NON-SURGICAL PROCEDURES FOR LUNG CANCER STAGING

M.H. Reyes Cotes, J.M. Sánchez Nieto.

Departamento de Neumología. Hospital Morales Meseguer. Murcia.

Abstract

Summary: Nonsurgical staging in lung cancer. The study of lung cancer requires a correct staging to optimize the treatment and to establish a disease prognosis, following the recommendations of the latest edition of the International Association for the Study of Lung Cancer (IASLC 7ºth ed.) with a stepwise diagnostic approach to avoid additional risks.

Key words: Lung cancer, staging, echoendoscopy.

PROCEDIMIENTOS DE ESTADIFICACIÓN NO QUIRÚRGICOS EN EL CÁNCER DE PULMÓN

Resumen

El estudio del cáncer de pulmón precisa de una correcta estadificación para optimizar la terapéutica y establecer pronósticos, siguiendo las recomendaciones de la última edición de la Asociación Internacional para el Estudio del Cáncer de Pulmón (IASL 7ºth ed.), con un abordaje diagnóstico escalonado con el fin de evitar riesgos añadidos.

Palabras clave: Cáncer de pulmón, estadificación, ecoendoscopia.

INTRODUCTION

Given the relevance of lung cancer and the natural course it entails, achieving correct staging is fundamental for appropriate management and treatment of the disease, whether it be surgical, medical or radiotherapeutic.The first step in staging is using non-invasive methods (clinical and imaging tests) which allow for the identification of affected areas, both locally and remotely.In most cases diagnostic confirmation will be necessary, collecting cytohistological samples through invasive methods according to a staggered approach as necessary.Selection of the type of test will be made according to doctor criteria and the patient's clinical presentation.

The different types of non-surgical procedures currently done for lung cancer staging are presented below, according to recommendations from the International Association for the Study of Lung Cancer published in its 7th edition (IASLC 7th ed. 2009)[1] and other more recent recommendations awaiting publication in the IASLC 8th ed.expected this year[2].

Received: February 27, 2016. Accepted: October 30, 2016.

Miguel Henrique Reyes Cotes
doctormiguelreyes@gmail.com

NON-INVASIVE STAGING PROCEDURES

Clinical: approximately 10% of lung cancer patients do not present symptoms at the time of diagnosis; the disease is detected through a routine chest x-ray[3]. The rest of patients present a clinical variable according to location, extent and the type of tumor.A correct medical history and physical examination must be done in order to collect data at an early stage and thus optimize time and resources to study it.The most common clinical findings were cough (50-75%), hemoptysis (30-50%) and constitutional syndrome (30%)[4, 5].There are clinical scales which provide guidance regarding the patient's general state including the Karnofsky Performance Scale Index which starts at an optimal level, 100% (asymptomatic patient), and decreases according to clinical severity (ex: 10% for a dying patient, 0% for a deceased patient).Another useful scale is the E.C.O.G. (East Cooperative Oncology Group) which ranges from grade 0 (asymptomatic patient) to grade 4 (permanently disabled or terminal patient), the latter scarcely undergoing palliative measures, for whom clinical diagnosis based on non-invasive measures and sputum cytology to confirm the diagnosis are proposed.The latter has a sensitivity (Sn) of around 66% (R: 43-97%) and a specificity (Sp) of 99% (R: 68-100%)[6].

Imaging tests: a chest x-ray is the most frequently used radiological technique in thoracic studies and should be indicated from two views: posteroanterior and lateral.The presence of a tumor (T) can be discoveredby its location (single or multiple, central or peripheral) and its effects (atelectasis, consolidation, elevated diaphragm, pleural effusion, bone titration), although this is limited to nodules larger than 7mm in diameter[7]. Lymph node assessment (N) is problematic and suspected in cases of mediastinal and/or hilar widening.Due to the low sensitivity of a chest x-ray, additional study with other imaging tests such as chest computed tomography (CT) is recommended to identify adenopathy and for the morphological characterization ofpulmonary nodules.

