

Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for the Diagnosis of Intrathoracic Lesions : Experience of a Single Academic Medical Center

Masanori YASUO^{1)2)*}, Takashi KOBAYASHI²⁾³⁾, Yayoi TOKORO²⁾, Toshimichi HORIUCHI²⁾
Michiko ITO²⁾, Kazushi KOJIMA⁴⁾, Kayoko IKEGAWA²⁾, Atsuhito USHIKI²⁾
Hiroshi YAMAMOTO²⁾, Masayuki HANAOKA²⁾, Tomonobu KOIZUMI³⁾
Akihiko YOSHIZAWA⁵⁾, Takayuki HONDA⁵⁾ and Keishi KUBO²⁾

- 1) *Endoscopic Examination Center, Shinshu University School of Medicine, Shinshu University Hospital*
- 2) *First Department of Internal Medicine, Shinshu University School of Medicine*
- 3) *Comprehensive Cancer Center, Division of Clinical Oncology, Shinshu University School of Medicine, Shinshu University Hospital*
- 4) *Undergraduate, School of Medicine, Shinshu University School of Medicine*
- 5) *Department of Laboratory Medicine, Shinshu University School of Medicine*

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been recognized as a minimally-invasive and effective method for the diagnosis and nodal staging of lung cancer.

We describe our initial experience with this method, including diagnostic sensitivity, safety, importance of obtaining histological samples, and diagnostic pitfalls. We retrospectively studied 100 patients (108 consecutive procedures) with radiologically suspicious intrathoracic lesions who were investigated by EBUS-TBNA.

The procedures were performed between January 2005 and December 2011 at our institute. Adequate sampling value was 91.7 %. Total diagnostic yield was 68.5 % (74/108). In diagnosed subjects, malignancy and benign disease were identified in 68 and 6 cases, respectively. Diagnostic yield was relatively high in malignancy (88.3 %), and poor in benign (19.4 %). In the subgroup of malignant subjects, the diagnostic yield was higher in lung cancer (96.2 %) than in other malignancies (72.0 %) but, the difference disappeared if malignant lymphoma was excluded. No major complications were associated with the procedure.

EBUS-TBNA is useful in accessing the circumference of the central airway tumor for diagnosis. Compared with previous studies, the diagnostic yield of mediastinal lymphoma and benign lesions is worse in our laboratory. Adequate tissue sampling and preparation are needed for the definitive diagnosis of malignant lymphoma and benign lesions. *Shinshu Med J 60 : 249–255, 2012*

(Received for publication May 11, 2012 ; accepted in revised form June 28, 2012)

Key words : EBUS-TBNA, bronchoscopy, diagnosis, mediastinal lymph node

I Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a novel, minimally invasive method for peribronchial mass sampling

under real-time ultrasonographic guidance¹⁾²⁾. The procedure is usually performed for the nodal staging of lung cancer and for the diagnosis of circumferential central airway lesions. There are many reports and reviews which have described its usefulness in the diagnosis of malignancy or nodal staging of lung cancer^{3)–7)}. EBUS-TBNA is now considered one of the most important diagnostic modalities for lymphnode staging in lung cancer before sur-

* Corresponding author : Masanori Yasuo
Endoscopic Examination Center, First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621 Japan

gery^{4)–7)}. Previous comparative studies have shown its superiority to positron emission tomography (PET) and/or chest computed tomography⁸⁾⁹⁾. Furthermore, EBUS-TBNA may replace the role of mediastinoscopy for the lymphnode staging of lung cancer before surgery³⁾.

There are some reports describing the application of EBUS-TBNA in benign disease such as sarcoidosis^{10)–12)} and tuberculosis¹³⁾. Recently, the effectiveness of the diagnosis in malignant lymphoma was also reported¹⁴⁾¹⁵⁾. However, few reports describe the total diagnostic value of EBUS-TBNA in serial subjects with undefined intrathoracic lesions¹⁶⁾¹⁷⁾.

