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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Endobronchial ultrasound transbronchial needle aspiration in older people

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Aim: The usefulness and safety of endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) have been established recently, but no study has evaluated whether or not aging increases the risk of the procedure. In the present study, we aimed to assess the usefulness and safety of EBUS-TBNA in older patients.

Methods: The medical records and database of 109 patients who received EBUS-TBNA between 2008 and 2011 at Nagoya University Hospital, Nagoya, Japan were reviewed retrospectively. All patients underwent bronchoscopy under light sedation with midazolam. A total of 34 patients were aged 70 years or older (the older group) and 75 were aged 69 years or younger (the younger group). We analyzed patients' characteristics, changes of clinical parameters, usage doses of midazolam and lidocaine, procedure duration, geographic data of biopsied lymph nodes, diagnostic yield, and complications in both groups.

Results: There were more comorbidities in the older group. Four patients (11.8%) in the older group had poor performance status (2–3). Systolic blood pressure at baseline was significantly higher in the older group. There were no statistical differences between the two groups in some clinical parameters (minimum oxygen saturation [SpO_2], reduction in SpO_2, maximum oxygen supplementation, elevation of systolic blood pressure, increase of heart rate) during the procedure. Diagnostic performance in older patients was similar to that found in younger patients. There was no difference in the frequency of complications between both groups.

Conclusion: Safety and usefulness of EBUS-TBNA in older people were comparable with those in younger people. **Geriatr Gerontol Int 2013; 13: 986–992.**

Keywords: bronchoscopy, hilar and mediastinal lymph nodes, lung cancer, older people, ultrasound.

Introduction

Lung cancer is still the leading cause of cancer deaths worldwide, and is mainly a disease of older people.[1] More than two-thirds of lung cancer cases occur in people aged 65 years or older, and the median age at diagnosis is 71 years.[2] Accurate staging of the disease is necessary to determine the appropriate treatment and prognosis. The key treatment decision lies in the distinction between those patients who can benefit from surgical resection and those who should receive chemotherapy and/or radiation therapy. In a previous report, lower rates of histological diagnosis, active treatment and survival were seen in older age groups. Older patients are less likely to receive surgery or other therapies, despite the fact that survival after surgery has been repeatedly reported to be independent of age.[3] Indication of surgical resection of non-small cell lung cancer (NSCLC) in older patients should not be denied on the basis of chronological age alone. The 90-day mortality among patients aged ≥70 years who undergo surgery for lung cancer compared acceptably with mortality among younger matched patients.[4] Although the role of surgery in patients with stage IIIA (N2) NSCLC remains undetermined,[5] preoperative evaluation of mediastinal lymph nodes is important for selecting the optimal treatment. Non-invasive staging with chest computed tomography (CT) or positron emission tomography (PET) is associated with high rates of false-positive and false-negative results, respectively.[6] The American College of Chest Physicians recommends invasive

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staging with tissue confirmation of suspected metastatic mediastinal lymph nodes.[7] Mediastinoscopy has traditionally been considered to be a standard for lymph node sampling, but it is rather invasive and might not be suitable for older patients.[8,9]

EBUS-TBNA is a minimally-invasive technique for sampling hilar and mediastinal lymph nodes.[10] Usefulness and safety of the procedures have been established recently,[10–12] but there have been few studies that have evaluated the safety and efficacy in older patients. In the present retrospective study, we assessed the usefulness and safety of EBUS-TBNA in older patients compared with those in younger patients.

Methods

Patients

A total of 109 consecutive adult patients underwent EBUS-TBNA at Nagoya University Hospital between April 2008 and November 2011. Their medical records were reviewed retrospectively in two groups: patients aged 70 years or older ($n = 34$; older group) and patients aged 69 years or younger ($n = 75$; younger group). Patients who underwent another procedure combined with EBUS-TBNA (EBUS-TBNA and bronchoalveolar lavage and/or endobronchial/transbronchial biopsies) were excluded from the study. Institutional review board approval was obtained, but specific informed consent was not required for this retrospective study. Informed consent for each bronchoscopy was obtained before the procedure.