Chest CT: the use of thin-slice CT (high-resolution or helical) is recommended, which includes upper abdominal slices.The use of intravenous contrast is recommended (although this would in theory make it a minimally invasive test), which would serve to distinguish the lymphatic ganglion structures of the vessels. Currently, iodinated contrast (I-131) is the most commonly used.CT provides us with information about the characteristics, the size and density of the tumor (speculation, ground glass opacity, calcification); the degree of parenchymal spread; additional nodules or "satellites"; and invasion of mediastinal, pleural and chest wall structures.Additionally, it can assess the presence of metastasis (M) at the abdominal (liver and adrenal glands) and bone level.An abnormal lymphatic ganglion (adenopathy) is defined as one which has a diameter greater or equal to 1cm on a short axis[2]. It is estimated that 40% of mediastinal adenopathies suggesting malignancy according to CT are benign and that 20% of the supposedly benign adenopathies are indeed not[8]. For this reason, lymph node staging should not be based solely on CT results given its low sensitivity and specificity (Table 1), thus cytohistological confirmation is recommended.Upper abdominal slices will help to identify hepatic lesions, where the majority will be benign cysts and hemangiomas. CT and magnetic resonance imaging (MRI) with contrast and/or ultrasound will be useful to study stages.A percutaneous biopsy will be done when diagnostic certainty is required to establish a diagnosis. Additionally, CT will help to evaluate the adrenal glands. The criteria for benignity (adenoma) are: size (lesions larger than 3cm are more likely to be metastatic, but benign disease is still possible), well-defined contours, low attenuation (fat density) <10 Hounsfield Units with simple CT (Sn 71%, Sp 98%)[2]. Thus, if criteria for benignity are met, follow-up may be chosen (simple CT, IV contrast or MR-IV gadolinium will be used for limited fat content).If a single metastasis is suspected, we will consider a PET/CT (Sn 97%, Sp 91%)[2] or a percutaneous adrenal biopsy, which is a relatively safe and efficient means of obtaining a diagnosis in borderline cases.When the results are indeterminate, the test should be repeated or an adrenalectomy should be considered for a curative diagnosis.

Positron emission tomography (PET): a nuclear imaging study which uses the physioanatomical traces of protons given off by low molecular weight isotopes, which translates to metabolic activity.For neoplastic studies of the lung, the most frequently used radioisotope is fluorodeoxyglucose (FDG), synthesized with radioactive fluorine (18F), a comparable D-glucose, which is phosphorylated after cell intake, accumulating intracellularly rather than being metabolized.As cancerous

lung cells have a higher glycolytic rate and overexpress glucose transporters, there is a preferential accumulation of FDG in the main tumor and potentially metastatic lesions.The criteria for an abnormal PET scan is either a standardized uptake value (SUVmax) of more than 2.5 or uptake in the lesion which is greater than the background mediastinal activity 8.9 (keeping in mind that the heart and brain uptake a great deal of FDG). PET scans are not convenient to assess malignant lesions smaller than 1.0 cm in diameter[9]. On the other hand, the combination of CT and PET offers higher diagnostic precision than doing either of the scans separately (Table 1), which supports their use for pulmonary neoplasm staging. PET scans can show distant metastatic disease in the bones, the liver and the adrenal glands which are not detected with CT (11%)[10]. If the PET mediastinal evaluation result is negative, it is considered acceptable to proceed to treatment without prior invasive tests, except in the following situations[8]:

a) centrally-located tumors, frequently in contact with the mediastinum
b) tumors with low metabolic activity
c) apparent N1 involvement
d) when the chest CT detects ganglia whose shortest axis is > 15 mm, whose probability of malignancy (N2) is 21%[8,10]

