34±2.47	2.96±4.69	0.329
Complication (n, %)				
Pneumothorax	3 (3)	2 (4)	1 (2)	0.209
Blood tinged sputum	1 (1)	0 (0)	1 (2)	

Table 4 shows the diagnostic yields for this study. Diagnostic yield did not differ significantly between two groups. VBN leads to a diagnosis 41/57 (72%) cases, and 49/61 (80%) cases were diagnostic in NVBN ($p = 0.284$).

Table 4. Diagnostic yield according to disease type

Variables	VBN (n=57)	NVBN (n =61)	P value
Overall yield : Result/Total(%)	41/57(72)	49/61(80)	0.284
Yield for malignant disease			
Sensitivity	26/41 (63)	30/39 (61)	0.188
Specificity	16/16 (100)	22/22(100)	-
Positive predictive value	26/26 (100)	30/30(100)	-
Negative predictive value	16/31 (52)	22/31(71)	0.307
Yield for benign disease			
Sensitivity	15/16 (94)	19/22(86)	0.464
Specificity	26/26 (100)	30/30(100)	-
Positive predictive value	15/15 (100)	19/19(100)	-
Negative predictive value	26/42 (62)	30/42(71)	0.355

In univariate analysis (Table 5), the placement of the EBUS probe and the presence of bronchus sign on CT cased a significant difference in yield. Lesion size and feature of PPL was not statistically significant. By multivariate analysis, placement of EBUS probe was statistically significant only.

Table 5. Logistic regression analysis of factors affecting diagnostic yield

Variables	Univariate analysis N/total N (%)	p-value	Multivariate analysis Odds ratio [95% CI]	p-value
Age (years), no (%)				
≤ 70	54/73 (74)	0.456		
> 70	36/45 (80)			
Gender, no (%)				
Male	52/71 (73)	0.343		
Female	38/47 (81)			
Lesion size				
≥ 20mm	67/83 (81)	0.084		
< 20mm	23/35 (66)			
Placement				
within	70/81 (86)	< 0.01	4.709 [1.843-12.036]	0.001
adjacent	20/37 (54)			
Bronchus sign on CT				
Yes	86/109 (79)	0.030		
No	4/9 (44)			
CT finding				
Not solid	16/24 (67)	0.219		
Solid	74/94 (79)			

DISCUSSION

Originally our study was planned to demonstrate that the utility of the CT workstation as a alternative candidate of virtual bronchoscopy for diagnostic bronchoscopy with rEBUS. In reports by Shinagawa et al., the diagnostic yield VBN for PLL < 20mm in diameter was 65-66% (26) Iwano et al. reported diagnostic yield of PLL by VBN was 79% (18). The diagnostic yield of VBN in ours study was 71.9% and it showed not inferior diagnostic yield for PLL compared to other studies. Through this, reconstruction image by CT workstation could be utilized as a VBN for PLL diagnosis.

In addition, the remarkable point in our study is that there is no statistical difference in the diagnostic yield between VBN group and NVBN group. This is probably owing to the limitation of resolution of VBN. VBN image start from central to peripheral with manual adjustment (17), so during VBN, when navigation finishes distal bronchus that could not be reconstructed in 3D image, the process is abruptly terminated or an incorrect route is generated within the bronchi. In contrast, in case of NVBN, operator can evaluate bronchial pathway from center to peripheral or peripheral to central with multiple direction view on chest CT to find pathway more flexibly and deleted unwanted artifacts along the involved bronchi or corresponding vessels. By draw detailed bronchial mapping, operator could fine even more detailed pathway and prepare secondary alternative pathway. Because of this reason, VBN performed using CT workstation is available tool for diagnosis of PLL, however, it is not superior to detailed manual bronchial map.

The results of secondary outcome such as total procedure time, navigation time, unlike the previous study (8), were similar in VBN and NVBN. We think that it dose not mean that both VBN and NVBN were ineffective modalities, rather it is an approve of the fact that detailed mapping of NVBN can be also useful.

In our study, factors which affect on diagnostic yield was placement of rEUBS probe and bronchus sign on chest CT in the univariate analysis. Previous reports have indicated that the placement of rEBUS is the only significant diagnostic factor (25, 26) and Okachi et al. reported that "within" probe position was found to be significantly associated with a successful diagnosis using radial EBUS (19). In case of bronchus sign on Chest CT, it has been shown to be a valuable factor for the diagnosis of PLL (19, 27, 28). Bronchus sign means that there are leading bronchus on chest CT which could make EBUS probe and biopsy forceps to get through to a higher order of bronchus, therefore bronchus sign on chest CT has been shown to be a important.