The minimal invasiveness, lower cost and repeatability of EBUS-TBNA have been reported many times⁴⁾¹⁸⁾; however, it is well recognized that performing EBUS-TBNA requires training. Not all institutions can achieve a diagnostic accuracy equivalent to that of mediastinoscopy, especially when a well-trained expert is absent⁵⁾¹⁹⁾.

The purpose of this study was to determine the diagnostic sensitivity of EBUS-TBNA in undefined intrathoracic lymphadenopathy. This report will also discuss the usefulness and pending improvements for the definitive diagnosis of undiagnosed intrathoracic lesions.

II Material and Methods

This was a retrospective analysis of 108 consecutive EBUS-TBNA procedures performed at Shinshu University Hospital (Endoscopic examination center) between January 2005, and December 2011. Written informed consent was obtained from all patients prior to the procedure. Because the EBUS-TBNA procedure has already been listed as a health insurance examination and because it was not a prospective controlled study, this study did not go through our Institutional Review Board. We performed the procedure in compliance with the Declaration of Helsinki. All patients enrolled this study were referred for EBUS-TBNA for definitive diagnosis of their mediastinal and/or hilar lymphadenopathy or mediastinal or lung mass. Although most of the patients were examined by

EBUS-TBNA at the time of their first bronchoscopy, it was the second procedure in a few patients after a prior negative result from conventional bronchoscopy with transbronchial biopsy or TBNA for peripheral or peribronchial lesions. A contrast enhanced chest computed tomography (CT) was routinely performed in all patients except when contraindicated. Positron emission tomography (PET)/CT was performed in most subjects, especially when malignancy was suspected.

A EBUS-TBNA technique

Local anesthesia and conscious sedation with intramuscular injection of pethidine hydrochloride or intravenous injection of midazolam were administered before the procedure as for conventional bronchoscopy. Topical anesthesia was achieved by endobronchial instillation of 2 % lidocaine. The pulse oximetry saturation, resting pulse and electrocardiograms were monitored during the procedure. Bronchoscopy was performed in all cases with a flexible videobronchoscope equipped with a 7.5-MHz linear ultrasound probe (Olympus model BF-UC260F-OL8; Olympus Ltd, Tokyo, Japan). All procedures were performed by at least three bronchoscopists experienced in EBUS-TBNA with exclusive nursing staff. As previously reported, this EBUS distal probe can produce linear parallel scans of the mediastinal and peribronchial tissues and a working channel suited to the performance of TBNA under direct ultrasound guidance¹⁶⁾. Biopsies were performed using a 21 or 22-gauge needle (NA-201SX-4012/4022, Olympus Optical Co Ltd.) specially designed for use with the ultrasound bronchoscope. The needle was guided through the channel to the airway lumen and then pushed forward from the sheath and inserted into the central airway wall under ultrasound guidance. A schematic of the procedure is shown in Fig. 1. Once the needle was inside the target, negative pressure was maintained with a syringe at the proximal end of the catheter while the needle was pushed back and forth.

B Sample preparation

The aspirated material in the needle was prepared for histological analysis by pushing it out of the



Fig. 1 Schematic sampling image of EBUS-TBNA
Peribronchial tissue is directly sampled. (with the permission of Olympus Ltd)

needle using a wire stylet included with the needle kit. In addition, we made cell-block preparations from the beginning of 2011. In our institute, if visible aspirated material was pushing out into the normal saline, the sample was picked up and prepared for histological analysis (i.e. paraffin embedded specimen), then the residual pieces of tissue and cells were centrifuged and made into a cell-block sample. The residual specimens in the needle were sprayed by a syringe onto slides for cytological analysis and fixed with 95 % ethanol.

C Definition of adequate sampling

If lymphocytes or malignant cells were identified in lymphnode sampling, or if bronchial epithelium or pigmented alveolar macrophages were identified in lung sampling in cytological samples, the sample was considered 'adequate'. If lymphocytes were found in LN sampling or bronchial epithelium or pigmented macrophages were found in lung sampling without the existence of malignant cells, the specimen was considered 'adequate' and diagnosed as "reactive lymphnode" or "benign/no-metastasis". If there was only blood and no lymphocytes and/or bronchial epithelial cells and cartilaginous tissues were identified, the case was interpreted as a

'inadequate' and diagnosed as "not diagnostic" as described previously¹⁷⁾.