Given their elevated sensitivity, when available, a PET or PET/CT scan should be done on patients who will potentially benefit from treatment in order to detect hidden distant metastases (Stage I 8%, III 24%)[8], thus avoiding unnecessary thoracotomies and improving the treatment plan. We must keep in mind that in the case of a positive mediastinal PET result, continuing with lymph node evaluation or possible resection mustn't be rejected, given the possibility of obtaining false positives (inflammatory or infectious lesions).PET/CT FDG-18 has proven superior (Sn 92%, Sp 98%) to bone scans with technetium 99MDP (Sn 86%, Sp 88%)[2] in the study of bone metastasis, in addition to the fact that the latter is not able to recognize bone marrow infiltration in the early stages.For these reasons, bone scans are no longer used in the study of lung cancer metastases to bone.In general, unless there is clinical and overwhelming imaging test evidence, image findings suggesting metastasis, especially regarding a single lesion with hyperuptake, should not exclude patients from potentially curative treatments until malignancy is confirmed with a cytohistological sample.Other uses for PET/CT include: marking the area to irradiate (complementary cases of external radiotherapy, radiofrequency (SBRT), and/or local brachytherapy), atelectasis of questionable origin (Figure 1) and iodinated contrast allergy[11].

Magnetic resonance: its use is limited by its scarce availability as well as having a limited diagnostic value without the additional data of the chest CT, except in the case of superior sulcus tumors, given its superiority in evaluating vessel, brachial plexus and medullary cavity infiltration, with diagnostic accuracy that can reach 94% compared to the 63% of CT[8]. Additionally, it is useful in assessing cerebral, liver and adrenal metastasis. With regard to the diagnosis of cerebral metastasis, a head CT or magnetic resonance imaging (MRI) scan must be done if there are any symptoms or suspicious neurological signs, as well as in asymptomatic Stage III patients for whom the possibility of radical treatment is being considered (surgery or thoracic radiation therapy)[8].Dynamic MRI has been proposed to differentiate visceral pleural invasion from parietal pleural invasion with a sensitivity of 100% and a specificity of 70%[2].

Thoracic ultrasound: its importance stems from its low cost, the fact it doesn't give off radiation, and the ease with which it can be moved and used.It can be used to evaluate the presence of pleural effusion which, if confirmed, will require cytology at the very least to classify it as metastatic effusion (M1a), according to the most recent classification (7th IASLC). Additionally, thickening of the pleura (if >1cm) or diaphragm (>0.7cm) and the pleural nodules can be identified, the presence of which is highly suggestive of a malignant disease[12]. Finally, the thoracic wall and supraclavicular and axillary adenopathies can be evaluated.

Table 1. Diagnostic yield of non-surgical tests in lung cancer staging

PROCEDURE	Sn%	Sp%	NPV	PPV	ACCU-RACY	PREVA-LENCE
Mediastinum evaluation:						
Non-invasive:						
CT	47-54	84-88	47-96	30-95	63-83	28
PET	50-89	77-90	50-100	43-100	69-89	29
PET/CT	47-89	60-100	85-99	37.5-100	62-93	52
Invasive, non-surgical:						
Blind TBNA	79-95	99	-	-	-	75
EBUS with linear FNA	79-95	99-100	86.99	100	97-98	53.2
EUS	86	96-98	73-83	97-99	-	61
Extrathoracic metastasis evaluation:						
CT	18	98	89	71	88	-
PET	50-79	75-100	89	75	89	-
PET/CT	92	98	98	89	97	-
EUS	85-93	100	-	-	97-99	-
Mediastinal restaging.Yield						
CT	59	62	53	66	60	-
PET	71	69	64	75	70	-
PET/CT	77	92	75	93	83	-
EBUS-FNA	75-77	100	18-22	100	-	76-79

Taken and adapted from J. Sánchez de Cos et al / ArchBronconeumol. 2011;47(9):458

