Romanian Journal of Rhinology, Vol. 2, No. 8, October - December 2012

LITERATURE REVIEW

The role of autofluorescence bronchoscopy in detecting dysplasia and incipient lung cancer

Ruxandra Ulmeanu[1,2], Ramona Nedelcu[1]

[1]"Marius Nasta" Institute of Pneumology, Bucharest, Romania

[2]Faculty of Medicine and Pharmacy, University of Oradea, Romania

ABSTRACT

Lung cancer remains the leading cause of cancer death worldwide. Progress in endoscopic technology has improved detection of precancerous bronchial lesions associated with the "proximal" appearance of squamous cell lung cancer in people at high risk. In the past years, an important role has been granted to the autofluorescence bronchoscopy, a minimally invasive method used to diagnose pre-invasive lesions. Since prognosis in patients with lung cancer correlates with the disease stage, the importance of early detection, followed by treatment as early as possible, might improve survival. Autofluorescence endoscopy is currently the most sensitive method for detecting proximal precancerous bronchial lesions.

KEYWORDS: autofluorescence bronchoscopy, dysplasia, lung cancer

INTRODUCTION

Lung cancer remains the leading cause of cancer death worldwide[1,2]. Renewed interest in lung cancer screening and applying new techniques for its early management can improve the prognosis and increase quality of life, which are highly dependent on the disease stage at diagnosis. Although there has been a lot of progress in this area over the last decade, the 5-year survival rate is only 15%.

Nowadays, only 16% of the cases of lung cancer are diagnosed when the disease is localized (Figure 1); therefore, far more sensitive methods are needed to detect the forms of "clinically silent" lung cancer. Progress in endoscopic technology has improved detection of precancerous bronchial lesions associated with the "proximal" appearance of squamous cell lung cancer (SCC) in people at high risk[3].

Nevertheless, patients with carcinoma *in situ* (CIS), micro-invasive and pre-invasive forms of cancer, represent a diagnostic challenge even for experienced bronchoscopists. Carcinoma *in situ* and dysplasia may have normal appearance during conventional white light bronchoscopy.

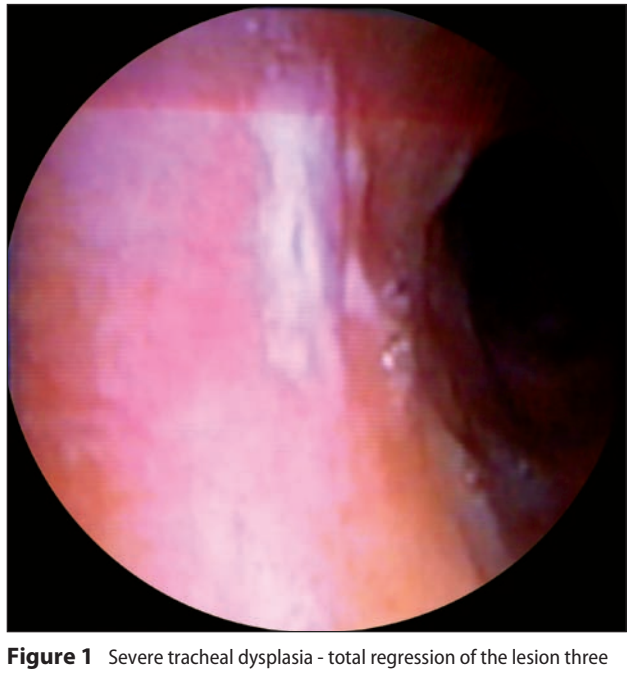

Figure 1 Severe tracheal dysplasia - total regression of the lesion three months after the first diagnosis (standard white light bronchoscopy) (archive Prof. Dr. Ruxandra Ulmeanu)

Currently, the only non-invasive means of diagnostic of pre-invasive lesions is the sputum cytological examination. Although the sputum presents atypia or carcinoma, 40%-71% of the lesions may

Corresponding author: Prof. Dr. Ruxandra Ulmeanu
email: r_ulmeanu@yahoo.com

not be detected during routine white light bronchoscopy[4,5,6].

