

Autofluorescence Bronchoscopy and Endobronchial Ultrasound

F. Falcone¹, M. Majori², D. Grosso¹, F. Fois¹, R. Trisolini³

Monaldi Arch Chest Dis 2011; 75: 1, 50-53.

Keywords: Endobronchial ultrasound, Autofluorescence, Early lung cancer diagnosis, Bronchoscopy, Transbronchial needle aspiration.

¹ U.O. di Pneumologia, Azienda USL di Bologna,

² U.O. di Pneumologia ed Endoscopia Toracica, Azienda Ospedaliera-Universitaria di Parma,

³ U.O. Endoscopia Toracica e Pneumologia, Dipartimento di Scienze Oncologiche, Ospedali Maggiore e Bellaria, Bologna, Italy.

Correspondence: Dr. Franco Falcone, Via del Colle 33, 40068 S. Lazzaro di Savena (BO), Italy; e-mail: franco.falcone@aiporicerche.it

Autofluorescence and ultrasound represent the imaging technologies applied to diagnostic bronchoscopy that have found the largest resonance in recent decades [1, 2]. Autofluorescence bronchoscopy (AFB) has gained an established role in the diagnosis of preneoplastic lesions or intraepithelial lung cancer [1-4]. Endobronchial ultrasound (EBUS) has been used for multiple purposes, such as [1, 5-7]: 1) facilitating identification and aspiration from hilar and mediastinal lesions in close contact with the airway's wall; 2) guiding transbronchial biopsies in patients with peripheral lesions; 3) differentiating airway invasion versus compression, as well as helping to determine the depth of invasion in patients with central airway tumours.

Autofluorescence bronchoscopy

The outcome of patients diagnosed with lung cancer is fairly poor, and the chances of survival are largely dependent on the stage of the disease allowing for curative surgery [8]. AFB is a screening measure that has been developed in an attempt to identify high-risk patients harbouring pre-neoplastic and early neoplastic lesions in their central airways [9]. The use of AFB is based on the observation that moderate to severe dysplasia and carcinoma *in situ* (CIS) show less fluorescence than normal tissue when excited by light with wave length ranging from 380-460 nm.

In the multicentric study leading to FDA approval, Lam *et al.* investigated the additional role of AFB, when added to white light bronchoscopy (WLB), in the identification of moderate/severe dysplasia and CIS in 173 patients with known or suspected lung cancer (*Level of evidence: III*) [3]. The investigators found that AFB + WLB had a relative sensitivity of 6.3 compared to WLB alone. The specificity of AFB was 66%.

Many subsequent literature studies (*Level of evidence: III*) including varying categories of patients with known/suspected lung cancer, or at

high-risk of developing lung cancer, confirmed the superiority of AFB + WLB versus WLB in the detection of dysplasia and CIS, even though the relative sensitivity of AFL + WLB was usually found to be lower than that reported in the 1998 study by Lam *et coll* [10-13].

More recently, the first prospective, randomised, multicentric study compared WLB + AFB versus WLB in 1173 smokers with additional risk factors for lung cancer (*Level of evidence: Ib*) [4]. The results of this study confirmed the superiority of AFB over WLB in the detection of preneoplastic and early neoplastic lesions, but did not support the high expectations raised by many previous studies. First, the prevalence of isolated pre-invasive lesions was much lower (3.9%) than in most former studies, probably due to the fact that the latter ones often included tumour associated lesions. Second, the relative sensitivity of WLB + AFB versus WLB alone found in this study (1.42) was much lower than in many previous studies, and the superiority of AFB over WLB was statistically significant only for moderate/severe dysplasia and not for CIS. The specificity was 58% for WLB + AFB, and 62% for WLB alone.

In conclusion, the experience with AFB accumulated so far suggests that [1, 3, 4, 10-14]: 1) this method is superior to WLB alone, especially in the detection of preneoplastic lesions (moderate to severe dysplasia); 2) it is quite clear that this depends mainly on the sensitivity of WLB. In those studies where the sensitivity was particularly low [Lam] the relative sensitivity of AFB + WLB versus WLB alone was markedly higher; 3) the prevalence of preneoplastic lesions in the population being studied is extremely important, and it has proved highly variable in studies into AFB published thus far.

As for the limitations, the specificity of AFB, averaging 60% in a review of the literature, is quite unsatisfactory [2, 4, 10-13]. This obviously leads to more biopsies being performed and evaluated at greater cost. However, studies have shown that up

to 50% of histologically normal biopsies taken from areas suspicious at AFB (“false positive” areas) may carry chromosome aberrations similar to those found in patients with overt malignant lesions [15, 16]. Furthermore, high sensitivity and low specificity are typical characteristics of many other screening tools such as low-dose CT scanning for peripheral nodules, mammography, occult blood testing, and PSA [4, 17, 18].

