Bronchopulmonary neoplasm - a “hidden” disease in its incipient stages

Bronchopulmonary cancer is the leading cause of neoplasia death worldwide, mainly due to the aggressive nature of this disease, but also to the late stage at the time of initial diagnosis. Despite the advances made during the last decade in both the diagnosis and the individualized treatment of this disease, the 5-year survival (for all stages of lung neoplasm) is only 17%.

For patients with in situ stage IA carcinoma (tumor <2 cm, no metastatic lesions), 5-year survival reaches 75%. The real 5-year survival is actually about 5-7% as 75% of patients are initially diagnosed with inoperable bronchopulmonary neoplasm. Therefore patients who can benefit from diagnosis and treatment in early stages have a much more favorable prognosis regarding survival.

The follow-up of patients who have pre-invasive endobronchial lesions for long time periods (over 10 years) leads to a 34% detection rate of bronchopulmonary neoplasm. Not all patients with endobronchial dysplasias will have an evolution towards neoplasm. Dysplastic lesions may transform into malignancies in a proportion of 40-83%, with a conversion period between 4 and 8 years. Dysplastic changes of the respiratory epithelium are classified in: mild, moderate, severe dysplasia, or in situ carcinoma. Evolution towards invasive carcinoma is much more likely for severe dysplasia or in situ neoplasm. Therefore the endoscopic assessment of preneoplastic lesions becomes in this moment an essential procedure for early diagnosis of bronchopulmonary neoplasm.

Endoscopic methods for diagnosis of bronchopulmonary neoplasm

Bronchoscopy is a minimally invasive procedure that is essential for the diagnosis of pulmonology diseases and mainly of bronchopulmonary neoplasm. The endoscopic investigation delivers useful information on the location and size of lesions, the macroscopic appearance of the adjacent area, thus guiding the location of the biopsy and the visualization of safety margins in case of surgical treatment. Among the endoscopic methods for early detection of preneoplastic or minimally invasive lesions of the respiratory epithelium are autofluorescence bronchoscopy, Narrow Band Imaging, Optical Coherence Tomography, and Probe-based Confocal Laser Endomicroscopy.
These techniques are based on the light-absorbing properties of tissues and blood vessels; this absorption is different for normal tissues and “preneoplastic” tissues.

There are also modern methods which combine various techniques for the diagnosis of respiratory diseases used in reference centers for the diagnosis of pulmonary pathology: Electromagnetic Navigation Bronchoscopy (ENB) and Virtual Bronchoscopy (VB).

**Autofluorescence bronchoscopy**

The procedure is based on the following principle: if tissues are stimulated by blue light (wavelength between 380 and 440 nm), dysplastic tissues will be visualized as reddish-brown, and normal tissues appear as green in color. It is considered that this reddish-brown color is due to the occurrence of neoformation vessels in dysplastic/carcinomatous tissues.

The autofluorescence bronchoscope uses a helium-cadmium laser beam (wavelength 380-440 nm) or a xenon beam. The autofluorescence phenomenon is based on the property of substances called fluorophores (tryptophan, collagen, elastin, and porphyrins) that exist in high concentration in normal tissues; these absorb and emit differently when they are excited by a light source. The alteration of the bronchial mucosa implies a decrease of the fluorophores concentration thus leading to a different luminosity than that of normal tissues.

Studies performed by experts and meta-analyses performed in the last 15 years demonstrated that combined use of autofluorescence bronchoscopy and white
light bronchoscopy improves the sensitivity of detection of premalignant airway lesions vs. use of standard bronchoscopy. The analysis of 14 studies (n=1359 and 3612 bronchial biopsies) shows a superior sensitivity of autofluorescence bronchoscopy vs. white light bronchoscopy, while specificity is comparable for both methods. Another meta-analysis of 21 studies with the same objectives (n=3266 patients) reported a significantly higher sensitivity and specificity for detection of bronchopulmonary neoplasms vs. standard light bronchoscopy. Therefore it is recommended to use autofluorescence bronchoscopy associated with white light bronchoscopy for monitoring the therapy in patients with severe dysplasia (at 3–6 months) or in situ carcinoma (at 3 months)\(^{(15)}\).

