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Lung Cancer Staging

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Summary

Lung cancer incidence has dramatically risen in the past century. It is now the leading cause of cancer death in the world, both among men and women. Accurate staging is important because treatment options and prognosis differ significantly by stage. If there are no distant metastases, the status of mediastinal lymph nodes is the critical point to distinct between patients who will benefit from surgical therapy, neoadjuvant therapy or clinical treatment. Noninvasive imaging studies including chest computed tomography and positron emission tomography scanning should be performed in all patients who are potentially candidates to pulmonary resection. The findings of these noninvasive studies are critical, and the invasive mediastinal staging must be performed according to the medical examination and the results of noninvasive tests. In patients with extensive mediastinal infiltration by lung cancer, the disease is considered advanced and invasive staging is not needed. In patients with mediastinal lymph node enlargement seen at computed tomography, a sample tissue of these nodes is necessary. In these cases there are several methods to invasive staging the mediastinum, but mediastinoscopy is the gold standard. In patients with clinical T2 or with central tumors, invasive staging of the mediastinal nodes is necessary. Patients with a peripheral clinical T1 lung cancer do not usually need invasive confirmation of mediastinal nodes unless there is an abnormal standard uptake value in the nodes, found on positron emission tomography scanning. The staging of patients with left upper lobe tumors should include an assessment of the preaortic and aortopulmonary window lymph nodes. Pancoast tumors always need invasive mediastinal staging if they are considered for surgical resection.

Keywords: Lung neoplasms; Bronchogenic carcinoma; Non-small cell lung cancer; TNM staging; Cancer staging; Bronchoscopy; Pancoast tumor

Introduction

There are many different histological subtypes of malignant neoplasms in the lungs, but the most common is bronchogenic carcinoma, which comprises 85 - 90% of all. Most texts refer to lung cancer as a synonym for bronchogenic carcinoma [1]. It arises in the bronchial epithelium of distal airways and may have different histological subtypes. In the past it was useful to subdivide the histological subtypes as "small cell lung cancer" (SCLC) and "non small cell lung cancer" (NSCLC). It was useful because of the difference in survival and treatment between both entities: SCLC is extremely aggressive and is rarely curable; NSCLC varies on its aggressiveness and, depending on the stage, may be eligible for surgical resection with intention to cure. With refinements in the treatment, especially in surgical technique, radiotherapy, and chemotherapy directed to specific targets, this subdivision became incomplete, albeit still used in many centers. The most up to date concept is to stage SCLC with the same staging system adopted as NSCLC, although treatment differ for same stage of these two neoplasms [2].

Currently, the choice for different regimens of chemotherapy will vary according to different subtypes of the NSCLC and also with specific genetic markers for the same histological subtypes. Therefore it is necessary a more specific diagnosis of the subtype of NSCLC, with the study of genetic characteristics of the tumor, to guide the more specific chemotherapeutic treatment, when necessary.

It is not necessary to have a diagnosis of NSCLC prior to surgical resection when there is a strong suspicion of this disease. The staging is based on the TNM system (***T***: *t*umor; ***N***: lymph *n*ode; ***M***: *m*etastasis). According to this system, each of the descriptors (***T***, ***N*** and ***M***) are subdivided into categories that are combined in order to provide a final classification, which aims to group patients with similar prognosis into the same staging category. This also helps in the selection of the best treatment for each case of lung cancer and facilitates the communication among thoracic surgeons, oncologists and pulmonologists [3].

The most important aspect when evaluating the patient's eligibility for surgical treatment is mediastinal staging with respect to neoplasic involvement of lymph nodes. The indications of an invasive mediastinal staging and the methods available will be further discussed in this paper.

Epidemiology

Most cases of lung cancer are consequence of cigarette smoking, being one of the leading causes of preventable death [4]. By the year of 1964 case-control and cohort studies led the *US Surgeon General* to support a conclusion that cigarette smoking causes lung cancer, which was the same conclusion, two years before, of the *Royal College of physicians* [5,6]. Passive smoking is also associated to this disease.

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Although other substances as radon, asbestos and arsenic are possibly associated to lung cancer, their contribution is not significant. Genetic characteristics are probably associated with the development of this disease, but its exact role is not still elucidated. The first report to suggest the link between lung cancer and tobacco exposure was a paper written from Ochsner and DeBakey in 1939 [7].

Lung cancer is currently the leading cause of cancer death in men and women in western countries. It accounted for more than 157,000 deaths in the US during 2010 and more than 1.3 million deaths worldwide [8]. In US, this neoplasm is responsible for more than 25% of all cancer deaths, exceeding deaths from breast, colon, and prostate cancers combined [9]. Presently, approximately 20% of the adults in United States are smokers. The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day [10].