Procedure and sedation

All patients were equipped with an intravenous line for drip infusion. Oxygen saturation (SpO_2) was continuously monitored using pulse oximetry, and blood pressure was monitored every 2 min during the procedure. Patients received oxygen through nasal cannula if required to maintain SpO_2 above 90%. Before starting the sedation, 2% lidocaine was administered topically on the pharynx and upper airways. For light sedation during bronchoscopy, we used intravenous midazolam.[13,14] Male patients aged 65 years or younger and female patients aged 70 years or younger received intravenous midazolam at a dose of 0.075 mg/kg just before initiating the procedure, and supplementary doses of 0.0375 mg were administered during the procedure at intervals of every 20 min. Male patients aged 66–84 years and female patients aged 71–84 years received intravenous midazolam at a dose of 0.05 mg/kg just before initiating the bronchoscopy, and supplementary doses of 0.025 mg/kg were administered during the procedure at intervals of every 20 min. Patients aged 85 years or older received intravenous midazolam at a dose of 0.05 mg/kg just before initiating the procedure, and no supplementary doses of midazolam were administered during the procedure.

Convex probe endobronchial ultrasound (CP-EBUS; BF-UC260FW; Olympus; Tokyo, Japan) was used to carry out EBUS-TBNA. It scans parallel to the insertion direction of the bronchoscope, and is connected to a dedicated ultrasound scanner (EU-C2000; Olympus) with Doppler-flow imaging for the detection of blood vessels. Images can be obtained by directly contacting the probe or by attaching a balloon to the tip and inflating it with saline solution. A dedicated 22-G needle equipped with a protective sheath was passed through the working channel of the bronchoscope. After visualizing the lymph node, the needle was passed out of the sheath, through the airway, and into the lymph node. After penetration into the lymph node, the internal stylet was removed, and negative pressure was applied with a syringe. The needle was moved back and forth inside the lymph node (Fig. 1). Finally, the needle was retrieved and the internal stylet was used once again to push the specimen out onto a slide for cytological and histological examination, followed by a needle rinse with saline.[15,16]

Data collection

We analyzed patients' characteristics, changes of clinical parameters during the procedure, usage doses of midazolam and lidocaine, time required for bronchoscopic procedure, geographic data of biopsied lymph nodes, diagnostic yield, and complications in both groups. The performance status scale described by the Eastern Cooperative Oncology Group (ECOG) was used in the present study.

Statistical analysis

Continuous data were expressed as mean ± standard deviation for normally distributed continuous variables, and median (interquartile range [IQR]) for non-normally distributed continuous variables. Mann–Whitney tests (or *t*-tests if data were normally distributed) and Pearson χ^2-tests were used for continuous and categorical variables, respectively, when comparing the older and younger groups. $P < 0.05$ was considered statistically significant. All analyses were carried out using SPSS version 20.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics are shown in Table 1. During the study period, 34 patients aged 70 years or older and 75 patients aged less than 70 years underwent EBUS-