D Diagnosis

A histological sample is important for the definitive diagnosis. However, for example, if a cytologist defined it was "Class V adenocarcinoma" and the origin of the lesion was easily presumed clinically (e.g. lymphnode metastasis of lung cancer), we considered the diagnosis to be definitive.

E Statistical analysis

Statistical analysis was performed using SPSS 14.0 software (SPSS Inc, Chicago, IL, USA) for Windows (Microsoft Inc, Redmond, WA, USA). Difference of diagnostic yields between malignancy and benign, and between lung cancer and other malignancies were analyzed by the χ^2 test. Differences between target diameters were analyzed by Welch's test. The target diameters are expressed as means $\pm$ standard deviation.

III Results

A total of 108 procedures were performed in 100 subjects (77 males and 23 females). EBUS-TBNA was administered to one patient three times and to 6 other patients two times. The average age of these 100 patients was 66.1 ± 12.6 years. The EBUS-TBNA diagnosis and patient outcomes are indicated in Fig. 2. The locations of the EBUS-TBNA sites are indicated in Table 1. The average number of passes in our series was 2.90 ± 1.03 per target lesion. According to the above criteria¹⁷⁾, we achieved 99 adequate samplings in a total of 108 procedures (91.7 %).

We obtained 74 positive results, thus the overall diagnostic yield was 68.5 % (74/108). 68 of these results were malignant and 6 were benign lesions. The diagnostic yield of overall and malignant (lung cancer or other malignancies) lesions are shown in Table 2. The diagnostic yield of lung cancer was significantly higher than that of other malignancies ($P < 0.005$). However, the difference between lung cancer and other malignancies disappeared when malignant lymphoma was excluded (3 diagnosed and 3 undiagnosed (Fig. 2)). The diagnostic yield

