Accurate and safe mediastinal restaging by combined endobronchial and endoscopic ultrasound-guided needle aspiration performed by single ultrasound bronchoscope[†]

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Abstract

OBJECTIVES: The aim of this prospective trial was to assess the diagnostic utility of combined endobronchial (EBUS) and endoscopic (EUS) ultrasound-guided needle aspiration by use of a single ultrasound bronchoscope (CUSb-NA) in non-small-cell lung cancer (NSCLC) restaging in patients after induction therapy.

METHODS: In a consecutive group of NSCLC patients with pathologically confirmed N2 disease (clinical stage IIIa and IIIb) who underwent induction chemotherapy, CUSb-NA was performed. All of the patients with negative or suspected for metastases (uncertain) diagnosed by endoscopy underwent subsequently transcervical extended mediastinal lymphadenectomy (TEMLA) as a confirmatory test.

RESULTS: From January 2009 to December 2012, 106 patients met the inclusion criteria and underwent restaging CUSb-NA under mild sedation, in whom 286 (mean 2.7, range 2–5) lymph node stations were biopsied, 127 (mean 1.2, range 1–3) by EBUS-transbronchial needle aspiration (TBNA) and 159 (mean 1.5, range 1–4) by EUS-fine needle aspiration (FNA). The CUSb-NA revealed metastatic lymph node involvement in 37/106 patients (34.9%). In 69 (65.1%) patients with negative and uncertain CUSb-NA in 4 (3.8%) out of them, who underwent subsequent TEMLA metastatic nodes were found in 18 patients (17.0%) and there were single lymph nodes found only in one mediastinal station (minimal N2) in 10 (9.4%) out of them. False-positive results were found in 2 (1.9%) patients. In 9 (8.5%) patients CUSb-NA occurred to be false negative in Stations 2R and 4R (only accessible for EBUS), exclusively in small nodes and in 4 (3.8%) patients in Station 5—not accessible for CUSb-NA. The prevalence of mediastinal lymph node metastases in the present study was 51.9%. Diagnostic sensitivity, specificity, total accuracy, positive predictive value and negative predictive value (NPV) of the restaging CUSb-NA were 67.3% (95% CI [confidence interval]—53–79), 96.0% (95% CI—86–99), 81.0% (95% CI—73–87), 95.0% (95% CI—83–99) and 73.0% (95% CI—61–83), respectively. The sensitivity, accuracy and NPV of CUSb-NA were higher compared with EBUS-TBNA and EUS-FNA alone. No complications of CUSb-NA were observed.

CONCLUSIONS: The CUSb-NA is a reasonable and safe technique in mediastinal restaging in NSCLC patients after induction therapy. Following our data, in patients with negative result of CUSb-NA, a surgical restaging of the mediastinum should be considered.

Keywords: Combined ultrasound-needle aspiration • Mediastinum • Non-small-cell lung cancer • Restaging

INTRODUCTION

Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) are actually well introduced methods of biopsy of mediastinal nodes [1–4]. A combined ultrasound-needle aspiration approach (CUS-NA) has been presented only in few publications in non-small-cell lung cancer (NSCLC) staging as an alternative to mediastinoscopy and in none in restaging after induction therapy exclusively [5–10]. The CUS-NA technique enables more accurate assessment of the mediastinum and increases the diagnostic yield, but both methods are still not being commonly used in one session. Both techniques are highly complementary, but the main disadvantage is the limited reach of EUS-FNA especially for pulmonologists and thoracic surgeons. Only dedicated endoscopists well experienced in bronchoscopy and oesophagoscopy may perform both

endoscopies as one procedure. In 2010, Herth et al. [11] and Bin et al. [12] introduced the combined ultrasound method by use of a single scope (CUSb) in NSCLC staging. In this variation, EBUS and EUS are performed using the same ultrasound bronchoscope. Although it allows imaging and biopsy of the left adrenal gland or liver metastases only in some patients, it is fully sufficient for mediastinal staging. Reduced length of time of the procedure and lower hospital costs are the major advantages of CUSb approach comparing with CUS [13].

