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The Importance Of Bronchoscopy In Early Lung Cancer (LC) Diagnosis

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ABSTRACT
Lung cancer is a leading cause of death worldwide, due to the fact that most patients are diagnosed in a fairly advanced stage. Screening tests such as sputum citology, chest x-rays or CT scans have their limitations and need further histological confirmation of the diagnosis.
Therefore, the need forfast and accurate detection and staging of lung cancer has determined the development of advanced medical procedures using bronchoscopic methods such as white light bronchoscopy, narrow-band imaging, auto-fluorescence bronchoscopy, confocal fluorescence microendoscopy or echoendoscopy.

Keywords: lung cancer, bronchoscopy with white light, diagnosis

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Introduction

It is a well-known fact that lung cancer (LC) has a globally increased incidence. It is considered that by 2020 there will be 20 million new cases a year, half of them in low and middle income countries[1].

LC is the most common type of cancer in men, with a 5-year survival rate of only 15%. The survival rate increases to 60-80% in case of early surgically resected LC.

LC is a tumor of extreme severity, 55% of them being discovered in the metastatic stage, 30% in the locally advanced stage, while only 15% are diagnosed in the localized stage. It represents an important cause of death worldwide, with 1,3 million deaths/year globally. LC is responsible for 13% of deaths worldwide, and signifies 28% of all cancer deaths. The mortality of LC is higher than the sum of breast, prostate and colorectal cancer mortality combined[1,2].

Early diagnosis of LC means for non-small cell lung cancer (NSCLC) to be diagnosed in 0, I

or II stages, while small cell lung cancer (SCLC) is preferred to be diagnosed in a limited stage. The ideal case scenario is for all lung cancers to be diagnosed in a preneoplasic stage or in situ carcinoma [3].

The TNM stadialization of lung cancer is represented in the figure 1 and is the following:

T (Tumor)

Tis – carcinoma *in situ*(does not exceed the basal membrane of the epithelium)

T1 – tumor size less than or equal to 3 cm across, surrounded by lung or visceral pleura, without invasion proximal to the lobar bronchus.

T1a Tumor size less than or equal to 2 cm;

T1b Tumor size more than 2 cm but less than or equal to 3 cm.

T2 – Any of:

Tumor size more than 3 cm but less than or equal to 7 cm across;

Involvement of the main bronchus at least 2 cm distal to the carina;

Invasion of visceral pleura;

Atelectasis/obstructive pneumonitis extending to the hilum but not involving the whole lung.

T2a Tumor size more than 3 cm but less than or equal to 5 cm;

T2b Tumor size more than 5 cm but less than or equal to 7 cm.

T3 – Any of:

Tumor size more than 7 cm across

Invasion into the chest wall, diaphragm, phrenic nerve, mediastinal, pleura or parietal pericardum;

Tumor less than 2 cm distal to the carina, but not involving the carina;

Atelectasis/obstructive pneumonitis of the whole lung;

Separate tumor nodule in the same lobe.

T4 – Any of:

Invasion of the mediastinum, heart, great vessels, trachea, carina, recurrent; laryngeal nerve, esophagus, or vertebra;

Separate tumor nodule in a different lobe of the same lung.

N (Lymph Node)

N1 – Metastasis to ipsilateralperibronchial and/or hilar lymph nodes

N2 – Metastasis to ipsilateralmediastinal and/or subcarinal lymph nodes

N3 – Any of: Metastasis to scalene or supraclavicular lymph nodes; Metastasis to contralateral hilar or mediastinal lymph nodes

M (Metastasis)

M0 – No distant metastasis

M1a – Any of: Separate tumor nodule in the other lung; Tumor with pleural nodules; Malignant pleural or pericardial effusion.

M1b – Distant metastasis [3].

	N0	N1	N2	N3	M1
T1	IA	IIA	IIIA	IIIB	IV
T2	IB	IIB	IIIA	IIIB	IV
T3	IIB	IIIA	IIIA	IIIB	IV
T4	IIIB	IIIB	IIIB	IIIB	IV
M1	IV	IV	IV	IV	

Figure 1 – LC staging (TNM staging system).