The disadvantage of autofluorescence bronchoscopy is the low specificity (65%): non-specific or granulomatous inflammation, traumas of the mucosa - including previous bronchial biopsies or infections - may lead to a false positive result! This drawback can be overcome by combined use with standard bronchoscopy that may increase the specificity of the detection of bronchopulmonary neoplasm to 71-80\%(22).

**Narrow Band Imaging (NBI)** is a bronchoscopic technique based on the properties of the hemoglobin to absorb light. The occurrence of dysplastic or carcinomatous processes at endobronchial level are almost always accompanied by the development of neoformation vessels that can be identified via the NBI technique; these changes occurring in persons at risk for bronchopulmonary neoplasm may improve the detection of the disease in incipient phases.

\[\text{Figure 3. Adenocarcinoma in the medium lobe (appearance in white light and autofluorescence)}\]

\[\text{Figure 4. Squamous carcinoma in the left upper lobe (appearance in white light and autofluorescence)}\]
Hemoglobin can optimally absorb light at a wavelength of 415 nm. The light source of conventional bronchoscopes has three wavelengths, corresponding to the three light beams it consists of: red – 600-700 nm, green – 500-600 nm, blue – 400-500 nm. The composed beam is reflected, scattered and absorbed, exceeding therefore the ability of the conventional bronchoscope to visualize the vascular elements that are present in incipient neoplastic lesions of the bronchial mucosa and submucosa (Figure 6, 7). The NBI mode has three filters for each light beam: B1 (400-430 nm), B2 (420-470 nm), and B3 (560-590 nm), leading to less light scattering; in the foreground of the final image is the vascularisation of the suspicious area(3,7,8).

Several vascular patterns associated with dysplasia were described, but generally in case of dysplasia or in situ carcinoma the superficial vessels appear in brownish shades, and the deep vessels appear colored in greenish-blue shades.

The results of meta-analyses which studied the detection rate of premalignant lesions of airways via NBI - mode bronchoscopy show a high sensitivity and specificity for this method vs. standard bronchoscopy(21).

In conclusion, the use of NBI technique in bronchial endoscopy could become a useful tool for the detection of dysplastic lesions of airways, for patients at high risk to develop BPN; future studies are needed to clearly demonstrate the efficacy and limitations of this method.

**Optical Coherence Tomography (OCT)**

OCT was first introduced in 1990 in ophthalmology and subsequently developed for other specialties(24). For the respiratory system this technique is subject of ongoing research, and it proved itself useful in the investigation of patients with a suspicion of bronchopulmonary neoplasm.

It is a technique that uses optical reflections of tissues to create slice images, using a light source of low coherence; the difference between the return time of the light from the deep tissues and the superficial tissues allows the system to re-construct images (bi- or tri-dimensional)(12).

The OCT system uses a probe with a size of 1.5 - 2.7 mm inserted via the work channel of a standard bronchoscope; this performs a radial scan of the area of interest at a depth of 1-2.2 mm.

Studies performed by OCT-associating bronchoscopy in patients that were later operated have demonstrated that this technique can differentiate between normal tissue, hyperplastic tissue, metaplastic tissue, dysplasia, in situ carcinoma and inflammation(12).

The limitations of the method are: the shallow depth of the image obtained by scanning and the low sensitivity and specificity compared to histopathologic examination; but the improvement of the technique could allow - at least in theory - to give up the examination by biopsy.

**Probe-based Confocal Laser Endomicroscopy (pCLE)**

It is a non-invasive technique that allows performing of real-time optical slices and is based on the natural autofluorescence properties of the tissues. This system was developed to investigate the gastro-intestinal tract and the respiratory system and uses different wavelengths (gastro-intestinal tract: 660 nm, respiratory system: 488 nm).

A 1.4 mm probe is used through the channel of the standard bronchoscope to detect alterations of the basal membrane of the airways or of the elastin network at alveolar level; the system allows the acquisition of 9-12 images/second at a maximum depth of 50 nm.