A mediastinal restaging after induction therapy is still a difficult and controversial issue. A discussion of the real diagnostic yield and utility of bioptic techniques in the NSCLC restaging is still open.

There are currently no accepted standards regarding mediastinal restaging, and many strategies, based on radiological, minimally invasive and surgical techniques are advocated [14]. According to the recent European Society of Thoracic Surgeons' and American College of Chest Physicians' guidelines, minimally invasive procedures, including EBUS-TBNA and EUS-FNA, may be alternatively used, but mediastinoscopy or remediastinoscopy should be preferably reserved for restaging [14–17].

MATERIALS AND METHODS

Clinical question

Is CUSb-NA an accurate and safe method in the NSCLC restaging after induction therapy?

What is the real sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of CUSb-NA in the NSCLC restaging, assessed using the bilateral mediastinal lymphadenectomy as the confirmatory test?

Design

This was a single-centre, prospective, cohort diagnostic study. The study was approved by the institutional ethic committee. No potential conflicts of interest are to report.

Location

Department of Thoracic Surgery and Endoscopy Unit, Pulmonary Hospital, Zakopane, Poland.

Patients

Inclusion criteria: (i) 4 years of period study, (ii) group of consecutive NSCLC patients in clinical stage IIIA–IIIB (in Stage IIIb either included N3 or T4N2 patients) confirmed only by EBUS-TBNA, EUS-FNA, CUS-NA or CUSb-NA, (iii) after 3–5 series of induction therapy (cis-platin + vinorelbine), (iv) enlarged or normal mediastinal lymph nodes on CT scans—defined by radiologists as having stable disease or partial response after induction therapy and (v) general condition enabling appropriate pulmonary resection.

Exclusion criteria: (i) no response after induction therapy—a progression of radiological or endobronchial lesions and (ii) lack of patient consent.

Intervention

Prior to the endoscopic procedure, the CT scans were carefully analysed. The CUSb-NA was performed under mild intravenous sedation (fentanyl 0.05–0.1 mg, midazolam 1–5 mg), using the BF-UC160F-OL8 and BF-UC180F ultrasound videobronchoscopes (Olympus Medical Systems Corporation, Tokyo, Japan). The ultrasound videobronchoscopes are 6.9 and 6.3 mm wide, have 2 and 2.2 mm working channels, respectively, and an oblique 35° optical system. The 7.5 MHz EU-C60 and 5–12 MHz EU-ME1 ultrasound processors were used, enabling 20–50 mm depth tissue imaging. As the ultrasound videobronchoscope is not designed for detailed assessment of the bronchial tree, the examination was preceded by the standard videobronchoscopy. For the biopsy, a cytological 22G needle with guidewire and marking facilitating its visualization on the ultrasound image was used (NA-201SX-4022, Olympus Medical Systems Corporation, Tokyo, Japan). CUSb-NA of detectable lymph nodes ≥5 mm on the short axis were performed (criterion of feasibility of lymph node biopsy according to Herth et al. [1] and Annema et al. [3]); first of all, enlarged nodes or those considered being suspicious based on the shape or echogenicity were biopsied. All pretherapy positive stations were punctured by CUSb-NA, if only appeared. If there were no bigger nodes visible, even those >3 mm were punctured. All biopsies were performed through the macroscopically normal bronchial wall. The range of biopsied nodal stations in 1 patient was 1–5.

The cytological smear and cell blocks were performed and fixed using 96% ethanol. The specimens were sent to the cytological laboratory and the standard haematoxylin-eosin staining was used. The immuno and molecular staining was performed additionally if N2 disease was recognized by CUSb-NA.