The positive diagnosis of LC always needs **bronchoscopy with white light** (WLB).

WLB can be used for the diagnosis (including histological assessment) and staging of central and peripheral tumors. This procedure can show 3 types of findings: intraluminal growth, damage of the bronchial wall, deformation of the normal anatomy due to extrinsic compression.

The endobronchial changes that can appear at the WLB are:

1. direct evidence (of the tumor itself):
   - endoluminal vegetations;
   - endobronchial stenosis due to neoplastic infiltration;
2. indirect signs of lung cancer:
   - extrinsic compression;
   - bronchial stiffness (during inspiration / expiration);
   - ± alterations of static lung compliance (slow installed in atelectasis);

3. indirect signs of lymph node invasion;
4. accompanying signs of bronchi and of the juxtatumoral lung tissue:
   - inflammation / hypersecretion;
   - granulation tissue (ongoing or previous) [4].

The endoscopic anomalies in LC after Ryosuka Ono are represented by:

1. tumor: polypoid, nodular, with/without necrosis(figure 2, 3);

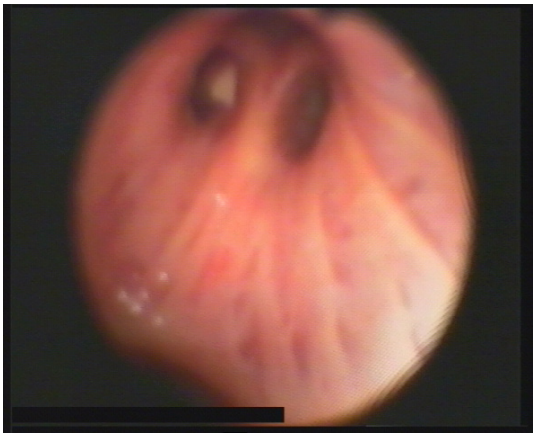

Figure 2 – Tumor in anterior segmental bronchus (of the right upper lobe) with necrotic deposit on its surface (Dr. Tofolean Doina archive).

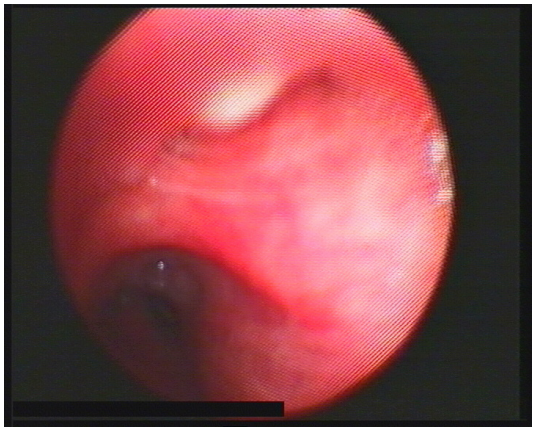

Figure 3 – White, 2-3 mm tumor located at the orifice of the right upper lobe bronchus. Biopsy: small cell carcinoma (Dr. Tofolean Doina archive).

2. infiltration: mucosa is irregular, pale, with diminished luster; vascularectasia (figure 4,5);

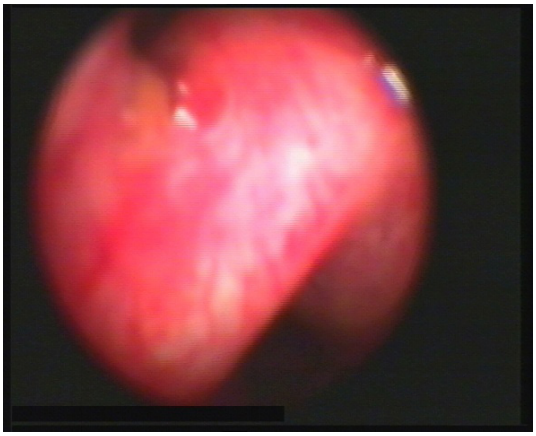

Figure 4 – Left upper lobe infiltrative process with secondary stenosis and interlobar spur infiltration (Dr. Tofolean Doina archive).