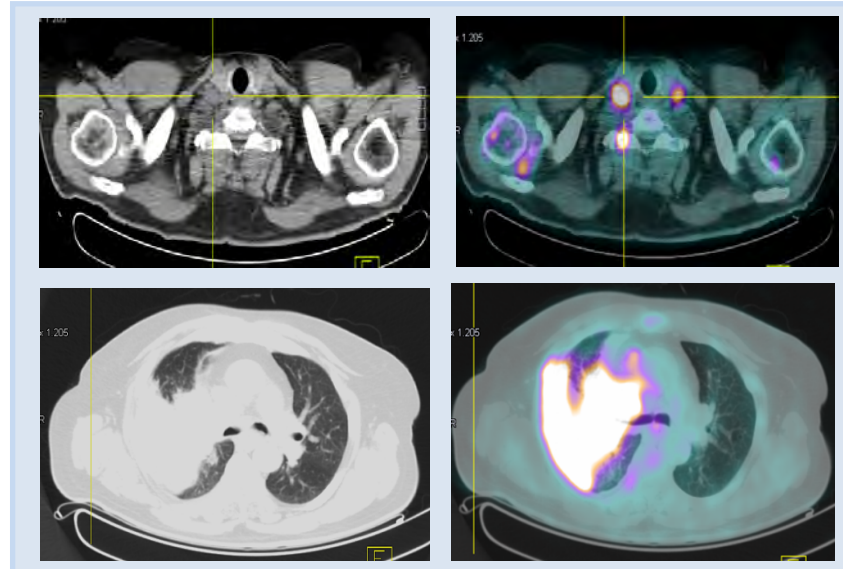


Figure 1. Image comparison of chest CT (left) and PET/CT (right) allowing the definition of hyperuptake areas (adenopathy and infiltrating tumor masses). Images provided by Dr. Renato Salguero, Oncology, Hospital Morales Meseguer. Murcia.

NON-SURGICAL INVASIVE STAGING PROCEDURES

This section includes exploratory procedures which involve tissue disruption (ex: punctures) or entering the organism through a natural orifice (endoscopy), with the aim of examination and collecting samples for cytohistological analysis (without requiring surgery).These include:

Endoscopic examination: this allows us to obtain samples using fine needle aspiration (FNA) through bronchoscopy and/or esophagoscopy (see yield in Table 1).

Bronchoscopy: considered highly useful, both for the diagnosis and staging of lung cancer, as lesions at the endobronchial level can be seen. It allows samples to be collected through bronchial suction, bronchial brushing, and bronchial and transbronchial biopsies whether they be blind, use radioscopy or include the new use of electromagnetic navigation (automa-

tic or manual).Additionally, it plays a fundamental role in determining lymph node involvement (N), obtaining samples through FNA in two ways: blind or ultrasound-guided (EBUS). The upper station mediastinal lymph nodes (2, 3p, 4), subcarinal nodes (7) and intrapulmonary hiliar (10) and lobar (11) nodes can be accessed.The importance of having an experienced cytopathologist when undergoing testing has been proven.With their help, an adequate lymph node sample can be taken, identifying the satisfactory samples (presence of lymphocytes, atypical cells) and avoiding more invasive procedures such as mediastinoscopy, mediastinotomy and thoracotomy.The standard method of mediastinal lymph node study is based on blind transbronchial FNA (also called TBNA).To complete the procedure, a prior chest CT (and PET scan according to availability) is recommended, which will guide us to the most involved lymph node group in order to take samples.Time management is essential for various reasons (patient comfort, safety, sedation).A plateau in malignancy yield has been proven to be achieved after seven TBNA procedures[13].

Echobronchoscopy (EBUS): a relatively safe procedure which can be done on an outpatient basis to collect samples from mediastinal and hiliar lesions.It is recommended:

1) to explore and biopsy all lymph nodes that were suspicious in the PET/CT scan, sequentially dismissing N3, N2 and N1 by their therapeutic implications.
2) to examine the N3 lymph node stations in all cases with a radical curative aim and to biopsy lymph nodes ≥5mm in diameter.

In the case of adenopathy detected by CT or PET scan, as well as when immediate cytopathological diagnosis is available, the Sn of the test increases to values of 94% and 97%, respectively.In the absence of an onsite pathologist, the diagnostic yield is based on the number of FNA procedures done for each lymph node station. Diagnostic yield does not increase when more than 3 procedures are done (1st procedure Sn: 69.8%, NPV: 86.5%; 2nd procedureSn: 83.7 NPV: 92.2%; and 3rd procedure Sn: 95.3%, NPV: 97.6%)[8, 14]. The ultrasound image allows us to differentiate the lymph nodes suggesting malignancy from those suggesting benignity (Figure 2)[15]. Collecting lymph node samples using EBUS can avoid between 30 and 56% of mediastinoscopies[8, 16]. An EBUS result is considered negative when there is no evidence of malignancy after 3 biopsies with the presence of perioperative lymphocytes.At the same time, if the sample is contaminated, necrotic, insufficient or contains blood, it would be considered indeterminate and a negative result for malignant cells would have to be confirmed with surgical techniques (Figure 3).