In patients with negative or suspected for metastases (uncertain) results of the CUSb-NA, transcervical extended mediastinal lymphadenectomy (TEMLA) was performed. TEMLA includes bilateral dissection of all mediastinal lymph nodes, except for Station 9. The use of a special retractor, elevating the sternum, enables access to the mediastinal structures and safe dissection of lymph nodes. The technique of the TEMLA has been implemented since 2005 and presented in some publications [9, 18, 19].

In patients with negative results of the TEMLA who are fit enough for surgery, an appropriate pulmonary resection with dissection of the mediastinum was performed. The extent of the mediastinal dissection corresponded to the systematic lymph node dissection. Minimal N2 in our study refers to single lymph nodes found only in one mediastinal station regardless of whether lymphadenectomy was performed either by TEMLA or by thoracotomy. The Mountain-Dresler lymph node classification and [20] the seventh edition of tumour nodes metastases (TNM) classification were used.

Statistical analysis

The sensitivity, specificity, accuracy, PPV and NPV (including 95% confidence interval [CI]) were calculated using the GraphPad InStat 3.05 software (GraphPad Software, San Diego, CA, USA) and were based on the standard definitions. The bootstrap method was used (in Statistica™ Statsoft, Inc., USA environment) to compare the diagnostic values of different medical tests. Asymptotic normality of maximum likelihood estimates of the parameters of multinomial distribution and delta method were used to derive the asymptotic distribution of test statistics. The bootstrap approximations of this

test statistics were obtain from 2000 bootstrap replications. The significance level was set at $P \leq 0.05$.

RESULTS

From January 2009 to December 2012, 106 patients met the inclusion criteria and underwent restaging CUSb-NA. Fifteen patients were excluded from the trial—in 12 patients there was no response after induction therapy and in the remaining three there was lack of consent.

There were 78 men and 28 women in the mean age $61.5 \pm$ (standard deviation) 8.1 years (range 45–83), respectively. In total, 286 mediastinal lymph node stations were biopsied: 1 (upper mediastinal) −3, 2R (right upper paratracheal) −12, 2L (left upper paratracheal)−12, 4R (right lower paratracheal)−52, 4L (left lower paratracheal)−97, 7 (subcarinal)−102, 8 (paraoesophageal)−6 and 9 (pulmonary ligament)−2. The number of nodes biopsied by CUSb-NA was 286 (mean 2.7, range 2–5) including 127 EBUS-TBNA (mean 1.2, range 1–3) and 159 EUS-FNA (mean 1.5, range 1–4).

The CUSb-NA established a diagnosis in 37/106 patients (34.9% true positive results): by EBUS-TBNA alone in 7 patients (6.6%), by EUS-FNA alone in 12 patients (11.3%) and by both methods in 18 patients (17.0%) (Figs 1 and 2).

In 69 (65.1%) patients with negative CUSb-NA, with 4 (3.8%) out of them with uncertain CUSb-NA, who underwent subsequent TEMLA, metastatic nodes were found in 18 patients (17.0%) and there was minimal N2 in 10 (9.4%). Among these 18 false-negative patients, there were 30 (10.5%) false-negative biopsies in stations: 2R−5, 2L−2, 4R−10, 4L−1, 5−4, 7−7 and 8−1. In 8 (7.6%) of these patients more than one station was involved: in 5 patients −2 stations (2R and 4R exclusively) and in 3 patients−multilevel stations. In 9 (8.5%) patients CUSb-NA occurred to be false negative in stations 2R and 4R (only accessible for EBUS), exclusively in small nodes (Fig. 3). In the remaining 4 (3.8%) patients, false-negative results were obtained in Station 5, not accessible for CUSb-NA. False-positive results were found in 2 (1.9%) patients out of the group with uncertain result of CUSb-NA.

The mean diameter of the biopsied nodes was 12.8 ± 7.6 mm in the long axis and 8.7 ± 5.8 mm in the short axis. The CUSb-NA was technically successful in 247 cases (86.5%), and in 92 of 286 biopsies (32.0%) the persistent nodal metastases were detected.

