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Minimally invasive diagnosis of sarcoidosis by EBUS when conventional diagnostics fail

J. Eckardt[1], K.E. Olsen[2], O.D. Jørgensen[1], P.B. Licht[1]

[1] Department of Cardiothoracic Surgery, Odense University Hospital, Odense, Denmark; [2] Department of Pathology, Odense University Hospital, Odense, Denmark

Abstract. *Background:* Endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS) is a minimally invasive method used routinely for mediastinal staging of patients with lung cancer. EBUS has also proved to be a valuable diagnostic tool for patients with different intrathoracic lesions who remain undiagnosed despite bronchoscopy and CT-guided fine-needle aspiration. *Objective:* The present study focused on EBUS for diagnosing sarcoidosis. *Design:* During a 3-year period 308 of 601 patients who underwent EBUS at our institution were referred for further diagnostic of a radiologically suspicious lesion in the lung parenchyma (n=195), enlarged lymph nodes in the mediastinum (n=89), a suspicious tumor in the mediastinum or pleural disease (n=24) but no one had a definite histological diagnosis. All charts were reviewed retrospectively. *Results:* Of the 308 patients 43 (14%) were eventually diagnosed with sarcoidosis. Thirty-three (77%) were diagnosed with EBUS. In the remaining 10 patients EBUS did not provide adequate tissue samples in 4 (9%) and in 6 patients (14%) EBUS provided adequate tissue but no definite diagnosis. EBUS was significantly better to establish the diagnosis in patients with enlarged mediastinal lymph nodes compared with isolated lung parenchymal involvement (85% vs 63%, p< 0.05). *Conclusion:* EBUS is a valuable minimally invasive diagnostic modality to establish the diagnosis of sarcoidosis of unselected patients with undiagnosed intrathoracic lesions after conventional work up – particularly if patients have enlarged mediastinal lymph nodes. This minimally invasive procedure provides a final diagnosis without exposing the patient to the risk of complications from more invasive procedures. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 43-48)*

Key words: EBUS, Pulmonary Sarcoidosis

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology with a mortality of 1-5% (1). The lung is often involved, and enlarged paratracheal or hilar lymph nodes are present in up to 85% of patients (2). Enlarged mediastinal lymph nodes may also represent malignancy and a quick diagnosis is important. Diagnostic tissue is essential and most often obtained by conventional bronchoscopy and bronchoalveolar lavage (BAL), transbronchial needle aspiration (TBNA), transbronchial lung biopsy (TBLB) or a CT guided fine needle aspiration (CT-FNA) (3). However, a number of patients remain undiagnosed despite these investigations, and commonly the next step to get a tissue diagnosis is mediastinoscopy which is an invasive surgical procedure that poses a small but significant risk to the patient (4).

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Correspondence: Jens Eckardt
Department of Cardiothoracic Surgery
Odense University Hospital
Sdr. Boulevard 29
Odense
DK-5000 Denmark
Tel. +45 24621770
Fax +45 65916935
E-mail: jens@eckardtmail.dk

Less invasive methods have emerged including endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and most recently endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS) which is a well established method for mediastinal staging of lung cancer (5-8). Although the echo image in EBUS may give a clue to whether a suspicious looking lymph node is malignant or not (9) it is still of paramount importance to obtain tissue for cytological or histological diagnostics. We have used EBUS routinely for three years and the aim of this study was to assess the value of EBUS for the diagnosis of sarcoidosis.

Methods

During a 36 months period (January 2006 to December 2008) 601 patients underwent EBUS at our institution. All patient charts and pathology reports were reviewed retrospectively. In accordance with Danish law the local ethics committee waives review and consent requirements in follow-up studies. The indication for EBUS in 293 patients was mediastinal staging of lung cancer and in the remaining 308 the indication was an undiagnosed radiologically suspicious lesion in the lung parenchyma (n=195), enlarged lymph nodes in the mediastinum (n=89), a suspicious tumor in the mediastinum or pleural disease (n=24). All 308 patients had a previous chest CT and bronchoscopy with biopsy, bronchoalveolar lavage and depending on our pulmunologists judgement a TBLB or TBNA but remained undiagnosed.