In the past years, an important role has been granted to the autofluorescence bronchoscopy (AFB), a minimally invasive method used to diagnose pre-invasive lesions. This method has been applied since 1990 by Lam S. et al, who have developed the concept of autofluorescence bronchoscopy for diagnosis[4,5].

The diagnostic yield seems to be higher for the pre-invasive squamous cell carcinoma and is based on the autofluorescence phenomenon. This is due to the presence in the tissues of fluorophores (NAD/NADH, flavins, tryptophan), which reach low values in the dysplastic one. An increase in mucosa thickness, as well as the blood flow intensification, modifies the autofluorescence process.

AUTOFLUORESCENCE BRONCHOSCOPY

The autofluorescence bronchoscope:

- uses a helium-cadmium laser beam
- emits a blue light with a wavelength between 380-460 nm
- normal tissues appear green
- dysplastic and carcinomatous tissue appears reddish-brown

Principles of autofluorescence

Although it requires 10-15 minutes additional time during the bronchoscopic examination, the autofluorescence bronchoscopy is worth being performed, given the fact that 8% of the subjects might have lung cancer or a pre-invasive lesion, diagnosed without additional risk.

- initially, a white light bronchoscope examination is performed;
- bronchial mucosal lesions caused by the tip of the endoscope or by the biopsy must be known because they give false positive images;
- biopsies are done after or during the autofluorescence bronchoscopy.

Images are intensified with a device that uses:

- a red filter with a wavelength ≥ 630 nm
- a green filter with wavelengths between 480-520 nm
- a helium-cadmium laser beam
- thus, it emits a blue light with a wavelength of 442 nm through the bronchoscope.

This blue light is used to stimulate the bronchial mucosa. Fluorescence is enhanced in the premalignant and malignant bronchial epithelium and low in the normal tissue. On examination, normal tissues appear green, while the dysplastic and carcinomatous tissue appears reddish-brown (Figure 2).

Indications for the autofluorescence bronchoscopy:

- suspicion of bronchopulmonary cancer after white light bronchoscopy;
- screening of patients with increased risk of bronchopulmonary cancer;
- postoperative surveillance of patients operated on for bronchopulmonar cancer;
- diagnosis of synchronous bronchopulmonary cancer;
- diagnosis of bronchopulmonary cancer recurrences;
- assessing the response to treatment of neoplasms and preneoplastic lesions.

Clinical studies have proven the superiority of AFB to white light bronchoscopy (WLB) in detecting cancerous lesions, but have not elucidated the impact on survival. WLB detects, on average, 40% of CIS and high grade dysplasias, while AFB increases the detection rate up to 88%[7,8].