In 49 patients (46.2%), the result of CUSb-NA was true negative (Fig. 4). In this group, the cytological diagnosis of benign, reactive lymph node was subsequently confirmed by the histological examination of the TEMLA operative specimen, and in 37 patients

(34.9%) with negative results of the TEMLA, additionally mediastinal dissection during thoracotomy was performed and no positive N2-3 nodes were found. The remaining 12 (11.3%) patients after TEMLA did not undergo lung resection. Eight (7.5%) patients out of them had a significant impairment of pulmonary function tests that made lung resection impossible, including 3 (2.8%) patients with temporary left nerve palsy, 4 (3.8%) patients with postoperative pulmonary insufficiency, suspected of having pulmonary embolism in whom 1 (0.9%) patient had pneumothorax, necessitating a chest drainage, and 1 (0.9%) had pleural effusion. One (0.9%) patient had a myocardial infarction and 3 (2.8%) patients refused the second surgery.

In 7 (6.6%) patients after TEMLA, asymptomatic widening of the mediastinum on chest X-ray was seen.

The prevalence of mediastinal lymph node metastases in the present study was 51.9%.

Figure 2: Positive restaging EUS in Station 8.

Figure 3: False-negative restaging EBUS in Station 4R.

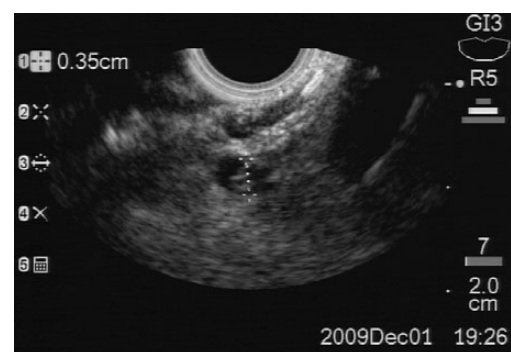**Figure 1:** Positive restaging EBUS in Station 7.

Figure 4: True negative restaging EUS-FNA in small nodes in Station 7.

Table 1: Diagnostic utility of bioptic techniques calculated on a per patient basis in NSCLC restaging after induction therapy

Bioptic technique	Diagnostic yield				
	Sensitivity (%)	Specificity (%)	Total accuracy (%)	PPV (%)	NPV (%)
EBUS-TBNA	48 (34–62)	98 (90–100)	74 (64–81)	96 (80–100)	66 (55–76)
EUS-FNA	61 (46–75)	98 (91–100)	81 (72–87)	97 (83–100)	71 (58–84)
CUSb-NA (in all mediastinal stations)	67 (53–79)	96 (86–99)	81 (73–87)	95 (83–99)	73 (61–83)
CUSb-NA (in stations accessible for CUS)	70 (56–82)	96 (87–99)	83 (75–89)	95 (83–99)	76 (64–86)

Table 2: A comparison of diagnostic yield of CUSb with that of EBUS and EUS alone

Diagnostic yield per patient	CUSb/EBUS, *P*-value	CUSb/EUS, *P*-value
Sensitivity	<0.001	0.02
Specificity	0.30	0.28
Total accuracy	0.006	0.99
Positive predictive value	0.70	0.48
Negative predictive value	0.30	0.28

The overall sensitivity of the CUSb-NA in NSCLC restaging calculated on a per patient basis was 67.3% (95% CI−53–79), specificity 96.0% (95% CI−86–99), total accuracy 81.0% (95% CI−73–87), PPV 95.0% (95% CI−83–99) and NPV 73.0% (95% CI−61–83).

The diagnostic yields of EBUS-TBNA, EUS-FNA and CUSb-NA calculated on a per patient basis are presented in Table 1.