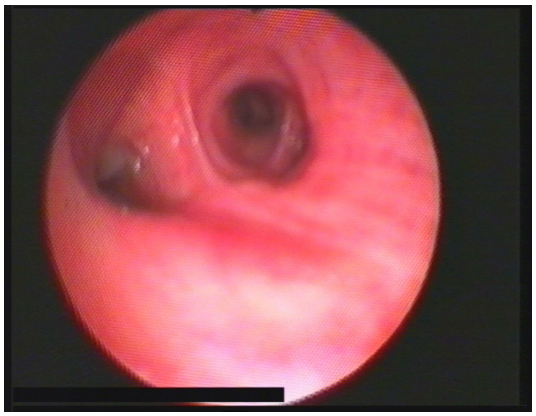

Figure 5 – Bronchoscopy: diffuse mucosal hyperemia; purulent secretions in the left bronchial tree. Transbronchial biopsy and hystopathological exam: adenocarcinoma (Dr. Tofolean Doina archive).

3. bronchial obstruction due to tumor, infiltration (figure 6);

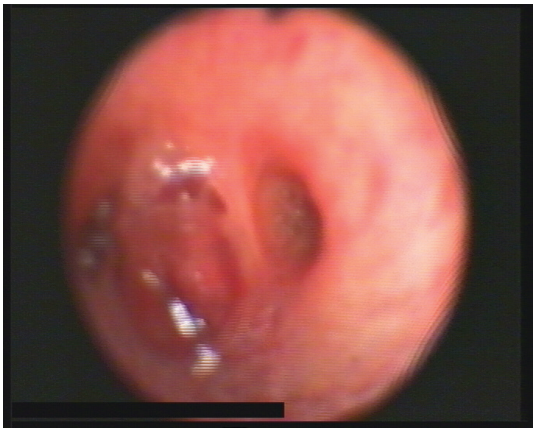

Figure 6 – Bleeding, protrusive tumor, with total obstruction of the bronchi, located in medio-bazal segment of right inferior bronchi. Biopsy: epidermoid carcinoma (Dr. Tofolean Doina archive).

4. bronchial stenosis determined infiltration, compression(figure 7);

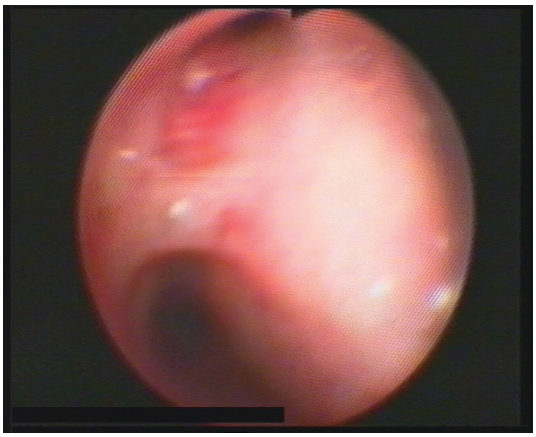

Figure 7 – Right upper lobe stenosis by extrinsic compression (Dr. Tofolean Doina archive). (Dr. Tofolean Doina archive).

5. extrinsic compression secondary to lymph node, tumor(figure 8)[4].

During bronchoscopy it is possible the prelevation of brochial material for cytological and histological examination.