Esophagoscopy: a transesophageal FNA is normally done guided by ultrasound (EUS), allowing us to reach the lower left paratracheal stations (4L) and other areas that are not accessible through EBUS such as the subaortic (5), paraesophageal (8) and pulmonary ligament (9) stations.It is also possible to access the 7, 4R, 2R and 2L mediastinal regions. EUS-FNA also allows us to detect left-hand pleural effusions, subdiaphragmatic metastases (left adrenal gland, celiac artery and liver lymph nodes, the left lobe and part of the right lobe) and evaluate the presence of mediastinal invasion of the tumor (T4) much more accurately than radiological techniques (Sn: 98%, Sp: 98%, FN: 1%, and FP: 30%)[8]. It reduces the number of unnecessary thoracotomies from 25% to 9%[8, 16]. The combined use of EBUS and EUS allows access to all of the mediastinal lymph node stations, except region 6, with efficacy that is no less than the gold standard (mediastinoscopy)[17]. The Sn for this combination (EBUS + EUS) is 93%, with a NPV of 97%[8].

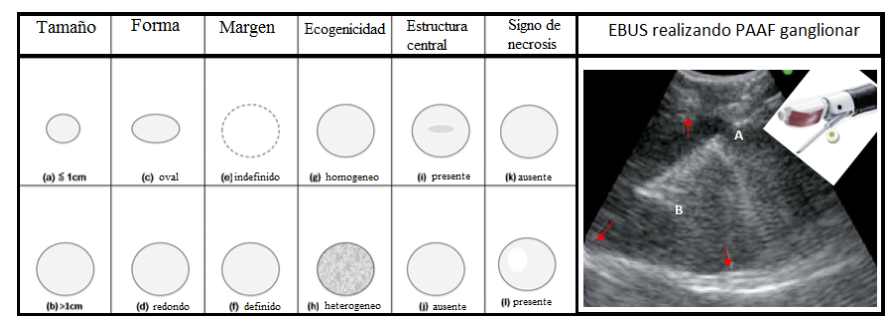
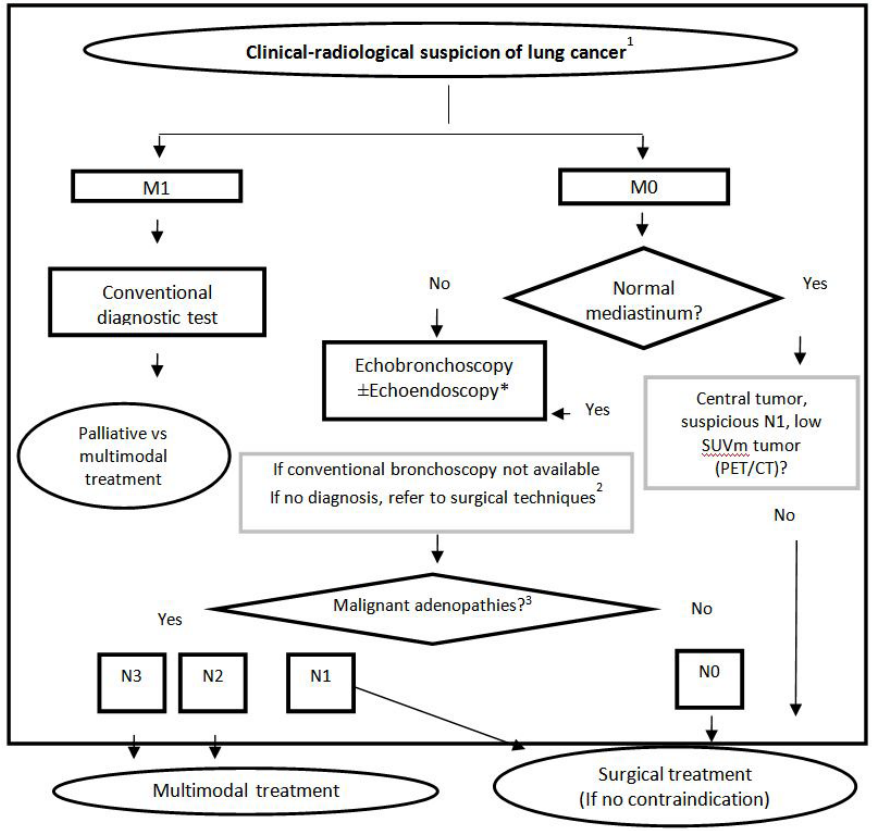