The sensitivity of CUSb-NA was significantly higher compared with EBUS-TBNA ($P < 0.001$) and EUS-FNA alone ($P = 0.02$). The total accuracy of CUSb-NA was also significantly higher compared with EBUS-TBNA alone ($P = 0.006$) and comparable with EUS-FNA alone ($P = 0.99$). The NPV of CUSb-NA was higher but not statistically significant compared with EBUS-TBNA ($P = 0.30$) and EUS-FNA alone ($P = 0.28$) (Table 2).

The durations of CUSb-NA, EBUS-TBNA, EUS-FNA and TEMLA were 15.2 ± 7.4 min (range 12–25), 12.1 ± 3.3 min (range 8–17), 5.1 ± 3.7 min (range 3–9) and 82.3 ± 24.4 min (range 55–106), respectively.

Neither complications nor morbidity and mortality were observed after CUSb-NA.

The cost of CUSb-NA procedure is slightly higher than that of separate EBUS-TBNA. The total consumption of bioptic needles during CUSb-NA is 15% higher than during EBUS-TBNA. The repair and depreciation cost of endoscopic equipment is also minimally higher (8%). The costs, medical materials and medicines for CUSb-NA and EBUS-TBNA are comparable.

DISCUSSION

The use of CUSb-NA performed simultaneously under mild sedation has never been presented as a standard method in minimally invasive endoscopic NSCLC restaging. The sensitivity of large studies aimed to assess the diagnostic yield of CUS in NSCLC staging was 91.1–93%, the NPV was 91–97% and the accuracy was 91–97% [6, 7]. In one study analysing patients with small lymph nodes only, sensitivity was 68%, NPV was 91% and accuracy was 91%. The sensitivity of CUS was significantly better than that of EBUS ($P = 0.04$) and better than that of EUS ($P = 0.07$). Also, the NPV of CUS was significantly better than that of EBUS ($P = 0.01$) and EUS ($P = 0.03$) [8]. These results compare favourably with all other commonly used techniques of mediastinal staging of lung cancer. Although widely accepted in NSCLC staging, little is known about the role of EBUS and EUS in lung cancer restaging after induction therapy. So far, there were only few publications presenting 61 and 124 NSCLC patients for EBUS restaging and 58, 28 and 19 patients for EUS restaging [21–25]. In those papers, the sensitivity of EBUS-TBNA was 67% and 76% and of EUS was 44, 83 and 75%, whereas the NPV of EBUS-TBNA was 20% and 78% and of EUS was 58, 91.6 and 67%, respectively. All authors suggested that EBUS-TBNA and EUS-FNA are effective, less than for initial staging and also safe for mediastinal restaging, but negative results of them should be confirmed by surgical staging before thoracotomy. Only in one study CUS-NA performed by use of two scopes in 50 patients was compared with TEMLA for NSCLC restaging. This study showed significantly better results for TEMLA than for CUS-NA (sensitivity 96.6 vs 64.3% and NPV 98.5 vs 82.1%, $P < 0.01$) [9]. Except in this paper, there are no data about the role of CUS-NA for NSCLC restaging. The sensitivity and NPV of remediastinoscopy after induction treatment based on the biggest series of studies is 29–78% [14]. There is no straight and randomized comparison between standard remediastinoscopy and combined endoscopic techniques including CUSb-NA, but the accuracy is possibly at least equal.

In the current study, the mean numbers of biopsied lymph node stations by use of EBUS-TBNA, EUS-FNA and CUSb-FNA were 1.2, 1.5 and 2.7, respectively in comparison with the mean number of 27.4 nodes removed during restaging TEMLA. Such a big difference in the number of examined nodes may be the main reason for the difference in the diagnostic yields among minimally invasive bioptic methods and TEMLA.

A major advantage of CUSb over TEMLA is that no morbidity and mortality was observed after CUSb-NA and the overall morbidity of restaging TEMLA was 7.5%.