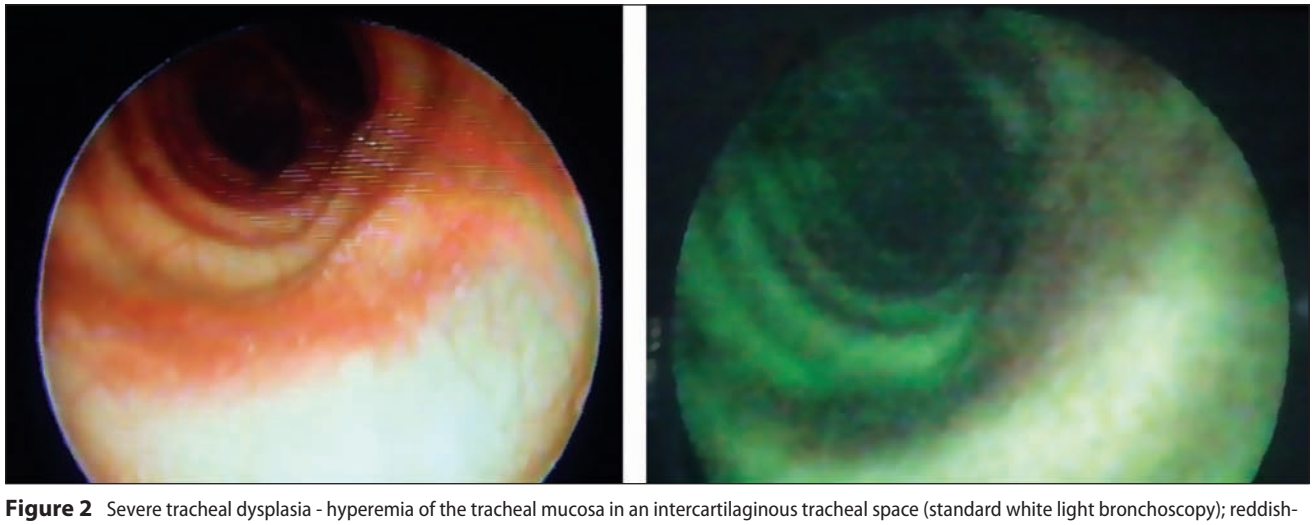

Figure 2 Severe tracheal dysplasia - hyperemia of the tracheal mucosa in an intercartilaginous tracheal space (standard white light bronchoscopy); reddish-brown appearance of the mucosa in the same intercartilaginous tracheal space and green normal tissue (blue light bronchoscopy); bronchial biopsy-severe dysplasia (archive Prof. Dr. Ruxandra Ulmeanu)

Although the role of autofluorescence bronchoscopy in detecting lung cancer remains to be determined, it has been proven that the combination WLB+AFB increased the diagnostic yield of invasive lesions by 1.1-6.3 times compared with WLB alone, especially in patients with atypical sputum cytology[9].

The pattern of progression from precancerous lesions to invasive cancer is the following[1-3,10]:

Basal cells hyperplasia
↓
Squamous metaplasia
↓
Mild dysplasia
↓
Moderate dysplasia
↓
Severe dysplasia
↓
Carcinoma *in situ* (CIS)

Autofluorescence endoscopy[10]

- locates with precision bronchial areas that were previously biopsied
- invasive lesions appear as defects that are easily recognizable by the bronchial fluorescence – extremely useful for histological monitoring
- allows us to accurately re-biopsy suspect bronchial areas previously biopsied
- contraindications are mostly relative and are not different from those of conventional bronchoscopy.

Limits

- Cost of the autofluorescence unit
- Lack of specificity: false 34% vs. 10% WL
- Monitoring of detected anomalies - there are no standards
- Who should undergo the procedure? - there are no standards
- Management of the detected lesion - there is no standardized algorithm
- Future studies are needed to elucidate the utility of routine AFB before the surgical intervention in patients with resectable lung cancer (Figure 3).

Since precancerous lesions present the risk of progress towards invasive cancer, they should be treated, and whenever possible, endobronchial treatment is preferred. Diagnosis and surgical resection of lung cancer in an early stage dramatically improve the survival rate[3,11].

The optimal and standardized solution for the management and treatment of these intraepithelial bronchial lesions has not yet been established[2]. For this reason, treatment outcome is suboptimal, although surgery in an early stage provides a relatively good prospect of healing.

There is limited knowledge about the natural history of bronchial precancerous lesions[10]. Carcinoma *in situ* is more common in patients with a history of cancer or concomitant cancer[1-3,10]. The progression from Carcinoma *in situ* to SCC is significantly higher for the severe dysplasia compared to preneoplastic lesions with low-grade dysplasia, such as: squamous metaplasia, mild and moderate dysplasia.

Natural course of preneoplastic lesions in the bronchial epithelium[2,3]:

- 54% of preneoplastic lesions regress
- 19%-46% of severe dysplasias progress towards cancer *in situ* or epidermoid carcinoma
- Epithelial lesions with low-grade dysplasia could be safely followed up 1 to 2 years
- Severe dysplasia should be treated if it persists for 3 months
- Immediate treatment for carcinoma *in situ*
- 63% of untreated severe dysplasias regress without recurrence in the first 2 years of follow-up.