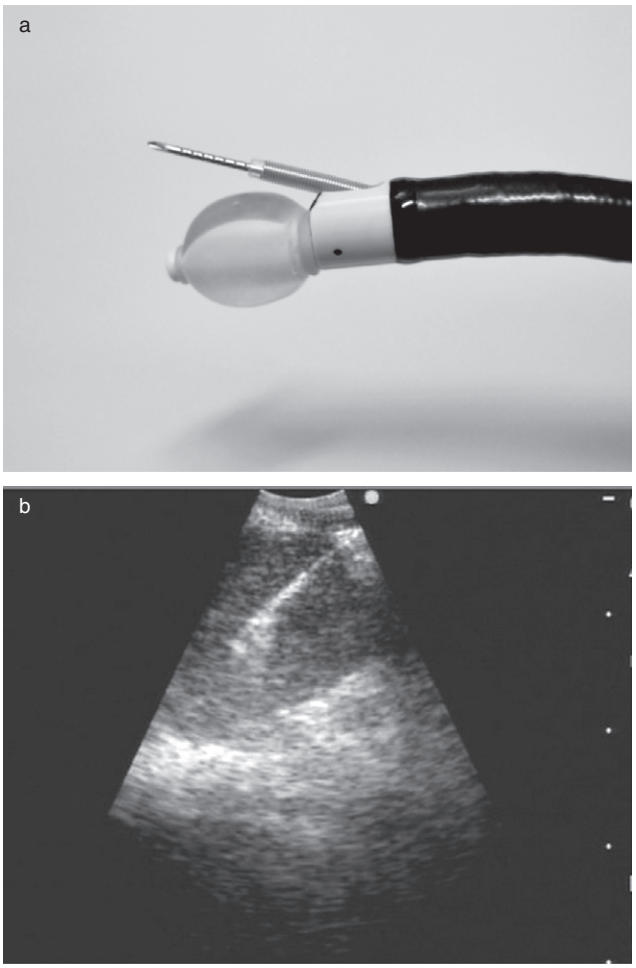

Figure 1 (a) Tip of the ultrasonic puncture bronchoscope (CP-EBUS; BF-UC260FW) with the linear curved-array ultrasonic transducer. The balloon attached to the tip of the bronchoscope is inflated with normal saline solution, and a dedicated transbronchial needle aspiration (TBNA) needle is inserted through the working channel. (b) Real-time CP-EBUS-guided TBNA was carried out. A 22-G needle is seen within the lymph node.

TBNA. The median age of the older group was 76 years (IQR 73–81) and that of the younger group was 62 years (IQR 58–67). We found no significant differences between the groups in the sex proportion and prevalence of smoking history. Four (11.8%) patients in the older group had poor performance status (2 and 3) and one (1.4%) in the younger group ($P = 0.032$). Median Charlson Comorbidity Index (CCI) was 1 (IQR 0–3) in the older group and 0 (IQR 0–1) in the younger group ($P = 0.041$). There were no significant differences in body mass index (BMI), forced expiratory volume in 1 s ($FEV_{1.0}$), $\%FEV_{1.0}$, $FEV_{1.0}$/forced vital capacity (FVC), VC, %VC, SpO_2 and heart rate at baseline. Systolic blood pressure at baseline was significantly higher in the older group.

Mean dose of midazolam and lidocaine, duration of procedure, and clinical parameters during the procedure are shown in Table 2. According to our protocol, the dose of midazolam for sedation varied with age and sex. Thus, the mean dose of midazolam was greater in the younger group than in the older group. There was no statistically significant difference in lidocaine dose between the two groups ($P = 0.618$). The mean procedure time (from insertion of bronchoscope to removal) was 47 min in the older group and 45 min in the younger group ($P = 0.442$). We found no significant difference between the two groups in the mean value of the minimum SpO_2 ($90.2 \pm 4.0\%$ in the older group *vs* $90.7 \pm 3.3\%$ in the younger group, $P = 0.338$), the reduction of SpO_2 ($6.2 \pm 4.0\%$ in the older group *vs* $5.5 \pm 3.5\%$ in the younger group, $P = 0.376$), the maximum O_2 supplementation (2.3 ± 1.7 L/min in the older group *vs* 2.3 ± 2.1 L/min in the younger group, $P = 0.688$), the increase of systolic blood pressure from baseline (18.2 ± 18.8 mmHg in the older group *vs* 20.8 ± 19.4 mmHg in the younger group, $P = 0.359$) and the increase of heart rate (18.8 ± 14.3/min in the older group *vs* 19.0 ± 12.8/min in the younger group, $P = 0.829$) during the procedure.