Figure 2. Echoendoscopic characteristics of the lymphatic ganglion. Taken and adapted from *Jujiwara et al. CHEST 2010; 138(3):643*. Note: The data in the lower line is indicative of malignancy. On the right, EBUS and echoendoscopic image with FNA (A) of adenopathy with malignant characteristics, note the distal end of the needle (B) and the edges of the adenopathy (arrows).

Figure 3: Diagnostic algorithm for lung cancer staging



Taken and edited from J. Sánchez de Cos et al / ArchBronconeumol. 2011;47(9):461. Observations: [1] Cranial study for patients with neurological focality and/or candidates for radical Stage III treatment. [2] Surgical techniques include simple and/or extended cervicalmediastinoscopy,thoracoscopy, mediastinal lymphadenectomy: transcervical extended (TEMLA) and video-assisted (VAMLA). *EBUS combined with EUS, if available, or EBUS alone[8,21]. **TBNA adenopathy transbronchial needle aspiration. A limit of 1cm for mediastinal lymph nodes is traditionally used.If a PET scan is available, the lower limit will be 1.5cm if there is no hyperuptake.

TRANSTHORACIC BIOPSIES

Thoracentesis: cytology of the pleural liquid will accurately confirm the presence of atypical cells, thus proving there is a metastatic effusion (M1a, IASLC7th ed.) with Sn 72% (R: 49-91%) after at least 2 serialized cytologies[12,18]. A pleural effusion should not be assumed to be metastatic until there is cytohistological confirmation, as it may be a paraneoplastic effusion (transudate or exudate) or a parapneumonic effusion (exudate).Tumor markers have poor specificity.

Pleural biopsy: a closed pleural biopsy has lower efficacy than a diagnostic thoracentesis, with a Sn around 50%, but higher in cases with a low pH and low glucose (indicative of advanced disease)[18]. Success depends on pleural area, the number of samples taken and the experience of the person taking the sample.This procedure is recommended in cases when the first cytology is not diagnostic and the effusion has not been identified[19].Even then, only 7-12% of patients with negative cytology who actually have a malignant effusion are diagnosed exclusively with this technique. A CT-guided pleural biopsy has an efficacy of 85%[18] and medical thoracoscopy with pleural biopsy has a sensitivity of around 97%[19].

Image guided lung biopsy: this consists of taking a sample at the thoracic level. In many cases, it is chosen for peripheral lesions. In general it is guided by real-time computed tomography. Two techniques can be included under this name: on one hand, fine needle aspiration (FNA), which has a diameter of less than 20G and, on the other, core needle biopsy (CNB) with a diameter larger than 20G.CT-guided CNB is the most effective. It has a specificity of approximately 90% and a risk of pneumothorax of 12-30%, of which only 3-15% require a chest tube to be inserted[20]. This risk is elevated in patients with emphysema and bullas.There is also a risk of bleeding, which is generally self-limited, although there is a higher risk in patients with pulmonary hypertension.

CONCLUSION

For patients diagnosed with or suspected of suffering from lung cancer, clinical assessment continues to be the first step in obtaining information about their status and proceeding to optimize the therapeutic diagnostic approach

which will have phases.The 8th edition of the IASLC TNM Classification for Lung Cancer is expected to be published by the end of the year.The published proposals call for changes to T and M22, maintaining the approach to study for now.PET/CT is considered the imaging test with the highest diagnostic value.The combination of EBUS + EUS is ideal for the study of mediastinal adenopathy, as it allows us to obtain lymph node material guided by a real-time ultrasound and, in indeterminate cases, it will lead to surgical methods.