All EBUS examinations were performed in general anesthesia (larynx mask) with a linear scanner (BF-UC160F, Olympus). Enlarged paratracheal or hilar lymph node stations 2, 3, 4, 7, 10 and 11 according to Mountain et al. (10) were systematically identified and punctured. Fine needle aspiration was performed with a 22G needle (NA-201SX-4022, Olympus) during real-time EBUS. Two aspirations were performed from each lesion to ensure that the biopsy contained sufficient material. Aspirated material was expelled onto glass slides and smeared for cytological examination and expelled into saline for preparation of cell blocks for histological examination. Rapid on-site evaluation was not performed. Instead, all biopsies were reviewed the following day by an experienced pathologist, and classified as "malignant", "benign" or "nondiagnostic" as shown in Figure 1.The latter group was further subdivided into biopsies with adequate cell sample (presence of lymphocytes) or inadequate cell sample without lymphatic tissue. The cytological diagnosis of epithelioid cells and giant cells without a background of necrosis in addition to relevant clinical findings provided the diagnosis of sarcoidosis. Patients without a definite diagnosis after EBUS were referred for more invasive investigations or followed in the outpatient clinic and were subsequently referred for more invasive procedures if their CT-scan did not demonstrate regression of the lesion.

Results

There was no operative mortality or any surgical complications during EBUS and all patients were discharged from the hospital on the day of surgery. Of all 308 patients 43 (14%) were eventually diagnosed with sarcoidosis. All were Caucasian with a median age of 53 years (range 27 to 75 years) and 23 were men (64%).

Thirty-three (77%) were diagnosed with EBUS. In the remaining 10 patients (23%) EBUS did not provide adequate tissue samples in 4 (9%) and for the last 6 patients (14%) EBUS provided adequate tissue but not the final diagnosis. Nine of these 10 patients were later diagnosed with sarcoidosis following mediastinoscopy and the last patient was diagnosed after thoracoscopy.

Six-teen patients (37%) had lesions in the lung parenchyma. In these patients a final diagnosis by EBUS was possible in 10 (63%) and in the remaining 6 patients, four had adequate tissue samples but without a definite diagnosis and two patients had inadequate tissue samples. In the remaining 27 patients (63%), who all had enlarged mediastinal lymph nodes without lung parenchymal involvement EBUS of provided the diagnosis in 23 cases (85%). In the remaining four patients, two had inadequate tissue samples and two had adequate tissue samples but without a definite diagnosis. EBUS was better to establish the diagnosis in patients with enlarged mediastinal lymph nodes compared with isolated lung parenchymal involvement (85% vs 63%) but not significant. Fisher´s Exact Test, $p < 0.05$). Prior to our

EBUS examination 9 out of the 27 patients with enlarged mediastinal lymph nodes had undergone a conventional broncoscopic TBNA and 5 of the 16 patients with lung parenchymal involvement had a TBLB but all remained undiagnosed.

During the same period our pulmonologists diagnosed 93 patients with sarcoidosis by broncoalveolar lavage in 40%, by TBLB in 27%, TBNA in 21% and by EBUS in local anaesthesia/sedation in 2%.

