

Impact of Endobronchial Ultrasound Guided Transbronchial Needle Aspiration on Clinical Practice Guideline

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Objective: Endobronchial ultrasound guided transbronchial needle aspiration (EBUS TBNA) is performed by using special bronchoscope which has an ultrasound probe at its tip that could demonstrate lymph node outside the airway and allow for real time observation of transbronchial needle aspiration. The sensitivity and specificity of EBUS TBNA are high in many studies. However, because of the high expense and special training required, the impact of this method on clinical practice guidelines (CPG) needs to be further evaluated.

Material and Method: The patients were classified to three groups. Group One included proven lung cancer patients who do not have distant metastasis and no mediastinal lymphadenopathy as demonstrated by computer tomography. Group Two was the same as group One except there was evidence of mediastinal lymphadenopathy. The Third Group included patients who only had mediastinal lymphadenopathy without lung lesion. All lymph node stations were examined by EBUS and their sizes were recorded. Selected puncture of a lymph node was done and tissue was sent for cytological examination. There was no rapid on site cytologic examination. The impact on CPG was calculated from the number of patients who be prevented from mediastinoscopy.

Results: There were 158 patients in the present study. The number of patients in group 1, 2 and 3 were 64, 57 and 37 respectively. The mean size of the mediastinal lymph node which detected by EBUS was 1.34 cm (range 0.36-3.81 cm). TBNAs were done in 164 nodes out of 353 nodes found by EBUS. The most common enlarged mediastinal node was at station 7 and those at station 4R and 3 were less common in sequence. In all three groups, malignant cells were established in 71 patients (44.9%). In group 1 malignancy was found in 21 (32.8%), in 39 patients (68.4%) in group 2 and in 11 patients (29.7%) in group 3.

Discussion: If the CPG recommend mediastinoscopy for all lung cancer patients, EBUS TBNA can save 49.5% of patients from the procedure. But if only enlarged mediastinal node would be considered for mediastinoscopy, EBUS TBNA can save up to 59.5% patients from mediastinal surgery.

Conclusion: EBUS TBNA has impact on CPG for assessment of mediastinal node in lung cancer and mediastinal lymphadenopathy patients.

Keywords: Endobronchial ultrasound guided transbronchial needle aspiration (EBUS TBNA), Mediastinal lymphadenopathy, Clinical practice guideline

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Mediastinal lymphadenopathy is one of the clinical problems facing the physician for whom no intervention except surgical, such as mediastinoscopy or thoracotomy, was offered in the past. Since Ko-Pen Wang introduced technique of transbronchial needle aspiration (TBNA) using flexible bronchoscope in

1984⁽¹⁾, the popularity of this method has slowly increased because of the wide range of the diagnostic yields among centers.

Endobronchial ultrasound (EBUS) is become the investigation tool in bronchoscopy field of respiratory medicine by the first model of radial scanning probe manufactured by Olympus company. The new model of special bronchoscope which incorporated a linear scanning ultrasound probe in its tip was marketed in 2005. This model makes real time transbronchial needle aspiration observation through ultrasound possible. The sensitivity, specificity and

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diagnostic yields of this procedure in diagnosing of mediastinal lymphadenopathy are high in many studies⁽²⁻⁴⁾.

The sampling of mediastinal lymph node is important in the cases of staging evaluation in patients with lung cancer and in patients who present with isolated mediastinal lymphadenopathy. Many guidelines⁽⁵⁻⁸⁾ recommend obtaining lymph node tissue by surgical intervention, which increases cost and morbidity for the patients. The present study aims to evaluate the impact of TBNA by using EBUS guided on the following of the guideline of mediastinal lymph node investigation.

Material and Method

Patients suspected of having lung cancer and who were referred for evaluation at Division of respiratory disease and tuberculosis, Department of medicine Siriraj Hospital which is the tertiary hospital in Bangkok, were included in the study. Also included were patients who had mediastinal lymphadenopathy. The eligible patients were categorized into three groups. The First Group included lung cancer patients in clinical stage I and II who did not have lymphadenopathy detected by thoracic computerized tomography. Group Two included patients who were suspected of having metastatic mediastinal lymph nodes as, for example, by revelation of demonstrated enlarged lymph nodes from thoracic computerized tomography (equal to or larger than 1 cm in transverse diameter). The patients who had isolated mediastinal lymphadenopathy were in Group Three.