The other important limitation of AFB is the uncertainty of the clinical impact in the detection of preneoplastic or early neoplastic lesions on the patient’s survival [1, 2, 4]. Although the available data is limited, it has been shown that dysplasia and even CIS may regress spontaneously, so that we do not reliably know whether or not these lesions are likely to shorten the patients’ death if left untreated [19, 20].

Recommendation

- **Autofluorescence bronchoscopy is superior to white light standard bronchoscopy in the identification of preneoplastic and early neoplastic lesions. It should be performed, whenever available, in patients at high risk of preneoplastic and early neoplastic lesions (heavy smokers; patients in follow-up after surgery for either lung or head/neck cancer; patients with known asbestos exposure; patients candidate to lung surgery to rule out synchronous lesions) (Grade A).**

Endobronchial ultrasound

After its widespread use in the setting of gastrointestinal endoscopy, ultrasounds are being increasingly used in the airways (EBUS) to guide both parenchymal and hilar/mediastinal biopsies, as well as to study in great detail the airway wall [1, 4-7].

EBUS to guide hilar / mediastinal aspiration / biopsy

The first studies assessing the role of EBUS for the localisation and sampling of mediastinal and hilar lymphadenopathy were performed through a ultrasonic catheter which was passed in the working channel of the bronchoscope, but did not allow real-time guidance for TBNA as the probe had to be removed from the bronchoscope for TBNA to be performed [1, 21, 22]. In a review of the literature, two studies compared standard TBNA versus EBUS-TBNA in patients with hilar/mediastinal lymphadenopathy [21, 22]. In a prospective, randomised, controlled trial, Shannon *et al.* failed to show any significant difference in terms of sensitivity, specificity, or diagnostic accuracy when comparing EBUS-guided and standard TBNA (*Level of evidence: Ib*) [21]. Herth and coll. conducted a randomised study comparing EBUS-

guided with standard-TBNA, in which the authors separately randomised and analysed the results of the TBNA procedures obtained from different LN stations (*Level of evidence: Ib*) [22]. In a first group they included exclusively the subcarinal nodes, since they are easily accessible by any method. In a second group they included all the TBNAs performed in the following LN stations according to the American Thoracic Society classification: 2 (right and left), 3, 4 (right or left), and 5. The authors concluded that EBUS guidance significantly increases the yield of TBNA in all lymph node stations except in the subcarinal one, but in-depth analysis of their study showed that similar diagnostic yields were obtained by both conventional and EBUS-guided TBNA also in the lower paratracheal area (4R, 4L) [23]. By considering this data, it seems that blind TBNA procedures proved to be as effective as ultrasound-guided ones in those stations (4 right, 4 left, 7), among those accessible to TBNA, where the majority of metastasis from non-small cell lung cancer occur [33]. In conclusion, literature data suggests that EBUS-guided TBNA performed with single-channel bronchoscopes is not superior to standard TBNA although it can be a useful tool to guide TBNA in some specific settings, such as “difficult mediastinal LN areas” (mainly 2, 3, 4L) and small LN size (<1 cm) [31, 45].

More recently, a new bronchoscope with a linear array transducer that allows real-time ultrasonic guidance to fine needle aspiration has been developed [24]. This is an instrument dedicated to ultrasound-guidance of TBNA, and it has to be used after examination of the bronchial tree has been performed in a standard fashion with a conventional bronchoscope [6]. The few literature studies in which this instrument was evaluated have provided excellent results, with sensitivities greater than 85% regardless of node size and location (*Level of evidence: III*) [24-26]. It should be noted that no studies comparing standard TBNA versus real-time EBUS-TBNA are available, to date.

Recommendation

- **Real-time ultrasonic guidance to fine needle aspiration should be performed, whenever available, in the diagnostic approach to hilar and mediastinal lymphadenopathy (Grade B).**

EBUS to study the airway’s wall

EBUS allows the possibility of examining in great detail the airway wall, which is therefore useful in differentiating airway invasion versus compression by tumour, in studying the depth of endobronchial tumour infiltration [7, 27-29]. The few studies that examined the relative role of EBUS and CT scan in differentiating airway invasion versus compression by tumour suggested that, in experienced hands, EBUS is more sensitive than CT

in the assessment of potential airway infiltration (*Level of evidence: III*) [7, 27, 28].