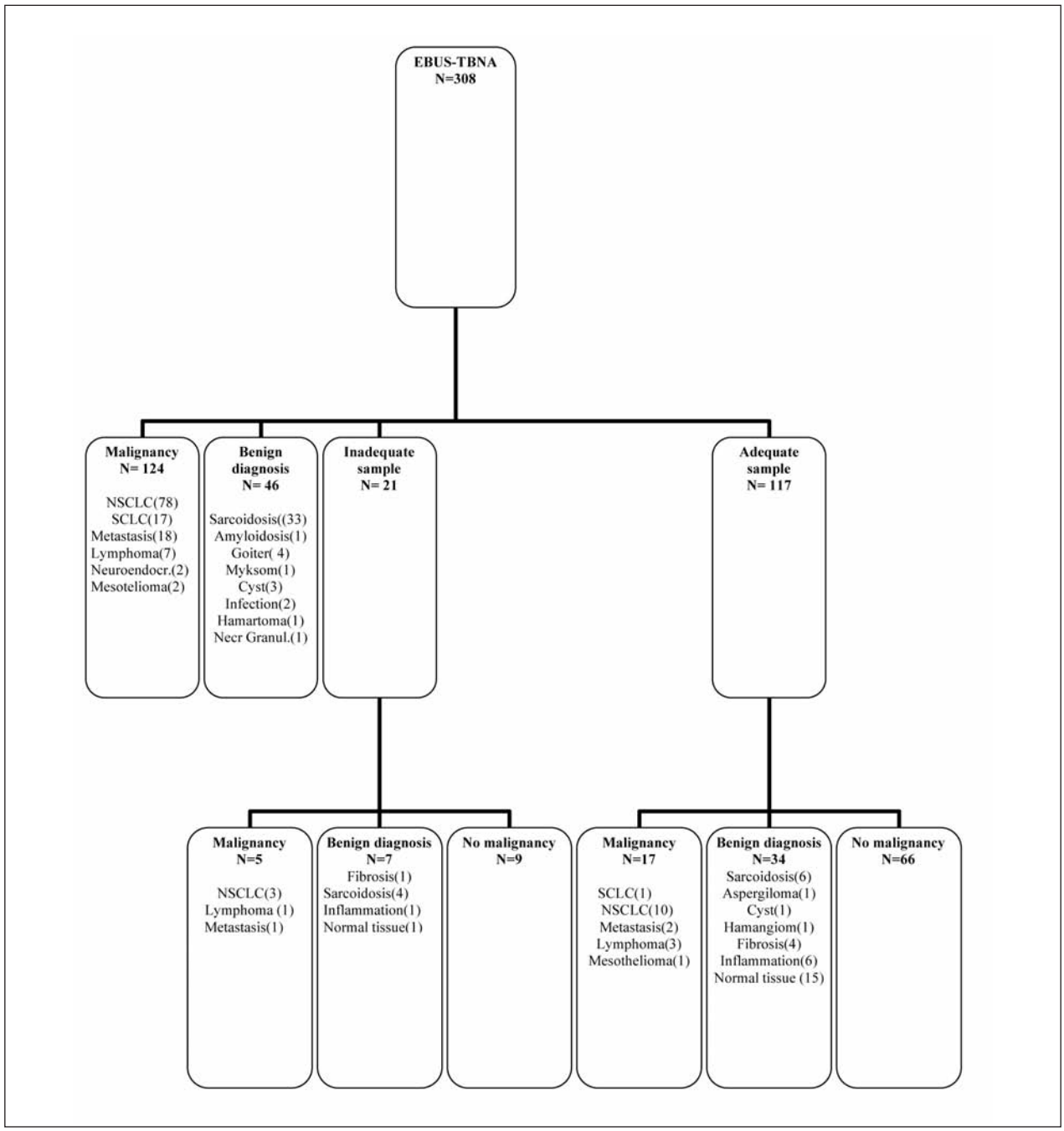

Fig. 1. All EBUS-FNA were classified as "malignant", "benign" or "nondiagnostic"

Discussion

EBUS is a relatively new diagnostic modality which is less invasive and less expensive than more invasive procedures because it allows investigation in an outpatient setting. It is most often used for mediastinal staging for NSCLC but may also be useful in patients with chest tumors who remain undiagnosed despite conventional investigations by bronchoscopy including bronchoalveolar lavage / TBNA/ TBLB or CT-FNA (11). This type of undiagnosed patients are often referred for more invasive procedures such as mediastinoscopy, thoracoscopy or even thoracotomy which carry a small but definite risk to the patient, and they are costly. In a previous study we demonstrated that in approximately 45% of such patients a valid diagnosis in general can be reached minimally invasive by EBUS (11). In the present study EBUS was able to establish the diagnosis in 77% patients with sarcoidosis. Others have used EBUS to diagnose sarcoidosis in patients suspected of sarcoidosis with higher yields of 83%-91% (12-14). Our study is slightly smaller and demonstrates a lower yield but, importantly, differs from the previous three studies because we used EBUS in patients who had already been seen and evaluated by our pulmonologists but remained undiagnosed. During the same periode our pulmonologists diagnosed 93 patients with sarcoidosis supporting our statement that patients in our study were highly selected. With TBNA Cetinkaya et al. demonstrated a yield of 76% with prevalence of sarcoidosis of 35% in unselected patients (15) whereas the prevalence of sarcoidosis in our cohort was only 14% suggesting that most patients with sarcoidosis have already been diagnosed by our pulmonologists. Despite the lower prevalence our results demonstrate that the diagnostic yield of EBUS remained high at 77% and it is not unlikely that it would be even higher if we had used EBUS as the primary investigation. One other study with a more similar approach to ours demonstrated a yield of 59% by EBUS in patients who had been investigated by simple bronchoscopy but remained undiagnosed (16).