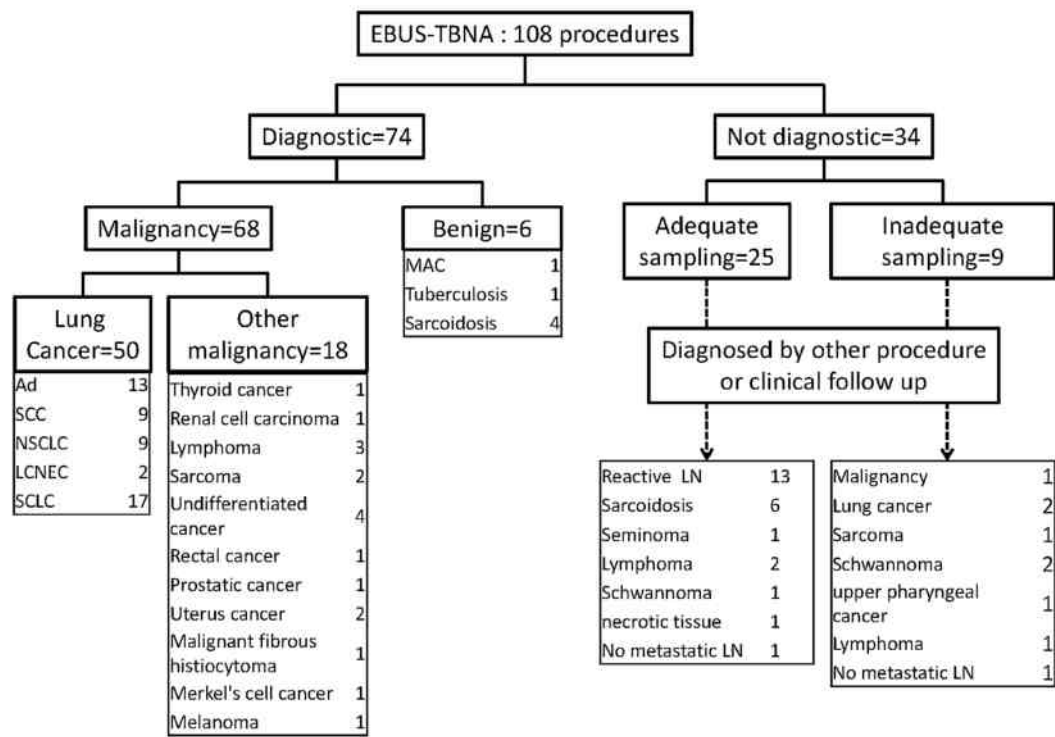


Fig. 2 Outcomes of patients undergoing EBUS-TBNA
Ad : adenocarcinoma, SCC : squamous cell carcinoma, NSCLC : non-small cell lung cancer,
LCNEC : large cell neuroendocrine cell carcinoma, SCLC : small cell lung cancer,
LN : lymphnode, MAC : mycobacterium avium complex

Table 1 The locations of the EBUS-TBNA sites

# 2R	2
# 2L	1
# 4R	26
# 4L	6
# 5	3
# 7	36
# 10R	2
# 10L	1
# 11R	14
# 11L	1
Mediastinal tumor	7
LN with tumor	5
Lung tumor	8

: number of the mediastinal lymph node stations

according to the lesion size is indicated in Table 3. It clearly shows the diagnostic yield worsened with smaller lesion size.

In benign lesions, the diagnostic yield was poor (6/31, 19.4 %) in our laboratory. Benign lesions are seldom diagnosed definitively only by cytology. We consider the fact that the definitive diagnosis of a benign lesion requires not only cytological samples but also histological samples as the major reason for the low diagnostic yield in benign lesions. Until the end of 2010, we did not request the pathologist to make cell-blocks. From 2011 on, we started to

Table 2 Diagnostic yields in several disease categories

	Overall	Malignancy	Lung cancer	Other malignancy
Diagnostic	74	68	50	18
Not diagnostic	34	9	2	7
Total	108	77	52	25
Diagnostic yield (%)	68.5	88.3	96.2 ^a	72.0

a : P=0.007 vs. Other malignancy

make cell-blocks to obtain improved histological information from the EBUS-TBNA samples. For example, we could not obtain a good diagnostic yield of sarcoidosis prior to making cell-blocks (1 diagnosed in 7 procedures). Afterwards, however, we established a definitive diagnosis in all sarcoidosis patients, although the data is still limited (three patients). The change in the diagnostic yields before and after making cell-blocks is shown in Table 4. The diagnostic yields after making cell-blocks tend to be higher than before in benign lesions, due to the 100 % diagnostic yield of sarcoidosis. There seemed to be no change in the diagnostic yield of malignant lymphoma between before and after making cell-blocks (Table 4).

As indicated in Fig. 2, no diagnosis was obtained in 34 patients. These patients were finally diagnosed by other modalities : surgery (5 patients), endoscopic ultrasound - guided fine needle aspiration (2 patients), re-try EBUS-TBNA (2 patients), peripheral lung nodule sampling by conventional bronchoscopy (one patient), muscle biopsy (one sarcoidosis patient) and clinical follow-up of more than 6 months (21 patients). No significant complications occurred during the procedures.

IV Discussion

This study describes the usefulness and safety of EBUS-TBNA for the definitive diagnosis of circum-

ferential central airway lesions. The procedure provided a high diagnostic yield in malignancy (88.3 %), especially in lung cancer (96.2 %). No major complications were associated with this procedure except for a small amount of bleeding at the sites penetrated by the TBNA needle.