All patients were evaluated according to their indications. The lymph node were evaluated by EBUS using special design bronchoscope (XBF-UC260F-OL8, Olympus, Tokyo, Japan). All detected lymph node diameters were measured and the widest one was chosen. The detected lymph nodes were sampled by

TBNA. Lymph node stations and diameters were recorded.

The patients were followed until the final diagnosis of their lymph nodes, whether by histologic section from surgical lymph node resection or clinical diagnosis.

The impact on CPG was calculated from the number of patients who was prevented from mediastinoscopy.

Statistical analysis

The demographic data of the patient, location of lymph node evaluated by EBUS and cytology results were recorded. Size of lymph nodes were reported in mean and standard deviation. Malignant cell recovered by EBUS guided TBNA in lymph node smaller and equal or larger than 1 cm were compared using the Chi-square test with statistically significant difference if $p < 0.05$.

Results

One hundred and fifty eight patients were enrolled to the study. Their mean age was 61 year-old. Three quarters were male. There were 121 patients in Group 1 and 2 (64 in Group 1, 57 in Group 2 as in Table 1). The number of nodes recovered from EBUS was 353 nodes and their mean maximal diameter was 1.34 cm 35 nodes detected were less than 1 cm in their maximal diameters. Most common site of mediastinal node was station 7 (Table 2). TBNAs were performed in 164 nodes.

In group 1, 33 nodes were found by EBUS to have diameters equal to or more than 1 cm in which 16(48.5%) was positive for malignancy by TBNA compared to 5 out of 31 (16.1%) in nodes that their diameter less than 1 cm ($p = 0.006$, Table 3).

In group 2, only one node was found by EBUS to be less than 1 cm in diameter, with no malignancy cell found. Malignant cells were found in 39 (69.6%) nodes that had diameter equal to or larger than 1 cm.

Table 1. Characteristics of patients undergoing endobronchial ultrasonography-guided transbronchial biopsy

| Baseline characteristics | Total | Group 1 | Group 2 | Group 3 |
|--------------------------|---------------------------|---------------------------|--------------------------|---------------------|
| Number of patients | 158 | 64 | 57 | 37 |
| Age (years) | 60.83 ± 12.06 (17-83)* | 60.98 ± 11.56 (26-82)* | 63.23 ± 9.63 (42-83)* | 57 ± 15 (17-78)* |
| Sex | | | | |
| Female | 38 (24.1) | 13 (20.3) | 11 (19.3) | 14 (37.8) |
| Male | 120 (75.9) | 51 (79.7) | 46 (80.7) | 23 (62.2) |

* Mean ± SD (range)

Table 2. Characteristic of mediastinal lymph node detected by EBUS

| Variables | Number (%) |
|---|-------------------|
| Number of the lymph node detected by EBUS** (nodes) | 353 |
| Mean size of lymph node detected by EBUS (cm) | 1.34 (0.36-3.81)* |
| Group 1 | 0.96 (0.36-2.16)* |
| Group 2 | 1.75 (0.43-3.81)* |
| Group 3 | 1.30 (0.56-3.51)* |
| Lymph node which TBNA*** was performed (nodes) | 164 (100) |
| Location | |
| 2R | 1 (0.6) |
| 2L | 4 (2.4) |
| 3 | 34 (20.7) |
| 4R | 38 (23.2) |
| 4L | 9 (5.5) |
| 7 | 61 (37.2) |
| 10R | 2 (1.2) |
| 10L | 9 (5.5) |
| 11S | 3 (1.7) |
| 11I | 1 (0.6) |
| 11L | 2 (1.2) |
| Size (cm) | |
| < 1 cm | 35 (21.3) |
| 1 cm or more | 129 (78.7) |

* mean (range), ** EBUS = endobronchial ultrasonography, *** TBNA = Transbronchial needle aspiration