NSCLC is responsible for about 80% of all new cases of bronchogenic carcinomas annually; in contrast, SCLC accounts for 20% of new cases. NSCLC can be subdivided in three major subtypes: squamous cell carcinoma (25%-30%), adenocarcinoma (30%-40%), and large cell lung carcinoma (less than 10%). Nowadays, this subdivision is no more sufficient to guide the best treatment possible because new genetic tumor markers are being used to select the best type of chemotherapy for each patient, and there are more specific histopathologic subdivisions.

Regarding socioeconomic status, lung cancer is slightly more common in the poor and less educated population. Although not well understood, this aspect may reflect differences in diet, exposure to environmental risks and workplace and availability of medical care.

General Considerations for Lung Cancer Staging

The TNM staging system for lung cancer has its origins with Dr. Pierre Denoix, a surgical oncologist from the Institut Gustave-Roussy in Paris [11]. He analyzed a series of papers published between 1943 and 1952, in the first effort to unify the lung tumor classification, being published by the International Union Against Cancer (UICC) in 1968 [12]. The second "international" recommendation came in 1974 with the support of the American Joint Committee on Cancer (AJCC). This task force made their recommendations based on the analysis of 2,155 cases of lung cancer, of which 1,712 were NSCLC, and its main contribution was the classification of the ***T*** descriptor, which some characteristics are still in use [13,14].

The sixth edition of TNM staging system occurred in 1997 and was based on the analysis of 5,319 cases of NSCLC in the USA, and nearly all of those patients had undergone surgical treatment between 1975 and 1988 [3]. The main limitations in this sixth edition were the geographically specific population and the absence of external validation in that analysis.

These deficiencies were discussed at the International Association for the Study of Lung Cancer (IASLC) workshop in London in 1996, prompting the establishment of the International Staging project and Committee (ISC), under the leadership of Professor Peter Goldstraw of the Royal Brompton Hospital in London [3,15]. The objective of that committee was to collect and analyze data from lung cancer patients worldwide [3,16]. Forty-six data sources in more than 20 countries from Europe, North America and Asia donated more than 100,000 cases. Of them, 81,495 cases had adequate data to be included in an analysis: 68,463 cases of NSCLC and 13,032 cases of SCLC. The recommendations for the seventh edition of TNM were based on analysis of the NSCLC cases, and included patients receiving surgery, chemotherapy, radiotherapy and also bimodality or multimodality treatment [2]. The analysis of this huge number of cases was conducted by Cancer Research and Biostatistics (CRAB) and supervised by several subcommittees [17]. All such recommendations were overseen by a validation and methodology subcommittee who established strict criteria for internal and external validation [17]. All this work resulted in the seventh edition of TNM for lung cancer, promulgated in January 2010 [3,18]. There were also analyzes involving patients with SCLC and carcinoid tumors, and these two histological types received the same TNM staging classification as NSCLC since the seventh TNM staging system for lung cancer.

Correctly staging lung cancer, as for any other malignant neoplasm, is important because treatment options and prognosis differ significantly by stage. The noninvasive staging must precede the invasive staging, which consists basically of evaluating the mediastinum. The most significant dividing line is between those patients who are candidates for surgical resection (surgical resection or resection preceded by neoadjuvant therapy) and those who are not candidates but will benefit from chemotherapy, radiation therapy, or both.

Noninvasive staging starts with history and physical examination of the patient. After a tissue diagnosis of lung cancer has been established or in patients in whom the clinical suspicion is high and surgery is a possibility, the consideration must turn toward the determination of the extent of disease. The most important decision during noninvasive staging is to subdivide patients in: 1) those who go straight to surgery with intention to cure; 2) patients that will need an invasive mediastinal staging before choosing the definitive treatment (discussed in next session); 3) patients that will benefit from the clinical treatment (chemotherapy and/or radiotherapy). In this last class of patients a tissue diagnosis of lung cancer is essential, while for the first two classes, the tissue diagnosis may be achieved during the surgical procedure or the invasive mediastinal staging [19].

Different from other types of tumor, the suspicion of lung cancer is enough to start the staging procedures, and the pursuit for tissue diagnosis is not required for initiating the staging [3,19,20].

According to the International Association for the Study of Lung Cancer (IASLC), the staging sequence must be simple and logical. As most carcinomas, lung cancer is staged according to the TNM staging system (***T***umo***r***, ***N***odes, ***M***etastasis); and the first descriptor to be searched for is the ***M***etastasis. The most common metastatic sites of lung cancer are: liver, brain, adrenals and bones [3,19]. This method is explained because the finding of metastasis will preclude the surgical resection of primary lung cancer in most cases. In cases which the metastasis may be completely resected, the patient will have the diagnosis (by tissue analysis of the metastasis) and, if the invasive mediastinal staging allows, will be eligible to resection of the primary tumor [19,20].