Complications were observed in one patient (2.9%; paroxysmal atrial fibrillation) in the older group, and four patients (5.3%; pneumonia in one, Intensive Care Unit admission because of oxygen desaturation in one, cerebral infarction in one and pneumomediastinum in one) in the younger group. The patient who suffered from cerebral infarction was a 55-year-old man. After the procedure, he had partial paralysis of his left arm and magnetic resonance imaging showed acute multiple brain infarcts. He showed clear improvement of his symptoms by having been treated, and left our hospital 5 days after the onset. The patient who suffered from pneumomediastinum was a 68-year-old woman. She was asymptomatic with no alterations in vital signs, but a routine chest X-ray on the next day showed pneumomediastinum, followed by spontaneous resolution. No death or sequelae occurred in either group. There were no significant differences between the older and younger group in overall incidence of complications (Table 2). These data clearly show that EBUS-TBNA could be carried out equally safely in older patients as in younger patients.

In total, 137 lymph nodes (44 lymph nodes in the older group and 93 in the younger group) were punctured (Table 3). Biopsy specimens were obtained from lymph nodes in region 4R (53 nodes), 7 (31 nodes), 4L (13 nodes) and others (2R, 10R, 11R and 11L). The mean size of the lymph nodes (short axis) was 21.6 ± 11.1 mm in the older group and 22.5 ± 10.2 mm in the younger group, and the mean number of punctures were 3.3 ± 1.0 and 3.6 ± 1.0, respectively. There was no significant difference between two groups in distribution, size of lymph node and number of punctures.

Table 1 Baseline characteristics and variables of patients

	Older (≥70 years) $n = 34$	Younger (≤69 years) $n = 75$	P-value†
Age, median (IQR)	76 (73–81)	62 (58–67)	
Sex			
Male, *n* (%)	27 (79.4)	62 (82.7)	0.684
Female, *n* (%)	7 (20.6)	13 (17.3)	
Body mass index (mean ± SD)‡	21.6 ± 2.9	22.4 ± 3.1	0.22*
Smoking history			
Current smoker (%)	10 (29.4)	33 (44.0)	0.349
Former smoker (%)	15 (44.2)	27 (36.0)	
Never smoker (%)	9 (26.4)	15 (20.0)	
Performance status (ECOG)			
0–1 (%)	30 (88.2)	74 (98.6)	0.032
2–3 (%)	4 (11.8)	1 (1.4)	
Charlson Comorbidity Index			
0 (%)	13 (38.2)	43 (57.3)	0.041
1–2 (%)	12 (35.3)	25 (33.3)	
≧3 (%)	9 (26.5)	7 (9.3)	
Median (IQR)	1 (0–3)	0 (0–1)	0.031**
Pulmonary function test (mean ± SD)			
$FEV_{1.0}$	2.12 ± 0.70	2.5 ± 0.74	0.067*
$\%FEV_{1.0}$	99.3 ± 24.3	96.9 ± 18.4	0.515*
$FEV_{1.0}$/FVC	69.0 ± 11.8	73.8 ± 8.5	0.077*
VC	3.04 ± 0.83	3.47 ± 1.01	0.125*
%VC	100.0 ± 22.4	104.4 ± 27.5	0.577*
SpO_2, mean ± SD (%)	96.3 ± 2.4	96.2 ± 2.2	0.649*
Systolic BP, mean ± SD (mmHg)	152.9 ± 25.7	143.4 ± 24.1	0.018*
Heart rate, mean ± SD (/min)	78.9 ± 14.1	83.2 ± 16.9	0.29*

*From *t*-test. **From Mann–Whitney test. †Pearson χ^2-test *P*-value except as noted. ‡Calculated as weight in kilograms divided by height in meters squared. BP, blood pressure; ECOG, Eastern Cooperative Oncology Group; $FEV_{1.0}$, forced expiratory volume in 1 s, $\%FEV_{1.0}$, percentage of predicted forced expiratory volume in 1 s; FVC, forced vital capacity, IQR, interquartile range; SD, standard deviation; VC, vital capacity; %VC, percentage of predicted vital capacity.