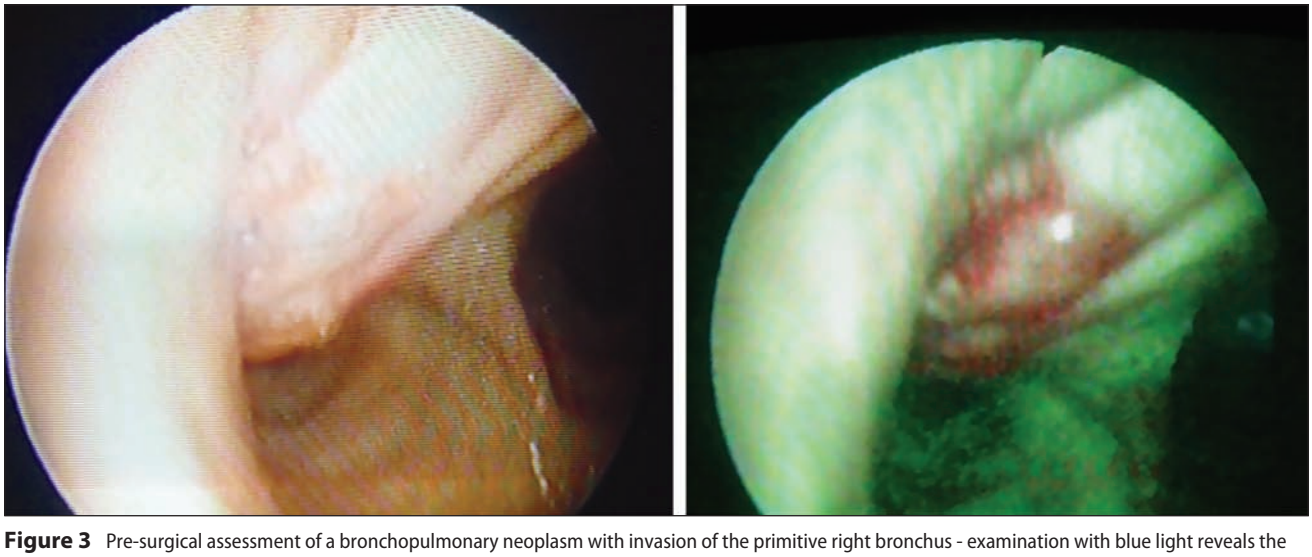

Figure 3 Pre-surgical assessment of a bronchopulmonary neoplasm with invasion of the primitive right bronchus - examination with blue light reveals the neoplastic invasion extended to the trachea (right pneumonectomy is contraindicated) (archive Prof. Dr. Ruxandra Ulmeanu)