The 7th edition of the TNM staging system of lung cancer was adopted in United States on January 1, 2010. The descriptors are listed in Table 1 and the staging system is shown in Table 2. The "Union Internationale Contre le Cancer" and the "American Joint Committee

T, N and M Descriptors of the 7th Edition for Lung Cancer Staging
***T* – Primary Tumor**
Tx - Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy T0 - No evidence of primary tumor Tis - Carcinoma *in situ* T1 - Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) T1a - Tumor 2 cm or less in greatest dimension[1] T1b - Tumor more than 2 cm but not more than 3 cm in greatest dimension T2 - Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features[2]: • Involves main bronchus, 2 cm or more distal to the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung T2a - Tumor more than 3 cm but not more than 5 cm in greatest dimension T2b - Tumor more than 5 cm but not more than 7 cm in greatest dimension T3 - Tumor more than 7 cm or one that directly invades any of the following: Chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal, pericardium; or tumour in the main bronchus less than 2 cm distal to the carina1 but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary T4 - Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary
***N* – Regional Lymph Nodes**
Nx - Regional lymph nodes cannot be assessed N0 - No regional lymph node metastasis N1 - Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension N2 - Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) N3 - Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
***M* – Distant Metastasis**
M0 – No distant metastasis M1 - Distant metastasis M1a - Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion[3] M1b - Distant metastasis

Notes:

[1]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a

[2]T2 tumors with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cm

[3]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopical examinations of pleural (pericardial) fluid are negative for tumor, and the fluid are non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0

Table 1: Complete *T*, *N* and *M* descriptors in 7th edition for lung cancer staging [3,21].

TNM Staging Group					
T / M	**Sub classification**	**N0**	**N1**	**N2**	**N3**
T1	**T1a**	IA	IIA	IIIA	IIIB
	T1b	IA	IIA	IIIA	IIIB
T2	**T2a**	IB	IIA	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	**T3**	IIB	IIIA	IIIA	IIIB
T4	**T4**	IIIA	IIIA	IIIB	IIIB
M	**M1a**	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Table 2: The 7th edition of *TNM* staging system for lung cancer [22].

on Cancer" are organizations that periodically review and define this system. There are two possible stage assessment: 1) clinical staging (prefix "c"), which is determined using the information available before treatment; and 2) pathologic staging (prefix "p"), which is determined after tumor resection. Obviously, the clinical staging may guide the initial treatment (or even a curative treatment), but only the pathologic staging can accurately determine the staging of lung cancer in each patient.

In patients having a suspicion of NSCLC, the diagnostic method must be dictated by the presumed stage of disease. Preferentially, patients

are first screened for metastatic disease by means of medical history and physical examination, what means to say that the ***M*** descriptor must be the first to be pursued. The initial work up consists of looking for some constitutional (eg, fatigue, weight loss, anorexia), organ specific signs or symptoms (eg, bone pain, neurologic symptoms), or abnormal laboratory findings (eg, anemia, elevated alkaline phospatase levels, elevated liver enzyme levels, hypercalcemia). If the patient has signs of advanced disease, if advanced metastatic disease is discovered or highly suspected, the diagnostic method must be the easiest disposable to confirm the cancer and to obtain a tissue sample in each case. In many of these patients, a fine needle aspiration (FNA) or needle biopsy of the suspected metastatic site is the most efficient way to diagnose and also to stage the disease. We must remember that genetic studies in tumor cells are available and may better guide a target therapy, especially for adenocarcinomas. However, in cases where the metastatic site is technically difficult to biopsy and there is a high degree of suspicion based on image studies (eg, multiple brain, liver or bone lesions), again the easiest and less invasive method to obtain a tissue diagnosis must be used. A joint decision involving the thoracic surgeon, radiologist, pulmonologist, and medical oncologist is the desirable approach to decide which invasive method should be used to get a histological or cytological sample.

As reported above, according to the AJCC, the staging provided by invasive and noninvasive tests is defined as clinical staging, and will guide the therapy selected in each case. The pathological staging refers to the staging after tumor's resection, being the most accurate staging; yet may only be accomplished after the surgery, what makes it non-applicable to select the strategy of the initial treatment.

Noninvasive Mediastinal Staging of Lung Cancer

After clinical history, physical examination, radiological examinations as dictated in each case and laboratory analysis, the mediastinum must be evaluated. Mediastinal staging refers to determining the involvement of the mediastinal lymph nodes, which is the most important part of the staging, but also the possible direct mediastinal invasion by the primary tumor. Mediastinal lymph nodes status and the presence or absence of direct tumor mediastinal invasion will determine the eligibility of the patient to treatment with intention to cure (surgical treatment) or a palliative care intending to prolong life and better quality of life. Moreover, the invasive mediastinal staging is dependent of the adequate noninvasive mediastinal staging, which will guide the necessity of that invasive stage.

After considerations listed above, some diagnostic modalities will be discussed:

Chest radiograph

The majority of lung cancers are initially detected by chest x ray. Although chest radiograph is important and, usually, the initial radiological modality, it must always be complemented by other imaging examinations for clinical staging when lung cancer is suspected [19]. It cannot accurately detect lymph node enlargement, chest wall or mediastinal invasion, or more specific characteristics of the nodule/mass. But it can detect pleural effusions that obliterate costofrenic recesses and lung nodules larger than 7 mm. Every patient suspected of having lung neoplasm must have a posterior-anterior and lateral chest radiograph [9,19].