The diagnostic yield in EBUS depends on the location of the lesion and is higher in central than peripheral lesions (17) which is also confirmed in the present study where the final diagnosis of sarcoidosis was established by EBUS in 85% of patients with mediastinal lymphadenopathy but only in 63% of the patients with lesions in the lung parenchyma. Two out of four biopsies with inadequate tissue samples came from patients with a lesion in the lung parenchyma and two patients with enlarged lymph nodes had an inadequate tissue sample. The lower diagnostic yield in lesions in the lung parenchyma may be explained by interposition of aerated lung tissue which disturbs the ultrasound image when targeting the actual peripheral lesion.

Until now transbronchial lung biopsy (TBLB) and bronchoscopic TBNA have been the primary procedures to diagnose sarcoidosis with yields of 76-91% (18-20) and 62-87% (15, 21) respectively. However, both procedures are performed blindly because the targeted lymph node or lung lesion are not visualized during biopsy or fine needle aspiration. Instead, aspiration is guided only by knowledge from prior CT imaging and, consequently, the technique is considered difficult (22). In the present study we used EBUS with real time ultrasound imaging of the target which allows for a quick and reproducible diagnostic examination which is also easy to perform. To illustrate this, previous investigators who focused on the learning curve in EBUS concluded that the number of investigations necessary to become experienced was just 10 (23).

Diagnostic yield for transbronchial lung biopsy (TBLB) in patients with characteristic radiographic findings of sarcoidosis without lung parenchymal involvement is low but increases up to 75% in later stages of the disease with involvement of the lung parenchyma (24). In patients suspected to have sarcoidosis but without the characteristic radiographic findings TBLB has a diagnostic yield of just 30% (25) and several severe complication have been reported following TBLB including parenchymal lung haemorhage and pneumothorax (18). CT-FNA is also a minimal invasive procedure but is generally not used for enlarged mediastinal lymph nodes. It is performed primarily in patients with lung parenchymal involvement where yield depends on the size of the lesion (26) but it is generally low and the procedure carries a risk of pneumothorax of 5.5% (27).

Mediastinoscopy has a high diagnostic yield for sarcoidosis (28) but is an invasive surgical procedure that poses a small but significant risk to the patient. Approximately 0.6% of patients undergoing mediastinoscopy develop hoarseness due to perioperative