Gaining skills and experience in the endobronchial and endoscopic ultrasound imaging and performing the biopsy in restaging is more time-consuming and operator-dependent than in standard staging performed by EBUS, EUS and CUSb. It is very difficult, even for experienced endoscopist, to distinguish between suspected region for metastases and postinflammatory adhesions, degenerative changes and fibrosis after oncological treatment. This may also be the reason of the technical failure in >13% of biopsies.

In our study, a diagnostic yield of CUSb-NA in restaging of NSCLC patients with 51.9% prevalence of metastatic nodes was quite high: sensitivity−67.3%, total accuracy−81.0% and NPV−73.0%. The NPV of CUS performed by use of two different scopes

was higher 82.1% [9]. A similar tendency was observed in the study comparing two methods CUS vs CUSb in primary NSCLC staging (90.7 vs 82.0%) [13].

But most importantly, the sensitivity of CUSb-NA was significantly higher compared with EBUS-TBNA ($P < 0.001$) and EUS-FNA alone ($P = 0.02$), and likewise the total accuracy of CUSb-NA was also significantly higher compared with EBUS-TBNA alone ($P = 0.006$). The NPV of CUSb-NA was higher compared with EBUS-TBNA ($P = 0.30$) and EUS-FNA alone ($P = 0.28$). It confirms the superiority of the combined approach compared with EBUS and EUS alone in detecting metastases. Moreover, the mean time of restaging CUSb-NA was 15.2 ± 7.4 min (range 12–25) and comparable with the mean time of staging CUSb-NA [13].

In our study, there was no straight comparison of an economical evaluation between CUS and CUSb. However, it seems that the CUSb has the advantage of being more economical than CUS, because of the use of only one ultrasound bronchoscope in one session but it requires further trials.

The cost of CUSb-NA is slightly higher than that of single EBUS-TBNA mainly because of the 15% higher use of bioptic needles and 8% higher cost of the repair and depreciation of endoscopic equipment.

The major limitation of our study was lack of routine use of positron emission tomograpy combined with computed tomograpy, which might increase the accuracy of the restaging CUSb-NA while indicating stations for precise puncturing. There are also several factors that might influence the reliability of the restaging CUSb-NA such as: primary invasive staging only performed by use of bioptic techniques or the number of chemotherapy cycles (3–5 in our study) and a different interval time between the date of the end of induction therapy and CUSb-NA. However, due to high efficiency and low invasiveness, a combined endoscopic technique by use of a single bronchoscope may become the method of choice in invasive NSCLC restaging.

CONCLUSIONS

(i) CUSb-NA is an accurate, reasonable and safe technique in mediastinal restaging in NSCLC patients after induction therapy.
(ii) Following our data, in patients with negative result of CUSb-NA, a further surgical restaging of the mediastinum should be thoroughly considered.

Conflict of interest: none declared.