Computed tomography of the chest

The computed tomography (CT) of the chest is an obligatory step for every patient suspected of having lung cancer, unless the patient is so debilitated that no treatment can be proposed. It is the most widely available and commonly used noninvasive method for evaluation of the chest; and is also important to evaluate the liver and adrenals. The exam should be performed with continuous intravenous injection of contrast, unless the patient has contraindication to its use. The contrast allows the identification of vascular structures, mediastinal lymph nodes and also permits to evaluate the contrast enhancement in the density of the lung lesion, measured by the "Hounsfield Unit". The CT scan must include all of the thoracic structures starting from the neck, and continue down through the abdomen to include the liver and adrenals.

Lymph node size is of particular importance in the clinical staging of lung cancer. When there is mediastinal lymph node enlargement in CT (defined as a node with more than 1 cm in the short axis), an invasive mediastinal staging method is obligatory if we think the patient is a possible candidate for surgical resection [3,19-22]. This evaluation may define the presence of N2 or N3 disease, what may preclude surgical resection or obviate the need for neoadjuvant therapy, depending on each case. Previous studies have shown that in the presence of enlarged mediastinal lymph nodes in a patient with lung cancer, 40% percent of these nodes will prove to be benign. By the other hand, approximately 20% of normal size mediastinal lymph nodes in lung cancer patients will prove to be malignant [19,20,23]. The indications to an invasive mediastinal staging with normal size mediastinal lymph nodes will be discussed in the section "invasive mediastinal staging of lung cancer".

An important aspect regarding to thoracic CT evaluation in lung cancer, is the correlation between the clinical stage of the primary tumor and the positivity of *normal-size* neoplastic lymph nodes identified by mediastinoscopy, as exemplified in Table 3 [24]. In this study, the authors analyzed 235 patients with ***N0*** clinical stage and different ***T*** clinical stage. All patients were evaluated by cervical mediastinoscopy and results of the ***N*** descriptor after mediastinoscopy is shown.

Routine chest CT may also evaluate the presence of distant metastasis to the liver, adrenals or bones, which are some of the commonest sites of metastatic disease. The lung lesion itself is also more specifically evaluated by CT scan, the limits of the lesion are better assessed and the rest of lung parenchyma may be screened for additional lesions.

Positron emission computed tomography

Positron emission tomography (PET) is better used in conjunction to CT (PET-CT). This modality intends to detect tumor physiology, while CT assesses the anatomy. PET uses 18-fluoro-2-deoxyglucose (FDG), a D-glucose analogue labeled with positron-emitting fluorine 18. The patient's cells take up the FDG for glycolysis, but cells with

T Clinical Stage	Positivity mediastinal lymph nodes at Mediastinoscopy
T1 N0	9,5%
T2 N0	17,7 %
T3 N0	31,2 %
T4 N0	33,3 %

Table 3: Presence of neoplastic mediastinal lymph nodes detected by mediastinoscopy in patients with normal-size nodes at CT [24].

increased metabolic activity accumulate more FDG because there is an upregulation in glycolysis in these cells. The combination of increased uptake of 18F-FDG and a decreased rate of dephosphorylation by glucose-6-phosphatase in malignant cells results in an accumulation of 18F-FDG-6-phosphate in these cells [25]. This accumulation makes the tissue appear brighter than the surrounding normal-metabolic surrounding tissues [26]. The brightness in PET-CT is expressed as the Standard Uptake Value (SUV), and, as higher the metabolic activity, higher the SUV. A standard uptake value of 2.5 is sometimes used as a threshold level for normalcy, but this measurement may vary according to factors that modify the serum glucose levels, such as diabetes, stress, temperature of the examination's room. Sometimes the SUV of the liver is used as the patient's "baseline SUV", but, actually, there is not a straight definition of a "normal" SUV, and each patient should be individually evaluated on this aspect.

Integrated PET-CT is more sensitive than dedicated PET and CT alone to evaluate patients suspected of having lung cancer, because it may better detect metastatic disease [23,26]. This exam is always performed through the whole body and, whenever there is metastatic disease, there will be a high probability of being detected by PET-CT. One exception is the brain evaluation; as this organ has a very high metabolic activity, metastatic disease to the brain do not present with an augmentation in metabolism when compared to basal brain metabolic rate; therefore, PET-CT is not appropriate to evaluate possible metastatic disease in the brain.

As discussed above, PET-CT evaluates metabolic activity, what means that it cannot distinguish between inflammatory or neoplastic disease. Therefore, an inflammatory lesion (such as tuberculosis or fungal disease) may present as false-positive neoplastic lesion. Some slow-growing neoplastic diseases may also present as false negative PET-CT, and classical examples are the carcinoid tumor and bronchioloalveolar carcinoma. Therefore, a suspected lesion detected by PET-CT must be confirmed histologically to have the accurate diagnosis.