Table 3. Group 1-2 Size of mediastinal lymph node and results of EBUS TBNA

| Variable | Malignancy, number (%) | Benign or negative, number (%) |
|----------------|------------------------|--------------------------------|
| Group 1 | | |
| < 1 cm | 5 (16.1) | 26 (83.9) |
| > 1 cm or more | 16 (48.5) | 17 (51.5) |
| Group 2 | | |
| < 1 cm | 0 (0) | 1 (100) |
| > 1 cm or more | 39 (69.6) | 17 (30.4) |
| Total | | |
| < 1 cm | 5 (15.6) | 27 (84.4) |
| > 1 cm or more | 55 (61.8) | 34 (38.2) |

The details are shown in Table 3. Malignant cell types by cytology were adenocarcinoma, undifferentiated non small cell carcinoma and squamous cell carcinoma; but unspecified malignancy cell was the most commonly found one. TBNA was not done in 8 nodes from Group 1 patients because of the small node size (Table 4).

In patients who presented with isolated mediastinal lymphadenopathy (group 3), a majority had nodes larger than 1cm and 28.6% had recovered malignant cell in the nodes being sampled by TBNA. The nodes size less than 1 cm also had malignancy cell

in 33.3% (Table 5).

If the CPG recommend mediastinoscopy for all lung cancer patients, EBUS TBNA can save 49.5% (60 out of 121) of patients from the procedure. But if only enlarged mediastinal node would be considered for mediastinoscopy, EBUS TBNA can save up to 59.5% (50 out of 84) patients from mediastinal surgery.

Discussion

The guidelines for evaluation of mediastinal lymph node in the staging step of lung cancer patient

Table 4. Cytologic results of group 1 and 2

| Variable | Group 1 number (%) | Group 2 number (%) | Group 1 and 2 number (%) |
|----------------------------|-----------------------|-----------------------|-----------------------------|
| Malignancy | | | |
| Adenocarcinoma | 4 (6.3) | 5 (8.8) | 9 (7.4) |
| Undifferentiated NSC | 8 (12.5) | 13 (22.8) | 21 (17.4) |
| Squamous cell carcinoma | 2 (3.1) | 1 (1.8) | 3 (2.5) |
| Malignancy, unspecified | 7 (10.9) | 20 (35.1) | 27 (22.3) |
| Benign or negative results | | | |
| Negative for malignancy | 26 (40.6) | 12 (21.1) | 38 (31.4) |
| Benign cellular change | 2 (3.1) | 2 (3.5) | 4 (3.3) |
| Necrotic tissue | 1 (1.6) | 1 (1.8) | 2 (1.7) |
| TBNA was not done | 8 (12.5) | 0 (0) | 8 (6.6) |
| Inadequate specimen | 6 (9.4) | 3 (5.3) | 9 (7.4) |
| Total | 64 (100) | 57 (100) | 121 (100) |

* NSC = non-small-cell carcinoma

Table 5. Group 3 size of mediastinal lymph node and results of EBUS TBNA

| Variable | Malignancy, number (%) | Benign or negative, number (%) |
|---|---------------------------|-----------------------------------|
| Group 3 | | |
| < 1 cm | 3 (33.3) | 6 (66.7) |
| > 1 cm or more | 8 (28.6) | 20 (71.4) |
| Final diagnosis in group 3 | | |
| Diagnosis | Number (%) | Diagnosed by EBUS TBNA, number |
| Bronchogenic cyst | 2 (7.7) | 2 |
| Malignancy | 3 (11.6) | 0 |
| Lymphoma | 1 (3.8) | 0 |
| Sarcoidosis | 1 (3.8) | 1 |
| Tuberculosis | 8 (30.8) | 0 |
| Benign mediastinal lymphadenopathy, unspecified | 7 (26.9) | 7 |
| Loss to follow-up | 4 (15.4) | - |
| Total | 26 (100) | 10 |
| Positive and negative results in group 3 | | |
| Results | Number (%) | |
| Positive results | 11 (50.0) | |
| False negative results | 11 (50.0) | |
| Final diagnosis was made by | | |
| Thoracotomy | 2 | |
| Mediastinoscopy | 1 | |
| Bronchoscopy | 2 | |
| Lymph node biopsy | 2 | |
| Sputum culture for mycobacteria | 1 | |
| Clinical follow-up | 3 | |
| Loss to follow-up | 4 (15.4) | |
| Total | 26 (100) | |