A few studies do also suggest that EBUS may be useful in the setting of therapeutic bronchoscopy, as it can guide tumour debriement, select proper stent size, and select patients for endoscopic versus surgical treatment (*Level of evidence: III*) [28, 30].

Recommendation

- **EBUS should be performed along with CT scan, whenever available, to differentiate airway invasion versus compression by tumour, as well as to determine the depth of airway tumour invasion (Grade B).**

EBUS for guiding biopsy of peripheral lesions

A few studies have evaluated the role of EBUS to guide sampling from the periphery of the lung (*Level of evidence: III*) [6, 31-33]. EBUS is superior to "blind" transbronchial biopsy (that is, transbronchial biopsy performed without any imaging guidance) in the diagnosis of peripheral lung lesions [31]. It is also clear that EBUS increases the diagnostic yield of transbronchial biopsy in the diagnosis of peripheral lesions that are not fluoroscopically visible [32]. As for lesions that are fluoroscopically visible, it looks like EBUS may be superior to fluoroscopy in guiding biopsies from peripheral lesions of small size (3 cm or less) [6, 33].

Recommendation

- **EBUS can be a useful imaging guide for transbronchial lung biopsy of peripheral pulmonary lesions. EBUS is the method of choice for guidance of transbronchial lung biopsy of fluoroscopically invisible peripheral lesions (Grade B).**

Summary of Recommendations

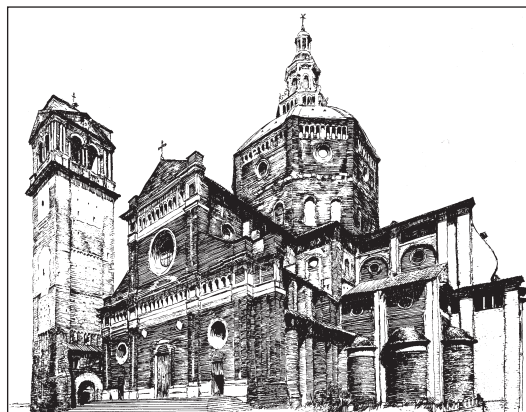
- **Autofluorescence bronchoscopy is superior to white light standard bronchoscopy in the identification of preneoplastic and early neoplastic lesions. It should be performed, whenever available, in patients at high risk of preneoplastic and early neoplastic lesions (heavy smokers; patients in follow-up after surgery for either lung or head/neck cancer; patients with known asbestos exposure; patients candidate to lung surgery to rule out synchronous lesions) (Grade A).**

- **Real-time ultrasonic guidance to fine needle aspiration should be performed, whenever available, in the diagnostic approach to hilar and mediastinal lymphadenopathy (Grade B).**
- **EBUS should be performed along with CT scan, whenever available, to differentiate airway invasion versus compression by tumour, as well as to determine the depth of airway tumour invasion (Grade B).**
- **EBUS can be a useful imaging guide for transbronchial lung biopsy of peripheral pulmonary lesions. EBUS is the method of choice for guidance of transbronchial lung biopsy of fluoroscopically invisible peripheral lesions (Grade B).**

References

1. Feller-Kopman D, Lunn W, Ernst A. Autofluorescence bronchoscopy and endobronchial ultrasound: a practical review. *Ann Thorac Surg* 2005; 80: 2395-401.
2. Lee P, Sutedja TG. Lung cancer screening: has there been any progress? Computed tomography and autofluorescence bronchoscopy. *Curr Opin Pulm Med* 2007; 13: 243-8.
3. Lam S, Kennedy T, Unger M, *et al.* Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. *Chest* 1998; 113: 696-72.
4. Hausinger H, Becker H, Stanzel F, *et al.* Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomized controlled multicentre study. *Thorax* 2005; 60: 496-503.
5. Herth FJ, Eberhard 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.
6. Herth FJ, Ernst A, Becker HD. Endobronchial ultrasound guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. *Eur Resp J* 2002; 20: 972-4.
7. Herth FJ, Ernst A, Shultz M, Becker H. Endobronchial ultrasound reliably differentiates between airway infiltration and compression by tumour. *Chest* 2003; 123: 458-62.
8. SEER Cancer Statistics Review, 1975-2000. Ries WR, Eisner MD, Kosary CL, *et al.* eds. Bethesda, MD; National Cancer Institute: 2003; seer.cancer.gov/report_to_nation/1975_2000.
9. Lam S, MacAuley, Hung J, LeRichie J, Profio AE, Palcic G. Detection of dysplasia and carcinoma in situ with a lung imaging fluorescence endoscope device. *J Thorac Cardiovasc Surg* 1993; 105: 1035-40.
10. Hirsh FR, Prindiville SA, Miller YE, *et al.* Fluorescence versus white light bronchoscopy for detection of preneoplastic lesions: a randomized study. *J Natl Cancer Inst* 2001; 93: 1385-91.
11. Moro-Sibilot D, Jeanmart M, Lantuejoul S, *et al.* Cigarette smoking, preinvasive bronchial lesions, and autofluorescence bronchoscopy. *Chest* 2002; 122: 1902-8.
12. Vermylen P, Pierard P, Roufosse C, *et al.* Detection of bronchial preneoplastic lesions and early lung cancer with fluorescence bronchoscopy: a study about its am-