BIBLIOGRAPHY

1.- Goldstraw, P. IASLC staging manual in thoracic oncology. 1st ed. Orange Park (FL). Rx Press; 2009.

2.- De Groot PM, Carter BW, Betancourt Cuellar SL et al. Staging of lung cancer". Clin Chest Med 2015; 36 (2): 179-196.

3.- Kocher F, Lunger F, Seeber A et al. Incidental diagnosis of asymptomatic non-small-cell lung cancer: A registry-based analysis. Clin Lung Cancer 2016; 17 (1): 62-7.

4.- Thomas KW, Gould MK, Jett JR et al. Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer. Literature review. Uptodate; 2015 [acceso 03 de noviembre de 2015]. Disponible en: http://www.uptodate.com.

5.- Álvarez-Sala Walther JL, Casan Clara P, Rodríguez de Castro F et al. Neumología Clínica. Elsevier; España 2010: 466-494.

6.- Rivera MP, Mehta AC: Initial diagnosis of lung cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd ed). Chest 2007; 132 (Suppl 3): 131S–148S.

7.- Ketai L, Malby M, Jordan K et al. Small nodules detected on chest radiography: does size predict calcification? Chest 2000; 118 (3): 610-4.

8.- Sánchez de Cos J, Hernández JH, López MF et al. Normativa SEPAR sobre estadificación del cáncer de pulmón. Arch Bronconeumol. 2011; 47 (9): 454-65.

9.- Sobin LH, Gospodarowicz MK, Wittekind C. International Union Against Cancer: TNM Classification of Malig¬nant Tumours, 7º ed. Oxford, UK. Wiley-Blackwell, 2009.

10.- De Langen AJ, Raijmakers P, Riphagen I et al. The size of mediastinal lymph nodes and its relation with metastatic involvement: a metaanalysis. Eur J Cardiothorac Surg 2006; 29: 26–9.

11.- Silvestri GA, Gonzalez AV, Jantz MA et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143 (Suppl 5): e211S–50S.

12.- Qureshi NR, Rahman NM, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. Thorax 2009; 64: 139–143.

13.- Chin R, McCain TW, Lucia MA et al: Transbronchial needle aspiration in diagnosing and staging lung cancer. Am J Respir Crit Care Med 2002; 166: 377–381.

14.- Lee HS, Lee GK, Lee HS et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest 2008; 134: 368–74.

15.- Fujiwara, T, Yasufuku K, Nakajima T et al. The utility of sonographic features during endobronchial ultrasound-guided transbronchial needle aspiration for lymph node staging in patients with lung cancer; a standard endobronchial ultrasound image classification system. Chest 2010; 138 (3): 641-647.

16.- Larsen SS, Vilmann P, Krasnik M et al. Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised trial. Lung Cancer 2005; 49: 377–85.

17.- Berania I, Kazakov J, Khereba M et al. Endoscopic Mediastinal Staging in Lung Cancer is Superior to "Gold Standard" Surgical Staging. Ann Thorac Surg. 2016; 101 (2): 547-50.

18.- Villena-Garrido V, Cases-Viedma E, Porcel-Pérez JM et al, Normativa SEPAR. Diagnóstico y tratamiento del derrame pleural. Arch bronconeumol 2014; 50 (6): 235-249.

19.- Jiménez HL, Bravo JB, Zapatero G. Diagnóstico y manejo del derrame pleural maligno. Rev Patol Respir 2007; 10(3): 140-145.

20.- Donado JR, Paz-Ares L, Bartolomé A et. al. OncoSur. Diagnóstico y tratamiento Cáncer de Pulmón. Fundación Médica Mutua Madrileña 2007; 1-49. Disponible en: http://www.seom.org/seomcms/images/stories/recursos/sociosyprofs/colectivos/grupocooperativo/2006/oncosur/guia_clinica_oncosur_cancerpulmon.pdf.

21.- Vilmann P, Clementsen PF, Colella S et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015; 47: 545–559.

22.- Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorarc Oncol. 2016; 11 (1): 39-51.