REFERENCES

[1] Herth FJ, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 2006;61:795–8.
[2] Szlubowski A, Kuzdzał J, Kołodziej M, Soja J, Pankowski J, Obrochta A et al. Endobronchial ultrasound-guided needle aspiration in the non-small cell lung cancer staging. Eur J Cardiothorac Surg 2009;35:332–5.
[3] Annema JT, Versteegh MI, Veseliç M, Voigt P, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of lung cancer and its impact on surgical staging. J Clin Oncol 2005;23: 8357–61.
[4] Annema JT, Versteegh MI, Veseliç M, Welker L, Mauad T, Sont JK et al. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. JAMA 2005;294:931–6.
[5] Larsen SS, Vilmann P, Krasnik M, Dirksen A, Clementsen P, Maltbaek N et al. Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial. Lung Cancer 2005;49:377–85.
[6] Wallace MB, Pascual JMS, Raimondo M, Woodward TA, McComb BL, Crook JE et al. Minimally invasive endoscopic staging of suspected lung cancer. JAMA 2008;299:540–6.
[7] Rintoul RC, Skwarski KM, Murchison JT, Wallace WA, Walker WS, Penman ID. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. Eur Respir J 2005; 25:416–21.
[8] Szlubowski A, Zieliński M, Soja J, Annema JT, Sośnicki W, Jakubiak M et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging—a prospective trial. Eur J Cardiothorac Surg 2010;37:1175–9.
[9] Zielinski M, Szlubowski A, Kołodziej M, Orzechowski S, Laczynska E, Pankowski J et al. Comparison of endobronchial ultrasound and/or endoesophageal ultrasound with transcervical extended mediastinal lymphadenectomy for staging and restaging of non-small-cell lung cancer. J Thorac Oncol 2013;8:630–6.
[10] Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA 2010;304:2245–52.
[11] Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. Chest 2010;138:790–4.
[12] Hwangbo B, Lee GK, Lee HS, Lim KY, Lee SH, Kim HY et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest 2010;138:795–802.
[13] Szlubowski A, Soja J, Kocon P, Talar P, Czajkowski W, Rudnicka-Sosin L et al. A comparison of the combined ultrasound of the mediastinum by use of a single ultrasound bronchoscope versus ultrasound bronchoscope plus ultrasound gastroscope in lung cancer staging: a prospective trial. Interact CardioVasc Thorac Surg 2012;15:442–6.
[14] De Leyn P, Lardinois D, Van Schil P, Rami-Porta R, Passlick B, Zielinski M et al. European trends in preoperative and intraoperative nodal staging: ESTS guidelines. J Thorac Oncol 2007;2:357–61.
[15] Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA. Invasive mediastinal staging of lung cancer. ACCP evidence-based clinical practice guidelines. Chest 2007;132:202S–20S.
[16] Surmont V, van Klaveren RJ, Goor C, Schramel F, Manegold C, Legrand C et al. Lessons to learn from EORTC study 08981: a feasibility study of induction chemoradiotherapy followed by surgical resection for stage IIIB non-small cell lung cancer. Lung Cancer 2007;55:95–9.
[17] Van Schil P, De Waele M, Hendriks J, Lauwers P. Remediastinoscopy. J Thorac Oncol 2007;2:365–6.
[18] Kuzdzal J, Zielinski M, Papla B, Szlubowski A, Hauer L, Nabialek T et al. Transcervical extended mediastinal lymphadenectomy the new operative technique and early results in lung cancer staging. Eur J Cardiothorac Surg 2005;27:384–90.
[19] Zielinski M. Transcervical extended mediastinal lymphadenectomy: results of staging in two hundred fifty-six patients with non-small cell lung cancer. J Thorac Oncol 2007;4:370–2.
[20] Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718–23.
[21] Herth FJ, Annema JT, Eberhardt R, Yasufuku K, Ernst A, Krasnik M et al. Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. J Clin Oncol 2008;26: 3346–50.
[22] Szlubowski A, Herth FJ, Soja J, Kołodziej M, Figura J, Ćmiel A et al. Endobronchial ultrasound-guided needle aspiration in non-small-cell lung cancer restaging verified by the transcervical bilateral extended mediastinal lymphadenectomy—a prospective study. Eur J Cardiothorac Surg 2010;37:1180–4.
[23] von Bartheld MB, Versteegh MI, Braun J, Willems LN, Rabe KF, Annema JT. Transesophageal ultrasound-guided fine-needle aspiration for the mediastinal restaging of non-small cell lung cancer. J Thorac Oncol 2011;6: 1510–5.
[24] Annema JT, Veseliç M, Versteegh MI, Willems LN, Rabe KF. Mediastinal restaging: EUS-FNA offers a new perspective. Lung Cancer 2003;42:311–8.
[25] Stigt JA, Oostdijk AH, Timmer PR, Shahin GM, Boers JE, Groen HJ. Comparison of EUS-guided fine needle aspiration and integrated PET-CT in restaging after treatment for locally advanced non-small cell lung cancer. Lung Cancer 2009;66:198–204.