Also important to discuss is the limitation of this method regarding to size. PET-CT may not adequately evaluate lesions (primary lesion, metastasis or lymph nodes) between 0.7 and 1 cm. For lesion smaller than 0.7 cm PET-CT is not capable to detect hipermetabolism, therefore, such a malignant lesion would not present a high SUV, even if its metabolic activity is elevated.

Although the actual recommendations of the American College of Chest Physicians do not formerly recommend PET-CT as a routine method [19,20], more recent studies have recommend its routine use for every lung cancer patient that will be submitted to pulmonary surgical resection [22,26-28]. Our routine is to perform the PET-CT in every patient who is a potential candidate to pulmonary resection.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an anatomical study. Studies evaluating its use in staging lung cancer, particularly the mediastinum, are more limited than with CT, but suggest similarities in these two methods regarding to mediastinal staging [29]. MRI has advantages when compared to CT when evaluating limits and possible invasion in soft tissue, bone and vascular structures but, with new generations of multislice CT scans that are capable to perform three-dimensional angiotomography, MRI has diminished one of its main indications, which is to evaluate vascular and neural invasion in superior sulcus tumor [30]. MRI is not routinely used to stage lung cancer, because there is no superiority when compared to CT to stage the mediastinum or lung parenchyma. Its main use is to image the brain when suspecting of metastasis at this organ [31].

Invasive Mediastinal Staging of Lung Cancer

The patient may be suspected of having lung cancer after a physician with experience with this disease performs a careful history, clinical examination and evaluation of the chest radiograph and chest CT. Currently, every patient with suspicion to have lung cancer, and who is a potential candidate for pulmonary resection must have a PET-CT.

After distant metastasis has been ruled out, the mediastinal staging is the most important aspect to focus in these patients. The invasive mediastinal staging (IMS) is always preceded by noninvasive mediastinal staging. However, noninvasive imaging tests can provide only a suspicion that involvement of the mediastinal nodes is present or absent, and in many clinical situations confirmation of the status of these nodes by an invasive test is necessary [32].

The main purpose of the IMS is to distinguish between patients candidate to surgical resection (curative intent) selected by noninvasive methods in: a) patients that will benefit from straight surgical resection; b) patients that will benefit from neoadjuvant therapy, followed by surgical resection; c) patients who will not benefit from surgical resection, and should receive only chemo and/or radiotherapy [3,20,32].

In general, patients with lung cancer may be divided in four categories, according to tomographic characteristics of the primary tumor and the mediastinum, regarding to size, location and extension of the disease (Figure 1). This division was proposed by Dr. Frank Detterbeck and adopted by the American College of Chest Physicians Guidelines for Diagnosis and Management of Lung Cancer [3,20]. It is a very useful and friendly classification, given the CT scan is relatively inexpensive and is essentially always performed as a preliminary step in a patient suspected to have lung cancer.

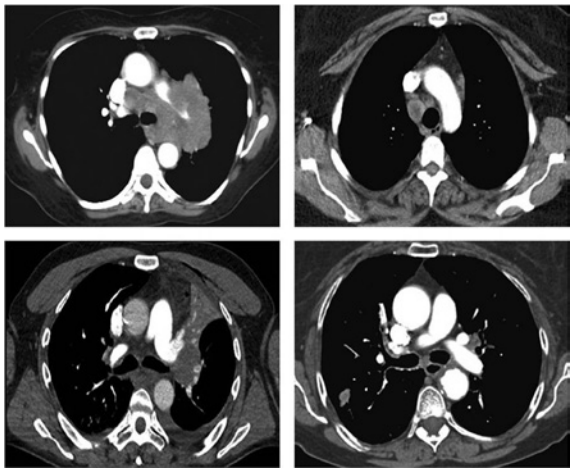

Figure 1: Group A: top left; extensive mediastinal infiltration by the primary tumor. Group B: top right; enlarged paratracheal lymph nodes. Group C: bottom left; central tumor with normal-sized mediastinal lymph nodes. Group D: bottom right; peripheral small tumor with normal-sized mediastinal lymph nodes [19,32].

The first group, Group A, encompasses patients whose tumor presents with extensive mediastinal infiltration, involving great vessels or the airway. In this situation, mediastinal neoplastic invasion may be accepted based only in tomographic studies and it is not necessary to perform an invasive staging of the mediastinum [19,20,32]. The main objective in these patients at Group A should be to establish a diagnosis by the easiest method available according to each case [20,32]. The second group, Group B, refers to patients presenting mediastinal lymph node enlargement at CT. In this group the IMS is indicated if there is intention to perform a pulmonary resection aiming to cure. This mediastinal evaluation will allow searching for N2 or N3 disease. Group C and Group D refer to patients presenting with *normal size* mediastinal lymph nodes at CT. In the third group, Group C, primary lesion is larger than 3 cm in any location or the lesion is a central located nodule. In these cases, a malignant mediastinal lymph node with a normal size is about 20 – 25% and therefore the IMS is indicated in Group C if there is intention to perform a pulmonary resection. Group D refers to patients with a peripheral nodule and normal size mediastinal lymph nodes; usually these patients do not need the IMS previous to pulmonary resection, given the incidence of N2 or N3 disease is extremely low. Still in Group D, one exception is when there is a *positive PET-CT* in mediastinum (with peripheral lung nodule and normal sized mediastinal lymph node); in these cases, an IMS test should be performed to confirm or exclude the suspicion of mediastinal lymph node involvement [3,19,20].