Advantages: it is possible to visualize subepithelial structures; the higher the elastin amount in the tissues, the better the image quality; it can identify structure abnormalities in both malignant and benign lesions; it is a safe technique and easily tolerable by the patient.

Disadvantages: the weak autofluorescent signal from pre-cancerous lesions (metaplasia, dysplasia, in situ carci-
noma) does not allow the exact classification of the changes - this can be improved by administering a non-toxic exogenous fluorophore such as methylene blue.

At the moment this technique is experimental and thorough studies are needed to determine its usefulness and limits in investigating certain diseases of the respiratory system(14).

White light bronchoscopy combined with autofluorescence bronchoscopy and with Narrow Band Imaging bronchoscopy

The combined use of these 3 examination types was studied in recent years and it became a valuable tool in early diagnosis of BPN.

In 2016 a meta-analysis that used data from 53 studies, including 6543 patients and 18,458 bronchial biopsies, was published. This meta-analysis had the purpose of investigating the accuracy of white light bronchoscopy (WLB) and advanced bronchoscopic techniques - autofluorescence bronchoscopy (AFB) and Narrow Band Imaging (NBI) in detecting pre-cancerous lesions and early BPN. Of all these studies only 12 contained data about the diagnosis of moderate dysplasia and in situ carcinoma.

This meta-analysis showed the benefits of using AFB and NBI regarding the high sensitivity (93% and respectively 96%) vs. standard bronchoscopy (51%) for the diagnosis of pre-cancerous lesions and in situ carcinoma. The specificity increases for autofluorescence bronchoscopy if it is used concomitantly with white light bronchoscopy. For NBI sensitivity was 96%; however, studies are needed to assess more thoroughly the specificity of this method(15).
Virtual bronchoscopy is based on a special program that transforms CT images in virtual tri-dimensional endobronchial images.

Studies performed to date demonstrate the accuracy of the program in the reconstruction of the images from the level of the trachea to the level of fourth-order subsegmental bronchi and first- and second-order bronchioles. The lower the distance between the tomography slices, the higher the accuracy of the reconstruction (2 mm). This technique would prove useful for investigating peripheral neoplastic lesions but it has the disadvantage that it is impossible to obtain a biotic material [4].

The use of virtual bronchoscopy together with Probe-based Confocal Laser Endomicroscopy demonstrated a high efficacy in early diagnosis of BPN, as studies showed a similarity between direct microscopy images and histopathologic images.

Electromagnetic Navigation Bronchoscopy (ENB) is an innovative technique whose advantages and limitations are in ongoing assessment especially for peripheral lung diseases. This investigation requires three key items: a special program for converting CT images in virtual bronchoscopy images; a probe (that has the role of a sensor) for GPS-like endoscopic guidance; and a device that generates an electromagnetic field around the patient’s chest. This technique implies the use of a standard bronroscope that is inserted in the segmental bronchi as close as possible to the parenchymal lesion; then the probe is advanced on the working channel of the bronchoscope – under CT control, in the presence of the electromagnetic field – until the desired level is reached. In this manner biotic material is subsequently obtained via a micro forceps. Prospective studies are absolutely needed to determine the variables that are conditioning the success of this procedure [16].

Conclusions

In 2017 mortality continues to show extremely worrying figures for bronchopulmonary neoplasm: it is the leading cancer death cause for men and the second for women (after breast cancer) [25].

Most often the diagnosis is established in advanced stages of the disease, therefore the prognosis depends of the time point of presentation in a clinic.

The advanced techniques of endoscopic diagnosis - developed in recent years - may contribute to the early diagnosis of the disease, thus improving the evolution, prognosis, survival and quality of life of the patient.

However, each of these endoscopic techniques also has limitations, they can be used in selected cases and their combined use - dictated by the complexity of the case - may very often lead to the early detection of bronchopulmonary neoplasm.

Further prospective studies are needed to clearly establish the indications and limitations of each technique.

References