# ARCHIVOS DE BRONCONEUMOLOGIA

Original Article

# Usefulness of a Lung Cancer Rapid Diagnosis Specialist Clinic. Contribution of Ultrasound Bronchoscopy

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## ARTICLE INFO

## ABSTRACT

*Objective:* To analyse the results obtained in the diagnosis and staging of lung cancer (LC) by a Lung Cancer Rapid Diagnosis Unit (LC-RDU) in which real-time endobronchial ultrasound-guided transbronchial needle aspiration (RT-EBUS guided-TBNA) is performed as part of the clinical evaluation of the patient prior to treatment.

*Method:* A four year observational study was conducted on a group of patients evaluated due to suspicion of LC in an LC-RDU. The times and the techniques required for the diagnosis, the treatment period and the level of the disease in the initial staging were recorded.

*Results:* Out of a total of 678 patients seen in the LC-RDU, the diagnosis in 352 was confirmed in one or more histopathology tests. In 170 patients (48.2%) the diagnosis was made with biopsies and/ or cytology samples obtained by fibrobronchoscopy, and RT-EBUS guided-TBNA confirmed the clinical suspicion in 70 patients (19.9%). In the 280 patients with NSCLC, 166 RT-EBUS guided-TBNA were performed for staging (59.3%), and in 105 of them the technique only showed local disease (37.5%). Eighty-three of these patients underwent therapeutic surgery, which was radical in 73 cases (87.9%).

*Conclusion:* In half of the patients referred to the LC-RDU due to suspected LC, the diagnosis was confirmed in 75% of cases using endoscopic techniques. RT-EBUS guided-TBNA, which was the diagnostic technique in 20% of the cases and for staging in more than half of them, led to reduced waiting times to diagnosis and onset to treatment.

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### Utilidad de una consulta monográfica de diagnóstico rápido de cáncer de pulmón. Aportaciones de la ecobroncoscopia

RESUMEN

*Objetivo:* Analizar los resultados conseguidos en diagnóstico y estadificación del cáncer de pulmón (CP) por una unidad de diagnóstico rápido de cáncer de tórax (UDR-CT) que incorpora la ultrasonografía endobronquial con punción transbronquial aspirativa en tiempo real (USEB-PTBA-tr) a la evaluación clínica del paciente previa al tratamiento.

*Método:* Se ha realizado un estudio observacional del conjunto de pacientes valorados por sospecha diagnóstica de CP en una UDR-CT durante cuatro años, registrando los tiempos y la técnica requeridos para el diagnóstico, el tiempo para el tratamiento, y el grado de identificación de enfermedad en estadio inicial.

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*Resultados:* Seiscientos setenta y ocho pacientes fueron atendidos en la UDR-CT, en 352 casos el diagnóstico fue confirmado en una o más muestras anatomopatológicas. En 170 pacientes el diagnóstico se obtuvo con biopsias y/o citologías obtenidas por fibrobroncoscopia (48,2%), la USEB-TTBA-rt confirmó la sospecha clínica en 70 pacientes (19,9%). En 280 pacientes afectos de carcinoma de pulmón no célula pequeña (CPNCP) se practicaron 166 USEB-PRBA-tr de estadificación (59,3%) y en 105 de ellos la técnica mostró únicamente enfermedad local (37,5%). En 83 de estos pacientes se procedió a cirugía terapéutica, que fue radical en 73 casos (87,9%).

*Conclusión:* En la mitad de pacientes remitidos a la UDR-CT por sospecha de CP el diagnóstico se confirma, por técnicas endoscópicas en tres cuartas partes de los casos. La USEB-TTBA-rt es la técnica diagnóstica en una quinta parte de los casos y de estadificación en más de la mitad de ellos, y permite reducir los tiempos de espera hasta el diagnóstico y el inicio de tratamiento.

## Introduction

In the European Union, lung cancer (LC) is the main cause of death due to neoplastic disease among men, and the third highest in women. The incidence of the disease depends on historical patterns of smoking in the region and, in the West, is approximately 50 new cases per 100 000 inhabitants, with a somewhat lower figure in women. The mortality rate for LC is very high, with survival at 5 years after diagnosis below 10% in most parts of the world, depending on the staging of the disease at the moment of diagnosis.[1] The survival rate at 5 years is over 80% when the diagnosis is made within a screening programme and there are no respiratory symptoms, and is around 60% in patients that visit a doctor due to the appearance of symptoms compatible with LC when the disease is still only in stage I.[1] Mediastinal involvement, typical of stage III LC, results in a slightly worse prognosis, with survival below 30% at 5 years after the diagnosis.[1]

In recent years, the hospitals within the public health system have introduced targeted rapid diagnosis units into their health services that are focused on diagnosing neoplastic diseases, as an alternative to hospitalisation,[2] with the objective of reducing the length of time before diagnosis and staging of the disease, thus facilitating early treatment. When symptoms appear that lead to the patient consulting the doctor and establishing a suspected diagnosis of LC, early referral to an appropriate specialist has been shown to have a positive effect on survival when LC is still in the early stages, allowing doctors to proceed with the diagnosis and staging of the disease.[3] Therefore, the creation of rapid diagnostic units for lung cancer (LC-RDU) can improve the prognosis of the disease by favoring early detection, and at the same time, decrease the anxiety associated with inaccurate diagnosis of a potentially severe disease.[4]

The objective of this study is to analyze the results obtained in the diagnosis and staging of LC by an LC-RDU and the contribution of a real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-guided TBNA) to this process, evaluating the delay until diagnosis in number of days, the technique that allowed diagnosis, the preoperative procedure used for staging the disease, and the percentage of LC cases identified in the potentially curable stage I.