According to the cytological and histological results, 27 of 34 patients (79.4%) in the older group (23 with malignancy and 4 with benign diseases) and 53 of 75 patients (70.7%) in the younger group (50 malignancies and 3 benign diseases) could be diagnosed. Among seven patients in the older group and 22 patients in the younger group in whom EBUS-TBNA did not result in pathological diagnosis, one in the older group and three in the younger group had been found to have malignant tumors (adenocarcinoma; lymphoma and 2 cases of adenocarcinoma, respectively) on surgery or re-examination carried out as further confirmation modalities (Table 3). In other words, 23 of 24 patients in the older group and 50 of 53 patients in the younger group with malignant lymph nodes were correctly diagnosed by EBUS-TBNA. As a result, the specificity and positive predictive value of EBUS-TBNA for detecting hilar and mediastinal malignancy were 100% in both groups. The sensitivity, negative predictive value (NPV), and diagnostic accuracy for detecting malignancy in the older and younger group were 95.8%, 90.9% and 97.1%, and 94.3%, 88.0% and 96.0%, respectively. There were no significant differences in the diagnostic yield for mediastinal malignancies between the groups.

Discussion

EBUS-TBNA is a well-established procedure for the diagnosis of mediastinal diseases, such as mediastinal lymph node metastasis from lung cancer. In a large multicenter study, routine samples from EBUS-TBNA were able to provide not only sufficient pathological information, but also molecular biological information in 90% of patients with NSCLC.[17,18] In the present retrospective study, we assessed the safety and usefulness of EBUS-TBNA for older patients compared with the younger patients. Although there were more patients with comorbidities or poor performance status in the older group, safety and diagnostic performance in older

Table 2 Safety profile of EBUS-TBNA in the older and younger group

	Older (≥70 years) *n* = 34	Younger (≤69 years) *n* = 75	*P*-value†
Midazolam dose, mean ± SD (mg)	4.98 ± 2.04	6.88 ± 2.61	0.000
Lidocaine dose, mean ± SD (mg)	325.6 ± 80.1	331.5 ± 77.0	0.618
Procedure duration, mean ± SD (min)‡	47 ± 16	45 ± 16	0.442
Minimum SpO_2, mean ± SD (%)	90.2 ± 4.0	90.7 ± 3.3	0.338
Reduction in SpO_2, mean ± SD (%)	6.2 ± 4.0	5.5 ± 3.5	0.376
Maximum O_2 supplementation, mean ± SD (L/min)	2.3 ± 1.7	2.3 ± 2.1	0.688
Elevation of systolic BP, mean ± SD (mmHg)	18.2 ± 18.8	20.8 ± 19.4	0.359
Increase of HR, mean ± SD (/min)	18.8 ± 14.3	19.0 ± 12.8	0.829
Complications			
All, *n* (%)	1 (2.9)	4 (5.3)	0.58*
Pneumonia	0	1	
Respiratory failure	0	1	
Cerebral infarction	0	1	
Atrial fibrillation (post-test)	1	0	
Pneumomediastinum	0	1	

*From Pearson χ^2-test. †The *t*-test *P*-value except as noted. ‡From insertion of bronchoscope to removal. BP, blood pressure; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; HR, heart rate; SD, standard deviation; SpO_2, oxygen saturation.

patients were similar to those found in younger patients. In addition, there was no difference in the frequency of complications between both groups. These findings in the present analysis suggested the usefulness and safety of EBUS-TBNA in older lung cancer patients. It also suggested that EBUS-TBNA could provide important information in older patients for selecting less toxic, but appropriate therapy.

In a systematic review of previous studies, sensitivities, specificities and NPV of EBUS-TBNA for detecting mediastinal malignancy ranged 85–100%, 100% and 11–97%, respectively.[19] In these studies, the mean (or median) age of patients were in the 50s or 60s.[19] In the present study, the sensitivity, specificity and NPV of the older group were 95.8%, 100% and 90.9%, respectively. The present study also showed that the diagnostic yield in the older group was comparable to that in the younger group. Some reports have shown that diagnostic yields of bronchoscopy in elderly patients are similar to those observed in younger patients.[20,21] The data of these reports and those in this analysis show that EBUS-TBNA is equally useful in older and younger lung cancer patients. Although non-invasive methods, such as CT or PET, are safer, several parameters that show the effectiveness of CT and PET were reported to be lower in a previous report; sensitivities of CT and PET for detecting mediastinal lymph node metastases were 76.9% and 80.0%, respectively; specificities were 55.3% and 70.1%; NPV were 87.5% and 91.5%; and diagnostic accuracies were 60.8% and 72.5%.[15] EBUS-TBNA could be more useful for the accurate diagnosis for mediastinal disease compared with CT or PET, even in older patients.