	EUS	EBUS
EUS and EBUS accessible lymph nodes	-	Superior mediastinal lymph nodes (1)
	Left upper paratracheal lymph nodes (2L)	Upper paratracheal lymph nodes (2)
	-	Prevascular lymph nodes (3)
	Left lower paratracheal lymph nodes (4L)	Lower paratracheal lymph nodes (4)
	Subaortic lymph nodes (5)	-
	-	-
	Subcarinal lymph nodes (7)	Subcarinal lymph nodes (7)
	Paraesophageal lymph nodes (8)	-
	Pulmonary ligament lymph nodes (9)	-
	-	Hilar lymph nodes (10)
	-	Lobar lymph nodes (11)
	Celiac lymph nodes	-

Figure 8 – Accesible lymph nodes to ecoendoscopy.

Bronchial aspiration is conducted under visual control of the area with changes that suggest malignancy. The technique requires injection and then aspiration in a container, through the bronchoscope, of 5-10 ml saline solution. The procedure has reduced diagnostic contribution (may increase after bronchial lavage and bronchial brush by increasing the number of exfoliated cells). The major cause of false positives in this case is signified by pavement metaplasia [5].

Bronchial brush consists of bronchial cells exfoliation, using brushes and their fixation to slides. This procedure har a significant higher output than bronchial aspirate (positive results in 88-94% of cases) [5].

Bronchial biopsy has a increased diagnostic accuracy by direct visualization and biopsy of the lesion, washing/aspiration of secretions, blood and necrotic material, "deep" biopsies in necrotic tumors, increased number of biopsies in central tumors (3-4-5). This procedure offers histological confirmation of tumors highlighted by bronchoscopy: 55-85%, but it has a major complication – bleeding [5].

Transbronchial biopsy (lung/lymph node biopsy) has the following indications:

- diagnosis of tumors developed in the submucosa;
- diagnosis of compressive and necrotic tumors;
- defining the proximal edges of surgical resection;
- LC staging through hilar and mediastinal lymph node biopsy (the most important indication).

The procedure has a sensibility of aproximately 50% (in the staging of the mediastinal lymph nodes) with a specificity of 95% and a sensitivity of 57% (17 – 80%). There are a few complications such as pneumothorax (1 – 4%) and hemoptysis.The purpose of the procedure is to biopsy the peripheral lesions located in the lung parenchyma [6].

Broncho-alveolar lavage (BAL)

The most important indication of this procedure is the diagnosis of peripheral lung tumors, but it also offers cytology, biochemistry, bacteriology and immunology assessments. BAL has an increased diagnostic accuracy in tumors larger than 3 cm in diameter and adenocarcinoma or broncho-alveolar carcinoma. The most common complications are fever, and impaired, but reversible respiratory tests [7].

Today we can do in BAL molecular markers like:

- P53 mutations, that appear in central tumors (squamous cell carcinomas), present in approximately 27% of all LC;
- K-ras mutations, that are more frequent in peripheral tumors (adenocarcinomas) and the mutation is present in 56% of all LC;
- Ag HnRNP A2/B1, that has a sensibility of 96% and a specificity of 82%;
- CpG p16, that shows the hypermethilation process in case of LC;
- microsatellites mutations models (LOH) in 4 out of 8 loci may lead to cancer; with a sensibility of 73,9% and a specificity of 76,5% there are more common in peripheral tumors compared to central ones (100% vs 29%;p= 0,032) [2].

Electromagnetic Navigation Bronchoscopy (ENB) is a new method based on 3D-CT images and virtual bronchoscopy performed in real time. It is addressed to the peripheral tumor masses, that can not be biopsied using a standard bronchoscope and the procedure increases the diagnosis rate of transbronchial biopsy.

ENB has a diagnose rate of approximately 70%, and presents a major advantage: enough tissue for histopathologicalexamination and molecular tests. The complications are similar to conventional bronchoscopy, but there is a major drawback, the costs [8,9].