Similar diagnostic yields have been reported in several studies⁶⁾. We experienced a variety of benign lesions, primary malignancy and metastatic cancer, and infectious disease in this study. Some patients were suspected of either malignant or benign lesions, others were referred to our hospital because of a mediastinal tumor or lymphadenopathy of unknown cause. In comparison to the systematic review⁶⁾, our data shows a high diagnostic yield in malignancy (especially lung cancer). Conversely, we had a low diagnostic yield (19.4 %) for the diagnosis of benign lesions. We expect that we will obtain better results after making cell-blocks as described above. The results for the diagnostic yield of malignant lymphoma were also poor. In our study, the sensitivity of a definitive diagnosis was 50 % (3 diagnosed in 6 procedures in the total period, 1 diagnosed in 3 procedures after the introduction of cell-blocks, Fig. 2). The poor diagnostic yield in this disease caused a significant difference in diagnostic yield between lung cancer and other malignancies. Although the usefulness for the definitive diagnosis of malignant lymphoma by EBUS-TBNA has not been defined⁶⁾, it has been reported by several institutes¹⁴⁾¹⁵⁾. In these reports, the diagnostic yield of malignant lymphoma varied between 57 to 90.9 %¹⁴⁾¹⁵⁾. Like benign lesions, sufficient tissue is also required for the definitive diagnosis of malignant lymphoma including examinations such as cytology, histology, molecular anal-

Table 3 Diagnostic yield according to the lesion size

Size	Diagnostic yield (%)
≤10 mm	40.0
10.1-20 mm	51.0
20.1-30 mm	72.4
>30 mm	87.5

Table 4 Transition of the diagnostic yields before and after making cell-blocks

	Total period (2005~2011)	before (~2010)	after (2011~)
All benign lesions	19.4 % (6/31)	13.0 % (3/23)	37.5 % (3/8)
Sarcoidosis	40.0 % (4/10)	14.3 % (1/7)	100 % (3/3)
Malignant lymphoma	50.0 % (3/6)	50.0 % (2/4)	50.5 % (1/2)

ysis, and immunophenotyping.

In addition to making cell-block samples, we may need more passes per lesion to obtain more samples. The average passes per lesion in our study was 2.89 ± 1.03 . The average passes per lesion in our positive result of lymphoma (3 cases) was 4.33. In contrast, the average passes in our negative result of lymphoma (3 cases) was 2.67. A review article⁵⁾ recommends that EBUS-TBNA needs three to four aspirations per one site for the diagnosis. Lymphoma may need more passes to reach a definitive diagnosis.

We thus need to perform histological analysis more than ever; however, it may be insufficient for the definitive diagnosis of malignant lymphoma because EBUS-TBNA usually obtains smaller amounts of samples. It is also insufficient for the definitive diagnosis of benign lesions if we cannot obtain sufficient histological samples. Furthermore, a definitive diagnosis of reactive lymphnode or no-metastasis may not be made only by the result of EBUS-TBNA. For the definitive diagnosis of such benign lesions, we need to wait for the surgical result or the long-term follow up result.

The safety of EBUS-TBNA has been already shown¹⁾²⁾⁵⁾⁶⁾. No major complications were seen in our series except for acceptable amounts of bleeding. We have not observed some of the other previously reported complications, including bacteremia,

mediastinal/ lung abscess, or empyema²⁰⁾²¹⁾. Mediastinal abscess is perhaps a very rare complication. Clinically significant bacteremia following EBUS-TBNA was also rare²⁰⁾.

V Conclusion

We reviewed our institute's results and compared the data with previous reports. EBUS-TBNA was a useful and safe procedure for the definitive diagnosis of undiagnosed lesions around the central airways. However, the definitive diagnosis of benign lesions and malignant lymphoma seems more difficult. Preparing cell-blocks for histological analysis may improve the diagnostic yield. Increasing the number of passes per lesion should also be considered to obtain more tissue samples.

Acknowledgement

The authors thank Yukihiro Kobayashi, Ph. D. from the Department of Laboratory Medicine, Shinshu University School of Medicine for his analysis of our cytological samples. The authors would like to thank Harm J. Bogaard, M. D., Ph. D. from the VU University Medical Center for his valuable advice and for kindly checking the English language usage in our manuscript. The authors also thank Thomas Taylor for kindly checking the English grammatical usage in our manuscript.