- bulatory feasibility under local anaesthesia. *Lung Cancer* 1999; 25: 161-8.
13. Shibuya K, Fujisawa T, Hoshino H, *et al.* Fluorescence bronchoscopy in the detection of preinvasive bronchial lesions in patients with sputum cytology suspicious or positive for malignancy. *Lung Cancer* 2001; 32: 19-25.
 14. Venmans BJW, van Boxem AJM, Smit EF, *et al.* Clinically relevant information obtained by performing autofluorescence bronchoscopy. *J Bronchol* 2000; 7: 118-21.
 15. Helfritzsch H, Junker K, Batel M, Scheele J. Differentiation of positive autofluorescence bronchoscopy findings by comparative genomic hybridization. *Oncol Rep* 2002; 9: 697-701.
 16. Wistuba II, Lam S, Behrens C, *et al.* Molecular damage in the bronchial epithelium of current and former smokers. *J Natl Cancer Inst* 1997; 89: 1366-73.
 17. Henschke CI, McCauley DI, Yankelevitz DF, *et al.* Early lung cancer action project: overall design and findings from baseline screening. *Lancet* 1999; 354: 99-105.
 18. Kennedy TC, Lam S, Hirsch FR. Review of recent advances in fluorescence bronchoscopy in early localization of central airway lung cancer. *The Oncologist* 2001; 6: 257-62.
 19. Ponticello A, Barra E, Giani U, *et al.* p53 immunohistochemistry can identify bronchial dysplastic lesions precedine lung cancer: a prospective study. *Eur Resp J* 2000; 15: 547-52.
 20. Bota S, Auliac JB, Paris C, *et al.* Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. *Am J Respir Crit Care Med* 2000; 164: 1688-93.
 21. Shannon JJ, Bude RO, Orens JB, *et al.* Endobronchial ultrasound-guided aspiration of mediastinal adenopathy. *Am J Respir Crit Care Med* 1996; 153: 1424-30.
 22. Herth F, Becker HD, Ernst A. Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration. A randomized trial. *Chest* 2004; 125: 322-25.
 23. Trisolini R, Lazzari Agli L, Patelli M. Conventional versus EBUS-guided transbronchial needle aspiration of the mediastinum. *Chest* 2004; 126: 1005-6.
 24. Krasnik M, Vilmann P, Larsen SS, Jacobse GK. Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. *Thorax* 2003; 58: 1083-86.
 25. 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: 122-8.
 26. Rintoul RC, Skwarski KM, Murchison JT, *et al.* Endobronchial and endoscopic ultrasound guided real-time fine needle aspiration for mediastinal staging. *Eur Resp J* 2005; 25: 416-21.
 27. Kurimoto N, Murayama M, Yoshioka S, Nishisaka T, Inai K, Dohi K. Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumour invasion. *Chest* 1999; 115: 1500-1506.
 28. Miyazu Y, Miyazawa T, Kurimoto N, Iwamoto Y, Kanoh K, Kohno N. Endobronchial ultrasonography in the assessment of centrally located early-stage lung cancer before photodynamic therapy. *Am J Respir Crit Care Med* 2002; 165: 832-837.
 29. Tanaka F, Muro K, Yamasaki S, *et al.* Evaluation of tracheo-bronchial wall invasion using transbronchial ultrasonography (TBUS). *Eur J Cardiothor Surg* 2000; 17: 570-574.
 30. Herth FJ, Becker HD, LoCicero J III, *et al.* Endobronchial ultrasound in therapeutic bronchoscopy. *Eur Resp J* 2002; 20: 118-21.
 31. Paone G, Nicastrì E, Lucantoni G, *et al.* Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. *Chest* 2005; 128: 3551-57.
 32. Herth FJ, Becker HD, Ernst A, *et al.* Endobronchial ultrasound-guided transbronchial biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. *Chest* 2006; 129: 147-50.
 33. Kurimoto N, Miyazawa T, Okimasa S, *et al.* Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. *Chest* 2004; 126: 959-65.



Pavia - Piazza Duomo