requires sampling of the lymph node. Mediastinoscopy is the procedure of choice even in normal size (less than 1 cm in short axis diameter by computerized tomography of the chest) mediastinal lymph node. To follow these guidelines is a problem in many medical centers because of the shortage of trained personnel and the tight time schedule of the surgeon, the poor condition of some patients and the unacceptably dangerous history of the two operative procedures. EBUS guided-TBNA has gained increase popularity in this situation because of its high sensitivity, specificity and positive predictive result.

Evaluation of mediastinal lymph node in patient with lung cancer with EBUS guided TBNA could have a diagnostic yield of 15.6% and 61.8% if the lymph node diameter was either less than 1 cm or equal or more than 1 cm, respectively. This could also prevent invasive, costly mediastinoscopy or thoracotomy procedures in the same percentage of patients.

The traditional radiologic evaluation for mediastinal lymph node is computerized tomography in which the short axis diameter of the lymph node that is equal to or greater than 1 cm is used to determine the enlarged lymph node. The prevalence of metastasis in mediastinal lymph node is increased in the enlarged node. The present study showed that 31 out of 64 (48.4%) of patients who had normal size mediastinal lymph node evaluated by computerized tomography were found to have lymph nodes of a diameter greater than 1 cm when evaluated by EBUS. This discrepancy may be due to the different axis of measurements because EBUS measures the longitudinal and inner-wall to outer-wall axis diameter of the lymph node instead of the short axis diameter, as measured by computerized tomography. The importance of other axis measurement was confirmed by higher positive yield of metastasis in group 1 patients who had a lymph node size greater than 1 cm (48.5% compare to 16.1%). The overall diagnostic yield of metastatic lymph nodes of less than 1 cm was 15.6% and is comparable to the results of Herth^(9,10).

In patients who present with isolated mediastinal lymphadenopathy, the diagnostic yield of EBUS guided TBNA is 63.6% with no difference statistically in yields, whether the lymph node diameter size was less than or equal to and more than 1 cm. An unexpected finding was that EBUS guided TBNA could not make diagnosis of tuberculous lymphadenopathy in any of the 8 patients in the present study. The reason may be because the organism was so scant in non-liquefaction lymph node and the finding of well formed

caseous granuloma was difficult to find in the cytologic specimen.

The limitations of the present study are the lack of definite results from patients whose lymph nodes were negative from EBUS guided TBNA, for which they were recommended for mediastinoscopy or thoracotomy. Not all patients underwent the tests. This makes the calculation of specificity and predictive value impossible.

In conclusion, the present study demonstrated that invasive procedures for sampling tissue of the lymph node could be prevented in about half of the patients with the use of bronchoscopic EBUS guided TBNA. The normal size lymph node evaluated by computerized tomography may be found to be larger under EBUS evaluation.

Potential conflicts of interest

None.

References

1. Wang KP, Haponik EF, Gupta PK, Erozan YS. Flexible transbronchial needle aspiration. Technical considerations. *Ann Otol Rhinol Laryngol* 1984; 93 (3 Pt 1): 233-6.
2. Nakajima T, Yasufuku K, Iyoda A, Yoshida S, Suzuki M, Sekine Y, et al. The evaluation of lymph node metastasis by endobronchial ultrasound-guided transbronchial needle aspiration: crucial for selection of surgical candidates with metastatic lung tumors. *J Thorac Cardiovasc Surg* 2007; 134: 1485-90.
3. Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006; 130: 710-8.
4. Yasufuku K, Chiyo M, Koh E, Moriya Y, Iyoda A, Sekine Y, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 2005; 50: 347-54.
5. Silvestri GA, Gould MK, Margolis ML, Tanoue LT, McCrory D, Toloza E, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007; 132 (3 Suppl): 178S-201S.
6. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132 (3 Suppl): 202S-205S.