The most common tests utilized to perform the IMS are summarized in Table 4. All these procedures must be done with the pathologist in the surgical room, for an immediate analysis of the material.

Techniques of Invasive Mediastinal Staging

Mediastinoscopy

Mediastinoscopy is performed in the operating room under general anesthesia, usually with patient discharge in the same day [33]. The procedure is done through a transverse cervical incision, with pretracheal dissection until the mediastinum and introduction of the mediastinoscope. Although variable with each patient's anatomy, it is possible to perform biopsies of the following lymph nodes: pretracheal; right and left high and low paratracheal; and subcarinal, respectively stations 1 and 3, 2R, 2L, 4R, 4L, and 7. Morbidity and mortality rates are respectively, 2% and 0,08% in centers with experience with this test [34]. The procedure may also be done with the videomediastinoscope, which uses a videocamera coupled to the mediastinoscope, allowing a magnification of the operative field and also very useful to teaching.

When performed guided by Groups A to D, as described above, mediastinoscopy has a sensibility in detecting mediastinal lymph node involvement of approximately 80%, with a false negative (FN) rate of approximately 10%. The specificity and the false positive (FP) rates of this test is, respectively, 100% and 0% [20,35,36]. Videomediastinoscopy may have a slight better sensitivity than mediastinoscopy, but further studies are necessary to elucidate this point.

Techniques of Invasive Mediastinal Staging
Mediastinoscopy
Video Assisted Thoracic Surgery
Anterior Mediastinotomy (Chamberlain procedure; anterior mediastinoscopy)
Endobronchial Ultrasound with Fine Needle Aspiration (EBUS-FNA)
Endoscopic Ultrasound with Fine Needle Aspiration(EUS-FNA)
Transbronchial Fine Needle Aspiration (TBNA-FNA)

Table 4: Tests utilized for invasive mediastinal staging.

Mediastinoscopy is the *gold standard* method to the invasive mediastinal staging, which the other methods should be compared [20,32,35,36].

Video assisted thoracic surgery

Video assisted thoracic surgery (VATS) is done in the surgical room, under general anesthesia, usually with discharge in one day. Its main limitation is the unilateral approach to the mediastinum. At the right side, paratracheal lymph nodes are relatively easily accessed, but left paratracheal lymph nodes are extremely difficult to be accessed by this method, due to the great vessel's anatomy. Morbidity and mortality rates are 2% and 0,09%, respectively [20,37].

Studies evaluating the videothoracoscopy's performance have shown a wide rate of sensibility, from 37% to 100%, and FN rates of approximately 15%. Specificity and FP rates are about 100% and 0%, respectively [20,32,38,39]. A interesting aspect of this method is the possibility to perform a better staging regarding the *T* descriptor, given we have the wide approach to the pleural cavity, making possible a better evaluation of pleural effusion, pleural metastatic disease, chest wall, diaphragm and vascular structures invasion [38,39].

VATS may not be used in substitution to the mediastinoscopy, but is a complementary procedure in many cases, especially when there is a left upper lobe tumor with enlarged lymph node station 5 and 6 (preaortic and aortopulmonary window) [39]. Some centers perform the videothoracoscopy in substitution to the Chamberlain procedure (as discussed below).

Anterior mediastinotomy (chamberlain procedure)

This procedure is performed in the operating room, under general anesthesia, usually with discharge at the same or the next day [20,33]. A horizontal incision is done through second left intercostal space, and the aortic arch and left pulmonary artery are identified by palpation. It is also referred as anterior mediastinoscopy, when the mediastinoscope is inserted through the incision to evaluate those lymph nodes. This procedure has been replaced by VATS (more commonly) or a robotic approach over Chamberlain procedure for stations 5 and 6 in most centers [40].

Regarding to lung cancer staging, anterior mediastinotomy is used exclusively in selected patients with left upper lobe (LUL) tumor, aiming to evaluate lymph nodes at the aortopulmonary window (station 5) and preaortic (station 6). These lymph node stations collect the lymphatic drainage from LUL. Some authors suggest that these two lymph node stations should not be viewed as mediastinal (N2) lymph nodes, because involvement of only these stations would have a better prognosis than involvement of other N2 stations [32,41]. These authors propose that these nodes (stations 5 and 6) should be faced as N1 lymph nodes; this classification is not widely accepted, but, when there is cancer spread only to these stations, usually patients have a better prognosis and, if patients are fit, there are two possible treatements: 1) neoadjuvant therapy aiming to posterior pulmonary resection intending to cure; 2) surgical resection followed by adjuvant chemotherapy.