Lesion size was known for significant factor for the diagnostic rate EBUS-TBLB using VBN, which was same for conventional bronchoscopy(18, 19). However, in our study, it was not a significant diagnostic factor. Like the study result of Eberhardt et al (9), lesion size is unlikely to confounding factor in our study.

Previous studies showed the diagnostic yield for a non solid PLL was lower than for a solid PLL.(17, 18) Same results was acquired in our study. It is related to the nature of non solid PLL. Usually non solid type PLL is considered an early stage of malignancy, cancer

cells might not be exposed on the surface of the bronchial wall without tumor obstruction (3, 18, 29). Fluoroscopy or EBUS might be detect even the non solid PLL (26, 30), however passed forceps through the target lesion couldn't get appropriate sample tissue.

In multivariate analysis, placement of probe was the significant factor. This result was similar to the previous randomized control trial of VBN with rEBUS (8).Therefore, we think CT workstation and bronchial mapping has a comparable potential like VBN as a additional modality for diagnostic bronchoscopy of PLL. Conversely, in the multivariate analysis, the diagnostic yield was similar regardless of the lesion size and bronchus sing on CT. In general, to reach smaller lesion or lesion without bronchus sign, it is necessary to trace detailed and fined bronchial branches. Unreachable lesion, we often place probe to a nearby branch. For this reason, diagnostic outcome of these lesions are known to be low (23, 31). In case of VBN, abrupt end of navigation was possible, however with detailed bronchial mapping by manual, it could be applied to make an expected route to outside lesion.

Except anatomical limitation, EBUS detection rate in our study was same in both group. The acquisition of an EBUS image during probe insertion meant that the lesion has been reached, indicating VBN made a correct route. EBUS detection has been reported to affect diagnostic yield (22, 26). The position of the probe, especially if the within the lesion, is known to be important for PPL diagnosis (17, 22, 26). Furthermore, precise guidance of PLL is needed in case of therapeutic approach (32).

In our study, diagnostic yield of malignancy was higher than benign disease. For benign disease, whether we obtain an adequate specimen, it is difficult to determine final diagnosis due to the lack of specific histologic characterization of benign disease (24).

Our study showed a low complication rate (3.12%) comparable to previously reported rEBUS studies(28, 33). This is much lower than general complication rate of TTNB (4). The occurrence of pneumothorax and other complication were similar in both group. Therefore, VBN by CT work station may be a viable option for diagnosing PLL and NVBN also could be utilized as a alternative option.

Our present study has several limitations to note. First, this study did not measure creation time of the VBI or bronchial mapping. In some situations, VBN may be preferable when the medical staffs did not have enough time or experience about procedure. Accuracy of bronchial mapping was affected on the experience and skill of operator, it could cause different result. Second, because the criteria for the diagnosis of benign disease for PLL have not yet been standardized and vary among studies, we followed criteria proposed by Shinagawa et al (34). Not only with histological examination of bronchial washing fluid, but also those of bacterial examination alone was used in this study. Third, this study was performed at a single institution. A Multicenter trial may be more accurate, because the difference in skill between medial staff could prove to be a confounding factor. Forth, indeterminate cases, 6months were defined previous study (24), however the longer period

could prove more accurate diagnosis

CONCLUSIONS

In conclusion, compared with bronchial mapping only in NVBN, VBN did not show to improve diagnostic yield and did not make differences in the procedure time. In case of experienced bronchoscopist, diagnosis of PPL could be performed with detailed bronchial manual map with CT images. A similar result can be obtained without help of 3D reconstruction of VBN.

Reference

1. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology. 1996;201(3):798-802.
2. Swensen SJ, Silverstein MD, Edell ES, Trastek VF, Aughenbaugh GL, Ilstrup DM, et al. Solitary pulmonary nodules: clinical prediction model versus physicians. Mayo Clin Proc. 1999;74(4):319-29.
3. Khouri NF, Meziane MA, Zerhouni EA, Fishman EK, Siegelman SS. The solitary pulmonary nodule. Assessment, diagnosis, and management. Chest. 1987;91(1):128-33.
4. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S-e120S.
5. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e65S.
6. Asano F, Eberhardt R, Herth FJ. Virtual bronchoscopic navigation for peripheral pulmonary lesions. Respiration. 2014;88(5):430-40.

7. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Ann Intern Med. 2011;155(3):137-44.

8. Ishida T, Asano F, Yamazaki K, Shinagawa N, Oizumi S, Moriya H, et al. Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial. Thorax. 2011;66(12):1072-7.

9. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med. 2007;176(1):36-41.

10. Noriaki Kurimoto Ti, Teruomi Miyazawa, Masamichi Mineshita. Endobronchial ultrasonography for peripheral pulmonary lesions. Ultrasound in medicine and biopoty. 2017;43(S1).

11. Kurimoto N. SC19.01 Diagnosis of Lung Cancer: Multimodal Devices for Peripheral Pulmonary Lesions. Journal of Thoracic Oncology. 2017;12(1):S120-S1.

12. Shepherd RW. Bronchoscopic pursuit of the peripheral pulmonary lesion: navigational bronchoscopy, radial endobronchial ultrasound, and ultrathin bronchoscopy. Curr Opin Pulm Med. 2016;22(3):257-64.

13. Becker A, Leber A, White CW, Becker C, Reiser MF, Knez A. Multislice computed tomography for determination of coronary artery disease in a symptomatic patient population. Int J Cardiovasc Imaging. 2007;23(3):361-7.

14. Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. Radiology. 2011;259(2):393-405.

15. Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med. 2008;359(12):1207-17.

16. Horton KM, Horton MR, Fishman EK. Advanced visualization of airways with 64-MDCT: 3D mapping and virtual bronchoscopy. AJR Am J Roentgenol. 2007;189(6):1387-96.

17. Matsumoto Y, Izumo T, Sasada S, Tsuchida T, Ohe Y. Diagnostic utility of endobronchial ultrasound with a guide sheath under the computed tomography workstation (ziostation) for small peripheral pulmonary lesions. Clin Respir J. 2017;11(2):185-92.

18. Iwano S, Imaizumi K, Okada T, Hasegawa Y, Naganawa S. Virtual bronchoscopy-guided transbronchial biopsy for aiding the diagnosis of peripheral lung cancer. Eur J Radiol. 2011;79(1):155-9.

19. Okachi S, Imai N, Imaizumi K, Iwano S, Ando M, Hase T, et al. Factors Affecting the Diagnostic Yield of Transbronchial Biopsy Using Endobronchial Ultrasonography with a Guide Sheath in Peripheral Lung Cancer. Intern Med. 2016;55(13):1705-12.

20. Asano F, Shinagawa N, Ishida T, Shindoh J, Anzai M, Tsuzuku A, et al. Virtual

bronchoscopic navigation combined with ultrathin bronchoscopy. A randomized clinical trial. Am J Respir Crit Care Med. 2013;188(3):327-33.

21. Katsurada M, Izumo T, Nagai Y, Chavez C, Kitagawa M, Torii J, et al. The dose and risk factors for radiation exposure to medical staff during endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions under X-ray fluoroscopy. Jpn J Clin Oncol. 2014;44(3):257-62.

22. Izumo T, Sasada S, Chavez C, Tsuchida T. The diagnostic utility of endobronchial ultrasonography with a guide sheath and tomosynthesis images for ground glass opacity pulmonary lesions. J Thorac Dis. 2013;5(6):745-50.

23. Gaeta M, Pandolfo I, Volta S, Russi EG, Bartiromo G, Girone G, et al. Bronchus sign on CT in peripheral carcinoma of the lung: value in predicting results of transbronchial biopsy. AJR Am J Roentgenol. 1991;157(6):1181-5.

24. Maekura T, Sugimoto C, Tamiya A, Saijo N, Naoki Y, Koba T, et al. Combination of virtual bronchoscopic navigation, endobronchial ultrasound, and rapid on-site evaluation for diagnosing small peripheral pulmonary lesions: a prospective phase II study. J Thorac Dis. 2017;9(7):1930-6.

25. Tamiya M, Okamoto N, Sasada S, Shiroyama T, Morishita N, Suzuki H, et al. Diagnostic yield of combined bronchoscopy and endobronchial ultrasonography, under LungPoint guidance for small peripheral pulmonary lesions. Respirology. 2013;18(5):834-9.