Autofluorescence bronchoscopy (AFB) is another investigation that helps at diagnosis of early lung cancer. Endoscopical aspects obtain in AFB are divided into 3 classes: class I - normal aspesct, class II: inflammation and mild dysplazia, class III: moderate or severe dysplasia, carcinoma in situ, invasive carcinoma. AFB helps the diagnosis of moderate / severe dysplasia (increase in sensitivity from 9% to 65%), and of carcinoma *in situ* (increase in sensitivity from 4% to 100, low specificity, 1/3 false positives), but is also used in preoperative screening (evaluating patients with operable cancer) - marking the resection lines or in the evaluation of lung cancer extention of endoscopically visible tumors [2,10,11,12].

Narrow–Band Imaging Bronchoscopy(NBI) may be used for the visualization of superficial capillary circulation and submucosa. Herth et al concluded that NBI offers better results in the diagnosis of intraepithelial neoplasia.

While WLB's sensibility is only of 18% andAFB's relative sensibility (compared to WLB) is 3.7(p=0,005), NBI's relative sensibility (compared to WLB) is of 3.0 (p=0,03). NBI's specificity is significantly increased compared to AFB, but there are no statistic differences when it comes to sensibility. Combining AFB with NBI does not bring any additional benefits [13].

Confocal Fluorescence Microendoscopy (CFM) is used in identifying cellular and subcellular microstructures, offeringblur-free, high-resolution images of living andexvivo biologic samples by reducing aut-of-focus light from above and below the focal plane.Offers a stack of deep-resolved optical images without physical sectioning.

Thiberville concluded that CFM can be used in diagnosing of dysplastic lesions and can offer a strong correlation between the number of smoked cigarettes/ day and the number of mobile macrophages noticed *in vivo* or the extent of macrophage alveolitis [2,10].

Echoendoscopy (EUS +/- EBUS + FNA) is indicated in the diagnosis and staging of LC: LC with hilar and/or mediastinal lymphadenopathy and also LC with positive PET- CT.

The accuracy of stadialization is essential for treatment. The CT and PET- CT are characterized the lung tumor (figure 9), mediastinum (figure 10)

and metastasis(figure 11). EBUS and EUS permited obtaining of tissue for histological examination with confirmation or exclusion of neoplastic affection. The chance of metastasis is around 50-80%, but sometimes exist false positive results (the adenomegaly is done by inflammation, no by lymphatic metastasis). Also EUS permits the investigation of left adrenal gland [4].

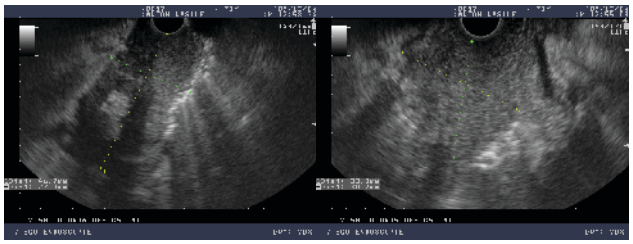

Figure 9 – Lung tumor (Dr. Dumitru Eugen archive)

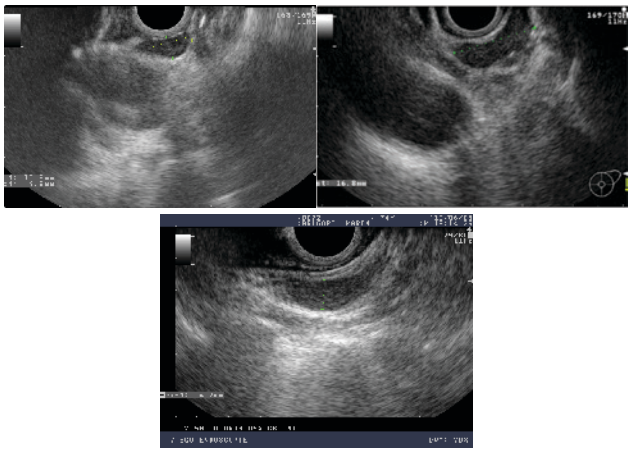

Figure 10 – Mediastinal lymph nodes (Dr. Dumitru Eugen archive).