7. De Leyn P, Lardinois D, Van Schil PE, Rami-Porta R, Passlick B, Zielinski M, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 2007; 32: 1-8.
8. Ettinger DS, Bepler G, Bueno R, Chang A, Chang JY, Chirieac LR, et al. Non-small cell lung cancer clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2006; 4: 548-82.
9. Herth FJ, Ernst A, Eberhardt R, Vilman P, Dienemann H, Krasnik M. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J* 2006; 28: 910-4.
10. Herth FJ, Eberhardt R, Krasnik M, Ernst A. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. *Chest* 2008; 133: 887-91.

ผลกระทบของการเจาะตรวจต่อมน้ำเหลืองต่อขั้นตอนการรักษาในผู้ป่วยโรคมะเร็งปอด

แจ่มศักดิ์ ไชยคุนา, ศุภฤกษ์ ดิษยบุตร

วัตถุประสงค์: การเจาะตรวจต่อมน้ำเหลืองที่ซั้วปอด โดยอาศัยการนำด้ายอัลตราซาวด์ทำได้โดยใช้กล้องส่องหลอดลมชนิดพิเศษที่มีเครื่องอัลตราซาวด์ที่ส่วนปลาย ทำให้สามารถเห็นต่อมน้ำเหลืองนอกหลอดลมขณะทำการเจาะตรวจได้ ความไวและความจำเพาะของการวินิจฉัยด้วยวิธีนี้ค่อนข้างสูง แต่เนื่องจากเครื่องมือนี้มีราคาแพงจึงมีความสำคัญที่ต้องมีข้อมูลเกี่ยวกับประโยชน์ที่ทำให้มีการเปลี่ยนแปลงการรักษามากน้อยหรือไม่

วัสดุและวิธีการ: ผู้ป่วยจะได้รับการจัดเป็น สามกลุ่ม กลุ่มที่หนึ่งคือผู้ที่เป็นโรคมะเร็งปอดแต่ไม่พบว่ามึต่อมน้ำเหลืองโตจากการตรวจด้วยเอกซเรย์คอมพิวเตอร์ กลุ่มที่สองเช่นเดียวกับกลุ่มแรกแต่มีการโตของต่อมน้ำเหลืองมากกว่า 1 ซม. กลุ่มที่สามคือผู้ที่มีแต่ต่อมน้ำเหลืองที่ซั้วปอดโดยเฉยๆ ผู้ป่วยทุกรายได้รับการเจาะตรวจต่อมน้ำเหลืองที่ซั้วปอดโดยวิธีดังกล่าวและนำผลมาเปรียบเทียบ

ผลการศึกษา: มีผู้ป่วยทั้งหมด 158 รายแบ่งเป็นกลุ่มที่หนึ่ง 64 ราย กลุ่มที่สอง 57 ราย กลุ่มที่สาม 37 ราย ต่อมน้ำเหลืองที่พบมีขนาดเส้นผ่านศูนย์กลางเฉลี่ย 1.34 ซม. ได้รับการเจาะตรวจทั้งหมด 164 ต่อมในจำนวน 353 ต่อม ต่อมน้ำเหลืองที่โตพบบ่อยที่สุดที่ตำแหน่ง 7 เซลล์มะเร็งพบในกลุ่มที่หนึ่ง ร้อยละ 32.8 กลุ่มที่สอง ร้อยละ 68.4 กลุ่มที่สามร้อยละ 29.7

วิจารณ์: ถ้าขั้นตอนของการรักษาผู้ป่วยมะเร็งปอดแนะนำให้ทำการผ่าตัด mediastinoscopy ในผู้ป่วยทุกราย การเจาะตรวจต่อมน้ำเหลืองจะสามารถทำให้ระงับการทำผ่าตัดนี้ได้ร้อยละ 49.5 แต่ถ้ากำหนดให้ทำเฉพาะผู้ที่มีต่อมน้ำเหลืองโตจะสามารถระงับการทำผ่าตัดนี้ได้ถึงร้อยละ 59.5

สรุป: การเจาะตรวจต่อมน้ำเหลืองมีผลกระทบอย่างมากต่อขั้นตอนการรักษาผู้ป่วยโรคมะเร็งปอดที่มีหรือไม่มีต่อมน้ำเหลืองที่ซั้วปอดโต