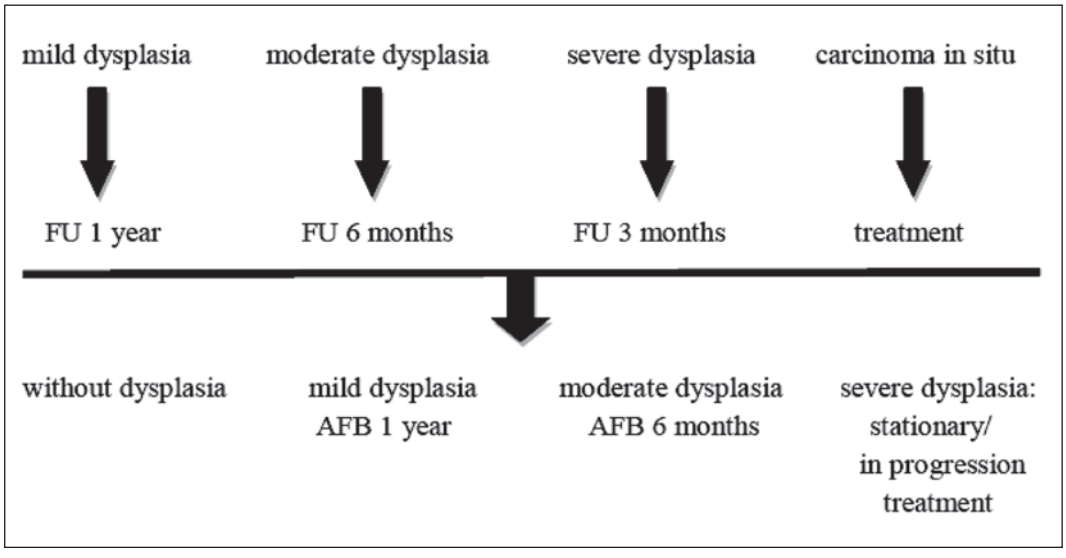

Figure 4 Diagnostic and treatment algorithm for incipient lung cancer

Since prognosis in patients with lung cancer correlates with the disease stage, the importance of early detection, followed by treatment as early as possible, might improve survival. For the treatment of pre-invasive bronchial lesions, surgery is still the gold standard.

Performing an AFB (FU) should be considered as preoperative screening in evaluating patients with operable lung cancer.

Autofluorescence endoscopy is currently the most sensitive method for detecting proximal precancerous bronchial lesions (Figure 4)[10,12].

AFB is used to detect synchronous malignancy and to delimit the degree of resecability.

The role of this investigation on the prognosis of early detected lung cancer, in operable stage, remains an issue that requires further evaluation[13].

REFERENCES

1. American Cancer Society Guidelines for the Early Detection of Cancer, 2009.
2. McWilliams A., Lam B., Sutedja T. - Early proximal lung cancer diagnosis and treatment. Eur Respir J., 2009; 33:656–665.
3. Bota S., Auliac J.B., Paris C., Métayer J., Sesboüé R., Nouvet G., Thiberville L. - Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy. American Journal Of Respiratory And Critical Care Medicine, 2001; 164:1688-1693.
4. Ulmeanu R., Rajnoveanu R., Halic E., Deleanu O., Mihaltan F. - Evolutia naturala a leziunilor bronsice neoplazice, Pneumologia, 2011;60(2):93-90.
5. Tofolean D., Tofolean I.T. - Cap III C Bronhoscopia cu autoluorescenta. In: „Actualitati in endoscopia toracica diagnostica si terapeutica", Editura Universitara „Carol Davila" Bucuresti, 2009.
6. Nakhosteen J., Khanavkar B. - Autoflurescence Bornchoscopy: The Laser Imaging Fluorescence Endoscope. In: Bollinger C.T., Mathur P.N. (eds) - Interventional Bronchoscopy. Prog Respir Res. basel, Karger, 2000;30:p237.
7. Kusunoki Y., Imamura F., Uda H., Mano M., Horai T. - Early Detection of Lung Cancer With Laser-Induced Fluorescence Endoscopy and Spectrofluorometry. CHEST, 2000; 118:1776–1782.
8. Hirsch, F.R. et al - Fluorescence Versus White-Light Bronchoscopy for Detection of Preneoplastic Lesions: a Randomized Study. Journal of the National Cancer Institute, 2001; 93(18):1385-1391.
9. Haußinger K. et al - Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomised controlled multicentre trial. Thorax, 2005;60:496–503.
10. Breuer R., Pasic A., Smit E., van Vliet E., Noordegraaf V.A., Risse E.J., Postmus P.E., Sutedja T.G. - The Natural Course of Preneoplastic Lesions in Bronchial Epithelium. Clinical Cancer Research, 2005; 11(2Pt1)537-43.
11. Field J.K., Brambilla C., Hirsch F.R., Hittelman W., Hogan M., Marshall D., Mulshine J.L., Rabbitts P., Sutedja T., Watson A., Weiss S. - Molecular Biomarkers Workshop. A European strategy for developing lung cancer molecular diagnostics in high risk populations. Lung Cancer, 2001; 31:339–345.
12. Kunst P. - With blue light into the depth. Annual Congress of ERS, Vienna 2009.
13. Lam B. et al - The clinical value of autofluorescence bronchoscopy for the diagnosis of lung cancer. Eur Respir J, 2006; 28:915–919.