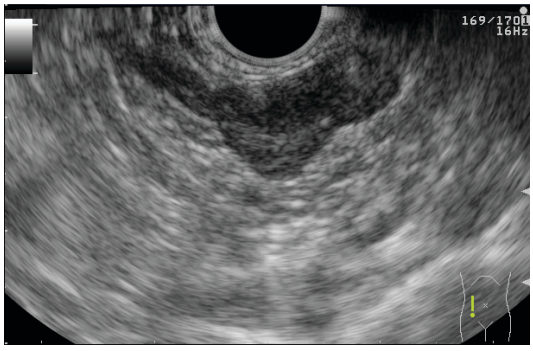

Figure. 11 – Left SR with hypertrophy (Dr. Dumitru Eugen archive).

Echoendoscopy permit the evalution of the mediastinal lymphnodes (table 1), with diff erentiation of N1 to N2.

The guideline of European Society of Gastrointestinal endoscopy(ESGE), in cooperation with the European respiratory Society(ERS) and the European Society of Thoracic Surgeons(ESTS) established the following recomandations for early diagnosis of lung cancer [14]:

For mediastinal nodal staging in patients with suspected or proven NSCLC with abnormal mediastinal and/or hilar nodes at computed tomography (CT) and/or positron emission tomography (PET), endosonography is recommended over surgical staging as the initial procedure (Recommendation grade A). The combination of EBUS-TBNA and EUS-FNA or EBUS (EUS-B-FNA) scope, is preferred over either test alone (Recommendation grade C).If the combination of EBUS and EUS-(B) is not available, we suggest that EBUS alone is acceptable (Recommendation grade C). Subsequent surgical staging is recommended, when endosonography does not show malignant nodal involvement (Recommendation grade B).

For mediastinal nodal staging in patients with suspected or proven NSCLC without mediastinal involvement at CT or CT-PET, we suggest that EBUS-TBNA and/or EUS-(B)-FNA should be performed before therapy, provided that one or more of the following conditions is present: (i) enlarged or fl uorodeoxyglucose (FDG)-PET-avid ipsilateral hilar nodes; (ii) primary tumor without FDG uptake; (iii) tumor size ≥3cm (Recommendation grade C). If endosonography does not show malignant nodal involvement, we suggest that mediastinoscopy is considered, especially in suspected N1 disease (Recommendation grade C). If PET is not available and CT does not reveal enlarged hilar or mediastinal lymph nodes, we suggest performance of EBUS-TBNA and/or EUS-(B)- FNA and/or surgical staging (Recommendation grade C).

In patients with suspected or proven<3cm peripheral NSCLC with normal mediastinal and hilar nodes at CT and/or PET, we suggest initiation of therapy without further mediastinal staging (Recommendation grade C).

For mediastinal staging in patients with centrally located suspected or proven NSCLC withoutmediastinal or hilar involvement at CT and/ or CTPET, we suggest performance of EBUS-TBNA, withor without EUS-(B)-FNA, in preference to surgical staging (Recommendation grade D).If endosonography does not show malignant nodal involvement, mediastinoscopy may be considered (Recommendation grade D).

A complete assessment of mediastinal and hilar nodal stations, and sampling of at least three different mediastinal nodal stations (4 R, 4L, 7)is suggested in patients with NSCLC and an abnormal mediastinum by CT or CT-PET (Recommendation grade D).

For diagnostic purposes, in patients with a centrally located lung tumor that is not visible at conventional bronchoscopy, endosonography is suggested, provided the tumor is located immediately adjacent to the larger airways (EBUS) or esophagus (EUS-(B)) (Recommendation grade D).

In patients with a left adrenal gland suspected for distant metastasis we suggest performance of EUS-FNA (Recommendation grade C), whilethe use of EUS-B with a transgastric approach is at present experimental (Recommendation grade D).

In conclusions, the early diagnosis and screening of LC are a continuous challenge.

Early diagnosis and treatment of LC assure an 3-4 times increased 5-year survival, which is a good reason for research to be continued in this area of interest.

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