Endobronchial ultrasound with fine needle aspiration (EBUS-FNA)

This technique is relatively recent (less than ten years in clinical

practice) and the experience with the method is growing. An ultrasound transducer is coupled to the tip of the flexible bronchoscope, which allows a mediastinal lymph node identification and fine needle aspiration in real time and under visualization through the ultrasound [42].

Accessible lymph nodes by this method are pretracheal, high and down right and left paratracheal and subcarinal, respectively stations 1, 2R, 2L, 4R, 4L and 7 [33,35,37]. As in any technique using needle aspiration, only a *cytological* evaluation can be done, and a lymph node biopsy (tissue) for *histopathological* evaluation is not possible. It may be used in substitution to mediastinoscopy, but, if the results are negative with the EBUS, the mediastinoscopy should be performed [32,35,37]. Because EBUS depends on identifying the lymph node through ultrasound guidance, the method is better performed for patients with enlarged mediastinal lymph nodes, as in tomographic Groups A and B (Figure 1), although there is no restriction to use it for normal sized lymph nodes if there is indication to IMS. Its use combined with EUS is discussed in next session. There are many false negatives with EBUS, thus, if a high index of suspicious exists, a mediastinoscopy should be performed when EBUS was negative.

Endoscopic ultrasound with fine needle aspiration (EUS-FNA)

Although routinely utilized for IMS only in few centers, given the wide availability of other methods, EUS has been subject of a growing interest to IMS, especially when performed in association with the EBUS [43-45]. EUS is performed using an ultrasound transducer coupled with the flexible esophagoscope. This device guides the needle through the esophageal wall and allows the approach of lymph nodes in pulmonary ligament, paraesophageal, subcarinal and aortopulmonary window, respectively stations 9, 8, 7 and 5 [37,45]. The risk of infection or bleeding is extremely low [46]. An experienced endoscopist is required and, similar to EBUS, enlarged lymph nodes can be more easily accessed. Additionally, EUS may be able to detect metastatic disease in sites as left adrenal gland, celiac lymph nodes and liver and also direct invasion to some mediastinal structures (T4) [20].

Combination of EBUS and EUS may allow a more complete access to all mediastinal lymph nodes, improving the sensitivity and diminishing the FN rate. The ideal procedure is when both methods are performed at the same session, with the patient under general anesthesia or sedation [47]. Some concern exists regarding the possibility of these two methods substitute the mediastinoscopy in the future [48,49], but most experts do not believe it will happen; and, probably, videomediastinoscopy will remain the gold standard for IMS.

The negativity of EUS should prompt the mediastinal evaluation by mediastinoscopy.

Transbronchial needle aspiration (TBNA)

TBNA utilizes a standard flexible bronchoscope and a needle, known as *Wang Needle* through the scope. Its main indication is to evaluate enlarged subcarinal lymph nodes (station 7) [37]. This test is not useful for mediastinal staging in the patient with normal size lymph nodes. In the patient who needs an IMS, the negativity of this test should prompt the mediastinal evaluation by other method, such as mediastinoscopy. TBNA is safe and performed in an outpatient basis.

Thoracocentesis

Although it is not a method of mediastinal invasion, thoracocentesis may add important information regarding staging of lung cancer. The presence of neoplastic cells in the fluid excludes surgical treatment, but biochemical and microbiological analysis should also be performed. Aspiration and cytological examination of pleural fluid in patients presenting with suspected malignant pleural effusion provides a diagnostic yield of approximately 60%; the addition of needle pleural biopsy may raise the possibility of detecting cancer to 75%.

The association of pleural effusion and lung cancer is not enough to exclude the patient from surgical treatment. In some cases the effusion may be a consequence of local inflammatory reaction, especially when the tumor is in contact with chest wall. In other cases, one may face a *ex-vacuum* pleural effusion; this situation happens when the patient presents with some degree of atelectasis with decrease in lung volume and a fall in intrapleural pressure, favoring the accumulation of pleural fluid. These situations corroborate the importance of establishing a correct etiologic diagnosis of pleural effusion in patients presenting or suspected of having lung cancer.

When there is no diagnosis of pleural fluid after thoracocentesis and the effusion is recurrent, one should perform a videothoracoscopy, which have a sensibility of 95% in detecting pleural metastasis (by pleural biopsy and fluid analysis), and also has the advantage of allowing to perform the pleurodesis at the same surgical procedure [50].

Special Situations

Left upper lobe tumors

Patients with left upper lobe (LUL) tumors deserve a special mention, because the lymphatic system drains preferentially to lymph nodes in the aortopulmonary window (station 5) and preaortic location (station 6). These nodes are rarely involved by tumors originating from other pulmonary lobes.