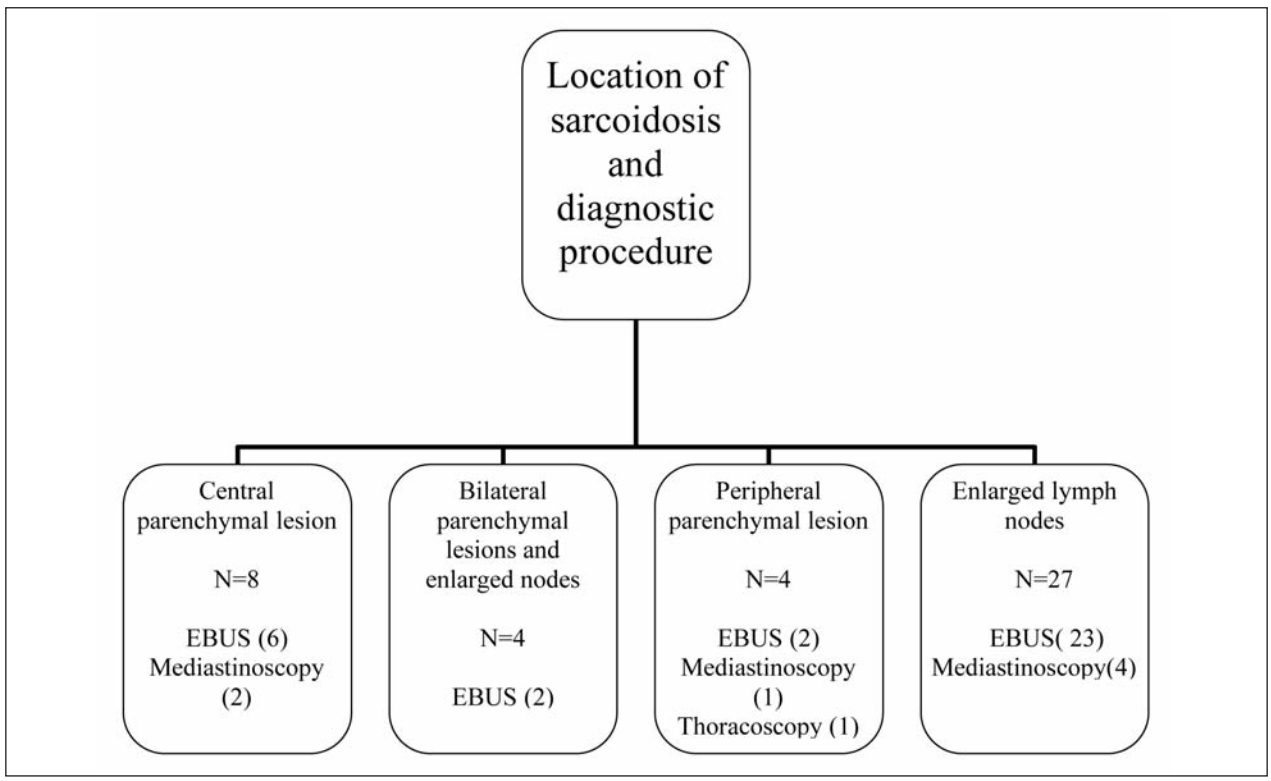

Fig. 2. Location of pathology and procedure used to diagnose sarcoidosis.

damage to the recurrent laryngeal nerve (4). In addition, mediastinoscopy only allows biopsy of central lymph node station station (10) but not perihilar lymph nodes or lung parenchyma which may be the only involvement of sarcoidosis. In contrast, EBUS allows biopsies from such peripheral lymph nodes and sometimes even from the lung parenchyma as demonstrated in the present study (Figure 2). Consequently, one may even suspect that the diagnostic yield of EBUS could be higher than mediastinoscopy but this is purely speculative and has not been tested prospectively. Furthermore, EBUS is considered a safe investigation and severe complications have never been reported (6, 29). Finally, if needed, EBUS allows routine reexaminations without exposing the patients of the increased risks of complications associated with a re-mediastinoscopy.

In conclusion, we have demonstrated that EBUS is also a valuable minimally invasive diagnostic modality to establish the diagnosis of sarcoidosis in patients with intrathoracic tumors who remained undiagnosed after conventional work up – particularly if patients have enlarged mediastinal lymph nodes. In the vast majority of patients with sarcoidosis this minimally invasive procedure provides a final diagnosis without exposing the patient to the risk of complications from more invasive procedures. However, if EBUS does not provide the diagnosis patients must be referred for a more invasive work-up.

References

1. Gribbin J, Hubbard RB, Le J, I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006; 61 (11): 980-5.
2. Lynch JP, III, Ma YL, Koss MN, White ES. Pulmonary sarcoidosis. Semin.Respir. Crit Care Med 2007; 28 (1): 53-74.
3. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16 (2): 149-73.
4. Lemaire A, Nikolic I, Petersen T, et al. Nine-year single center experience with cervical mediastinoscopy: complications and false negative rate. Ann Thorac Surg 2006; 82 (4): 1185-9.