Many previous works have shown that EBUS-TBNA is a safe procedure for the examination of mediastinal and hilar lymph nodes in patients with lung malignancy.[19] Gu *et al*. reported just two complications in 1299 patients (0.15%) in their meta-analysis of EBUS-TBNA.[22] However, Asano *et al*. reported that one patient developed interstitial pneumonia that deteriorated rapidly and died after EBUS-TBNA in their nationwide survey on the safety of bronchoscopic procedures in Japan.[23] The report also presented three cases of mediastinitis and/or pericarditis after EBUS-TBNA.[23] The Asano report might suggest that severe complications related to EBUS-TBNA are not so rare as we currently recognize. Although some previous reports have shown that older patients tolerate bronchoscopy as well as younger patients,[20,21] the safety of EBUS-TBNA in older patients has not been established so far and should be evaluated urgently. In the present study, the proportion of patients with poor performance status and higher median CCI was significantly higher in the older group. However, no severe complication had occurred in the older group, except for one patient who had developed a transient paroxysmal atrial fibrillation after the procedure. Although one patient in the younger group required overnight intensive care because of temporary oxygen desaturation, all other desaturation events were transient and easily corrected with nasal oxygen administration in both groups. There was no significant difference between the older and younger group in overall incidence of complications and fluctuation of vital signs during the EBUS-TBNA. All studied patients including the older group received topical anesthesia with lidocaine and intravenous administration of midazolam

Table 3 Results of EBUS-TBNA in the older and younger group

	Older (≥70 years) $n = 34$	Younger (≤69) $n = 75$	P-value†
Lymph node station			
#4R	16	37	0.911*
# 7	12	19	
#4L	4	9	
Others	12	28	
Total	42	93	
Size of lymph node (short axis), mean ± SD (mm)	21.6 ± 11.1	22.5 ± 10.2	0.354
No. lymph node punctures (mean ± SD)	3.3 ± 1.0	3.6 ± 1.0	0.384
Diagnoses established from EBUS-TBNA			
All, *n* (%)	27 (79.4)	53 (70.7)	0.198*
Adenocarcinoma	11	18	
Squamous cell carcinoma	2	11	
NSCLC	2	8	
SCLC	5	6	
Lymphoma	1	1	
Other malignant tumors	2	6	
Sarcoidosis	2	1	
Tuberculosis	2	1	
Hamartoma	0	1	
Undiagnosed patients and further confirmation modalities			
All, *n* (%)	7 (20.6)	22 (29.3)	
Operation	3	11	
Re-examination	0	2	
Follow up	2	6	
Missing	2	3	
Diagnostic performance of EBUS-TBNA for detecting malignancy			
Sensitivity (%)	95.8	94.3	
Specificity (%)	100	100	
Positive predict value (%)	100	100	
Negative predict value (%)	90.9	88.0	
Accuracy (%)	97.1	96.0	

*From Pearson χ^2-test. †The *t*-test *P*-value except as noted. EBUS-TBNA, endobronchial ultrasoundguided transbronchial needle aspiration; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation.

for light sedation. There was no adverse effect or complication related to topical anesthesia in both groups. Taken together, although there might be a potential risk for adverse events with increasing age, we concluded that EBUS-TBNA could be carried out safely in older patients.

Limitations of the present study must be recognized. First, our conclusions might not be generalized because the sample size was small and the study was a retrospective study carried out at a single medical institution. Second, there is the possibility that fit patients for bronchoscopy were selected and that this could have influenced the results.

In conclusion, the present findings suggest that the safety and usefulness of EBUS-TBNA in older people were comparable to those in younger people regardless of their poorer performance status and higher comorbidity index.

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Disclosure statement

The authors have no conflicts of interest to declare.

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