Indications to perform the IMS have the same general rules described above; thereby the routine invasive investigation must include paratracheal (stations 2 and 4, left and right) and subcarinal (station 7). If samples from these stations are negative for lymph node cancer, the approach of the stations 5 and 6 are controverse, given some papers report that these mediastinal stations would, actually, have the significance of some N1 station [19,20,32].

Our routine is to perform the investigation of stations 5 and 6 in LUL tumors when there is lymph node enlargement or PET-CT positive at these stations, and the other stations were negative for nodal involvement by the tumor. If only stations 5 and 6 (or one of them) are positive, we prefer to send the patient to neoadjuvant therapy aiming to perform a pulmonary resection after this initial treatment, but the routine to perform pulmonary resection followed by adjuvant chemotherapy is also acceptable. The approach to station 5 and 6 must be done by anterior mediastinoscopy or videothoracoscopy, and choosing between these two methods must be individualized according to each patient [20,39].

Pancoast tumors

Described by Henry Pancoast, a radiologist, in 1924 [51], only in 1932 it was recognized as a malignant neoplasm, by the Argentine surgeon called Tobias [52]. Pancoast tumors usually have an aggressive presentation at diagnosis and often invade the subclavian vessels, chest wall and brachial plexus roots. When correctly staged, the resection *en bloc* with these structures may be performed, although diffuse invasion to brachial plexus is a contraindication to surgery.

Despite this aggressive local presentation, the main determinant of the patient's eligibility to curative pulmonary resection, excluded distant metastasis, still is the mediastinal lymph node staging.

After histological diagnosis, if noninvasive staging points to the possibility of a pulmonary resection, the mediastinum must *obligatory* be invasive staged. In the absence of N2 disease the patient is usually sent for neoadjuvant therapy with chemo plus radiotherapy and, if mediastinal nodal do not advance (do not emerge N2 disease), the patient will have pulmonary resection. In the presence of N2 disease at any time, the surgery is usually contraindicated [20,32].

An interesting aspect regarding to Pancoast tumor refers to *ipsilateral supraclavicular* lymph nodes. Although subject of some controversy, these nodes, usually considered N3 disease, are staged as *peritumoral* lymph nodes in Pancoast tumor, being staged as N1 disease according to some authors [53]. This issue is somewhat controversial, and each patient should be individually evaluated regarding the general status, presence mediastinal lymph node involvement and possibility to perform a pulmonary resection.

Invasive re-staging after neoadjuvant treatment

There is much discussion regarding the better method to re-stage these patients after neoadjuvant therapy. Although is possible to perform a "re-mediastinoscopy", most groups of thoracic surgeons agree that this is a difficult and potentially dangerous procedure. An interesting option is to perform the IMS previous to neoadjuvant therapy by methods using needle aspiration (especially the combination of EBUS and EUS) and, if necessary to re-stage the mediastinum after neoadjuvant therapy, then mediastinoscopy would be the option, given there is no previous mediastinal dissection, what would make difficult, or even impossible, the "re-mediastinoscopy". After neoadjuvant therapy, regarding to mediastinal lymph nodes, we may have three situations: 1 - if previous IMS was positive, it is obligatory to repeat it, more commonly with the mediastinoscopy; 2 - if previous IMS was negative and the new CT and PET-CT show neither enlargement nor augmentation in the SUV when compared to the CT and PET-CT performed before the neoadjuvant therapy, it is not necessary to repeat the IMS; 3 - if previous IMS was negative, but the new CT and PET-CT reveal mediastinal node enlargement and/or augmentation in SUV comparing to the CT and PET-CT performed before the neoadjuvant therapy, the IMS must be performed again, usually by mediastinoscopy. Finally, after neoadjuvant therapy, if N2 or N3 disease is detected in this second IMS, the patient will not benefit from surgical resection; if there is no N2 or N3 disease, the patient should have a pulmonary resection.

Conclusion

Lung cancer staging must have a simple and logical sequence. The only possible method to cure this neoplasm is by surgical resection, therefore a correct staging should be offered to every patient facing this disease. The most important point when evaluating a patient suspected of having lung cancer, refers to the oncological status of mediastinal lymph nodes, and its evaluation, by means of radiological examinations or invasive procedures, is the critical part for every patient.

Every patient should start the investigation with a chest radiograph and chest CT with intravenous contrast. After this initial evaluation, the mediastinal evaluation should be complemented based on the size of mediastinal lymph nodes, the location and size of the lung lesion. Recently, PET-CT has been added to the investigation of every patient who is a potential candidate for pulmonary surgical resection, and its limitation in a patient with lung cancer is in the evaluation of the brain (MRI should be performed if there is suspicion of cerebral metastasis) and structures measuring less than 8mm (especially mediastinal lymph nodes).

Finally, the patient who is suspected of having lung cancer must be evaluated by a multidisciplinary team, involving, at least, the pulmonologist, general physician, thoracic surgeon and physical therapist. A detailed preoperative workup is essential to choose the most appropriate therapeutic plan to each patient, with best results regarding to possible cure, improvement of quality of life, rational use of medical resources and less morbidity and mortality.

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