26. Yamada N, Yamazaki K, Kurimoto N, Asahina H, Kikuchi E, Shinagawa N, et al. Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest. 2007;132(2):603-8.

27. Wang C, Li X, Zhou Z, Zhao H, Li Z, Jiang G, et al. Endobronchial ultrasonography with guide sheath versus computed tomography guided transthoracic needle biopsy for peripheral pulmonary lesions: a propensity score matched analysis. J Thorac Dis. 2016;8(10):2758-64.

28. Yoshikawa M, Sukoh N, Yamazaki K, Kanazawa K, Fukumoto S, Harada M, et al. Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without X-ray fluoroscopy. Chest. 2007;131(6):1788-93.

29. Ikezawa Y, Sukoh N, Shinagawa N, Nakano K, Oizumi S, Nishimura M. Endobronchial ultrasonography with a guide sheath for pure or mixed ground-glass opacity lesions. Respiration. 2014;88(2):137-43.

30. Asano F, Matsuno Y, Tsuzuku A, Anzai M, Shinagawa N, Yamazaki K, et al. Diagnosisof peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. Lung Cancer. 2008;60(3):366-73.

31. Sasada S, Izumo T, Chavez C, Matsumoto Y, Tsuchida T. A new middle-range

diameter bronchoscope with large channel for transbronchial sampling of peripheral pulmonary lesions. Jpn J Clin Oncol. 2014;44(9):826-34.

32. Hagmeyer L, Priegnitz C, Kocher M, Schilcher B, Budach W, Treml M, et al. Fiducial marker placement via conventional or electromagnetic navigation bronchoscopy (ENB): an interdisciplinary approach to the curative management of lung cancer. Clin Respir J. 2016;10(3):291-7.

33. Kikuchi E, Yamazaki K, Sukoh N, Kikuchi J, Asahina H, Imura M, et al. Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. Eur Respir J. 2004;24(4):533-7.

34. Shinagawa N, Nakano K, Asahina H, Kikuchi E, Ito T, Matsuno Y, et al. Endobronchial ultrasonography with a guide sheath in the diagnosis of benign peripheral diseases. Ann Thorac Surg. 2012;93(3):951-7.

Abstract

Background: Bronchoscopy is useful tool in the diagnosis of lung nodule. But the yield of peripheral lung lesion (PLL) is lower compared with central and intermediate lesion. Endobronchial ultrasound guide-sheath transbronchial lung biopsy (EBUS-GS-TBLB) has been used to overcome such limitation, Recent studies show combined method, such as radial EBUS(rEBUS) and electronic magnetic navigation (EMN) or rEBUS an virtual bronchoscopy navigation (VBN) improve the diagnostic yield in PLL. However, those system impose a high cost burden to hospital. Accordingly we attempted to use CT work station as a VBN to raise diagnostic yield of EBUS-GS-TBLB for PLL.

Methods: From February 2017 to February 2018, 128 patients underwent EBUS-GS to diagnosis PLL at Ulsan University Hospital. The patients were randomized to VBN group (the group using CT work station to reconstruct bronchus) or non-VBN (NVBN, the group not using CT work station and proceeded procedure with manual bronchial mapping by CT images only).Biopsy site were verified using EBUS-GS and fluoroscopy.

Results: Of the 128 patients, 64 were in VBN group. Diagnostic yield of EBUS-GS-TBLB in VBN group was 72% (41/57) and 80% (49/61) in NVBN group. No statistically significant differences were found between VBN and NVBN group (p=0.284). Also, in terms of the duration of total procedure time (26.53 ± 10.24 vs. 25.81 ± 9.22 min, respectively, p=0.932), duration of EBUS time (22.10 ± 9.30 vs. 22.28 ± 9.51 min, respectively, p =0.565), and duration of navigation time (10.02 ± 7.30 vs. 8.67 ± 7.02 min,

respectively, p =0.917) were similar.

Conclusion: Compared with bronchial mapping only in NVBN, VBN did not show to improve diagnostic yield and did not make differences in the procedure time. In case of experienced bronchoscopist, diagnosis of PPL could be performed with detailed bronchial manual mapping with CT images. A similar result can be obtained without help of 3D reconstruction of VBN.

Keywords: Peripheral lung lesion, Virtual bronchoscopy navigation, manual bronchial map, CT workstation