References

- 1) Currie GP, McKean ME, Kerr KM, Denison AR, Chetty M: Endobronchial ultrasound-transbronchial needle aspiration and its practical application. *QJM* 104: 653-662, 2011
- 2) Yasufuku K: Current clinical applications of endobronchial ultrasound. *Expert Rev Respir Med* 4: 491-498, 2010
- 3) Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, da Cunha Santos G, Geddie W, Boerner S, Le LW, Keshavjee S: A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 142: 1393-1400, 2011
- 4) Cameron SE, Andrade RS, Pambuccian SE: Endobronchial ultrasound-guided transbronchial needle aspiration cytology: a state of the art review. *Cytopathology* 21: 6-26, 2010
- 5) Medford AR: Endobronchial ultrasound-guided transbronchial needle aspiration. *Pol Arch Med Wewn* 120: 459-466, 2010
- 6) Varela-Lema L, Fernández-Villar A, Ruano-Ravina A: Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *Eur Respir J* 33: 1156-1164, 2009

- 7) Medford AR, Bennett JA, Free CM, Agrawal S : Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) : applications in chest disease. *Respirology* 15 : 71-79, 2010
- 8) Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, Fujisawa T : Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 130 : 710-718, 2006
- 9) Hwangbo B, Kim SK, Lee HS, Lee HS, Kim MS, Lee JM, Kim HY, Lee GK, Nam BH, Zo JI : Application of endobronchial ultrasound-guided transbronchial needle aspiration following integrated PET/CT in mediastinal staging of potentially operable non-small cell lung cancer. *Chest* 135 : 1280-1287, 2009
- 10) Wong M, Yasufuku K, Nakajima T, Herth FJ, Sekine Y, Shibuya K, Iizasa T, Hiroshima K, Lam WK, Fujisawa T : Endobronchial ultrasound : new insight for the diagnosis of sarcoidosis. *Eur Respir J* 29 : 1182-1186, 2007
- 11) Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P : Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. *Chest* 132 : 1298-1304, 2007
- 12) Oki M, Saka H, Kitagawa C, Kogure Y, Murata N, Ichihara S, Moritani S : Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J Thorac Cardiovasc Surg* 2012 Feb 14. [Epub ahead of print]
- 13) Navani N, Molyneaux PL, Breen RA, Connell DW, Jepson A, Nankivell M, Brown JM, Morris-Jones S, Ng B, Wickremasinghe M, Lalvani A, Rintoul RC, Santis G, Kon OM, Janes SM : Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy : a multicentre study. *Thorax* 66 : 889-893, 2011
- 14) Steinfert DP, Conron M, Tsui A, Pasricha SR, Renwick WE, Antippa P, Irving LB : Endobronchial ultrasound-guided transbronchial needle aspiration for the evaluation of suspected lymphoma. *J Thorac Oncol* 5 : 804-809, 2010
- 15) Kennedy MP, Jimenez CA, Bruzzi JF, Mhatre AD, Lei X, Giles FJ, Fanning T, Morice RC, Eapen GA : Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Thorax* 63 : 360-365, 2008
- 16) Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, Fujisawa T : Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest* 126 : 122-128, 2004
- 17) Eckardt J, Petersen HO, Hakami-Kermani A, Olsen KE, Jørgensen OD, Licht PB : Endobronchial ultrasound-guided transbronchial needle aspiration of undiagnosed intrathoracic lesions. *Interact Cardiovasc Thorac Surg* 9 : 232-235, 2009
- 18) Steinfert DP, Liew D, Conron M, Hutchinson AF, Irving LB : Cost-benefit of minimally invasive staging of non-small cell lung cancer : a decision tree sensitivity analysis. *J Thorac Oncol* 5 : 1564-1570, 2010
- 19) Unroe MA, Shofer SL, Wahidi MM : Training for endobronchial ultrasound : methods for proper training in new bronchoscopic techniques. *Curr Opin Pulm Med* 16 : 295-300, 2010
- 20) Steinfert DP, Johnson DF, Irving LB : Incidence of bacteraemia following endobronchial ultrasound-guided transbronchial needle aspiration. *Eur Respir J* 36 : 28-32, 2010
- 21) Huang CT, Chen CY, Ho CC, Yu CJ : A rare constellation of empyema, lung abscess, and mediastinal abscess as a complication of endobronchial ultrasound-guided transbronchial needle aspiration. *Eur J Cardiothorac Surg* 40 : 264-265, 2011

(2012. 5. 11 received ; 2012. 6. 28 accepted)