5. De LP, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg 2007; 32 (1): 1-8.
6. 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 (9): 795-8.
7. Omark PH, Eckardt J, Hakami A, Olsen KE, Jorgensen OD. The value of mediastinal staging with endobronchial ultrasound-guided transbronchial needle aspiration in patients with lung cancer. Eur J Cardiothorac Surg 2009 Jun 5.
8. Yasufuku K, Chiyo M, Koh E, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer 2005; 50 (3): 347-54.
9. Chao TY, Lie CH, Chung YH, Wang JL, Wang YH, Lin MC. Differentiating peripheral pulmonary lesions based on images of endobronchial ultrasonography. Chest 2006; 130 (4): 1191-7.
10. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997; 111 (6): 1718-23.
11. Eckardt J, Petersen HO, Hakami-Kermani A, Olsen KE, Jorgensen OD, Licht PB. Endobronchial ultrasound-guided transbronchial needle aspiration of undiagnosed intrathoracic lesions. Interact Cardiovasc Thorac Surg 2009 May 15.
12. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 2007; 132 (4): 1298-304.
13. Tremblay A, Stather DR, Maceachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. Chest 2009; 136 (2): 340-6.
14. Wong M, Yasufuku K, Nakajima T, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. Eur Respir J 2007; 29 (6): 1182-6.
15. Cetinkaya E, Yildiz P, Altin S, Yilmaz V. Diagnostic value of transbronchial needle aspiration by Wang 22-gauge cytology needle in intrathoracic lymphadenopathy. Chest 2004; 125 (2): 527-31.
16. Tournoy KG, Bolly A, Aerts JG, et al. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. Eur Respir J 2009 Nov 6.
17. Rivera MP, Mehta AC. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132 (3 Suppl): 131S-48S.
18. Bilaceroglu S, Perim K, Gunel O, Cagirici U, Buyuksirin M. Combining transbronchial aspiration with endobronchial and transbronchial biopsy in sarcoidosis. Monaldi Arch Chest Dis 1999; 54 (3): 217-23.
19. Trisolini R, Tinelli C, Cancellieri A, et al. Transbronchial needle aspiration in sarcoidosis: yield and predictors of a positive aspirate. J Thorac Cardiovasc Surg 2008; 135 (4): 837-42.
20. Wang KP, Fuenning C, Johns CJ, Terry PB. Flexible transbronchial needle aspiration for the diagnosis of sarcoidosis. Ann Otol Rhinol Laryngol 1989; 98 (4 Pt 1): 298-300.
21. Cetinkaya E, Yildiz P, Kadakal F, et al. Transbronchial needle aspiration in the diagnosis of intrathoracic lymphadenopathy. Respiration 2002; 69 (4): 335-8.
22. Haponik EF, Cappellari JO, Chin R, et al. Education and experience improve transbronchial needle aspiration performance. Am J Respir Crit Care Med 1995; 151 (6): 1998-2002.
23. Groth SS, Whitson BA, D'Cunha J, Maddaus MA, Alsharif M, Andrade RS. Endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes: a single institution's early learning curve. Ann Thorac Surg 2008; 86 (4): 1104-9.
24. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax 2001; 56 Suppl 1: i1-21.
25. Annema JT, Veselic M, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Eur Respir J 2005; 25 (3): 405-9.
26. Priola AM, Priola SM, Cataldi A, et al. Accuracy of CT-guided transthoracic needle biopsy of lung lesions: factors affecting diagnostic yield. Radiol Med 2007; 112 (8): 1142-59.
27. Priola AM, Priola SM, Cataldi A, et al. CT-guided percutaneous transthoracic biopsy in the diagnosis of mediastinal masses: evaluation of 73 procedures. Radiol Med 2008; 113 (1): 3-15.
28. Pakhale SS, Unruh H, Tan L, Sharma S. Has mediastinoscopy still a role in suspected stage I sarcoidosis? Sarcoidosis Vasc Diffuse Lung Dis 2006; 23 (1): 66-9.
29. Yasufuku K, Chiyo M, Sekine Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest 2004; 126 (1): 122-8.