## Design and Methods

### Population

We performed an observational study on all patients evaluated due to suspected diagnosis of LC in the LC-RDU at a Barcelonés Nord Hospital during the 4-year period from October 2005 to September 2009. The patients were referred to the LC-RDU by different local health centers for which the unit acts as a referral centre, with a total population of 210,000 people seen. All patients, who had been referred from other primary or specialized outpatient clinics and emergency rooms, were examined in the LC-RDU if there was radiological/clinical suspicion of LC and when their state of health allowed for a diagnostic study to be performed at an outpatient clinic. The LC-RDU has a nursing staff and is attended by three pneumologists that combine this health care with respiratory endoscopies at the centre. The first clinical exam in the LC-RDU was followed by other tests under a preferential programme that included hemogram, clotting tests, renal and liver function tests, chest x-rays and computed tomography (CT), diagnostic fiberoptic bronchoscopy, lung function tests, and exploratory thoracocentesis in patients with pleural effusion. When the fiberoptic bronchoscopy did not lead to a diagnosis, CT-guided transthoracic needle aspirations were performed, as well as extrathoracic punctures (needle aspirations of the peripheral ganglia, bone lesions, or other organs in cases where imaging tests indicated distant involvement), EBUS, and surgery for diagnostic samples. In patients diagnosed with non-small cell lung carcinoma (NSCLC), the TNM[5] staging was established using clinical and radiological criteria (chest CT and/or positron emission tomography) when the histopathologic staging of the mediastinum was not considered as well defined due to the evidence of distant metastasis or when there were contraindications for invasive examinations. In other cases, staging of the ganglia was performed using EBUS or a mediastinoscopy (when lymph nodes were suspected of being inaccessible by EBUS). All patients gave informed consent to the diagnostic and staging study, which was approved by the center's ethics committee.

### Measurements

The clinical information compiled for each patient included demographic data, smoking habits, radiologic and endoscopic data on the disease, and the final diagnosis of the patient. Patients were considered to be non-smokers when they had been active smokers for less than 1 year and consumption was less than 1 cigarette per day, and ex-smokers when they had ceased smoking at least 12 months earlier. In all cases, a CT scan of the chest and upper half of the abdomen was performed using a multidetector scanner (Marconi M8000, Phillips®, Best, Netherlands). Lymph nodes were considered to be enlarged when their smallest diameter was >10 mm.

In patients with histopathologically confirmed neoplasia, the diagnostic technique was recorded along with the histological type of the disease. In these patients, the original health centre from which the patient was referred was determined, and we recorded the time between the family doctor requesting an appointment with a specialist and the appointment date, the days between this visit and the definitive histopathological diagnosis, and the time between the diagnosis and treatment (surgery, chemotherapy, radiation therapy, or palliative care). In patients diagnosed with NSCLC, we determined the preoperative TNM stage,[5] and the postoperative

stage in stage I/II patients treated with surgery.[6] In patients in whom comorbidity or age contraindicated invasive complementary tests in order to achieve a decisive histopathological diagnosis, this was established using clinical and radiological criteria, and its tabulation was ruled out in further analyses.

Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-guided TBNA)

In the patients in which a RT-EBUS-guided TBNA was indicated for obtaining a diagnosis or for tumor staging, this was performed under local anesthesia with lidocaine and sedation with midazolam, in accordance with the published recommendations for this procedure.[7] They used a sectoral echo-bronchoscope equipped with a distal transducer obtaining mediastinal images (BF-UC160-F, Olympus® Optical Co. Ltd. Tokyo, Japan) and a channel allowing for TBNA of the masses and lymph nodes under direct visual control. Mediastinal lymph nodes (right and left paratracheal, subcarinal) and lobar lymph nodes were examined and the diameter of each was recorded (EU-C60, Olympus® Optical Co Ltd.). Those with a diameter equal to or greater than 5 mm were punctured under direct visual control,[8] using a cytological needle specifically designed for this purpose (NA2015X-4022, Olympus® Optical Co. Ltd.), and the samples obtained were examined before surgery in the cytology unit. They were labelled as normal nodes when only lymphocytes were present and as metastatic nodes when groups of neoplastic cells were found. The aspirates with only bronchial cells or erythrocytes or insufficient material were considered unsatisfactory and, in these cases, the procedure was repeated a maximum of 3 times. The specificity and positive predictive value of the procedure is considered to be near 100%, based on previously published studies.[9]

*Statistical Analysis*

For the descriptive statistical analysis of the data we used the SPSS statistical software package version 15 (Chicago, Illinois, USA). We expressed the categorical variables as absolute and relative frequencies, the continuous variables as a mean (SD) when they had a normal distribution, and as median and interquartile range (IQR) when they did not.

First, we tabulated all clinical characteristics of patients with a final diagnosis of neoplasia. We then determined their origin, the time lapse between the request for a consultation and the first consultation to the LC-RDU, and the time required for the diagnosis. We compared the time required for diagnosis by the procedure used for histopathologic confirmation, using patients who had been diagnosed by fiberoptic bronchoscopy as reference values (chi-squared test). The time to diagnosis was also compared by stage of the tumor (chi-squared test) in patients with a final diagnosis of NSCLC. Lastly, in patients with this diagnosis, we tabulated the preoperative stage of the tumor and the technique used to establish this value. In those patients who underwent surgery, a systematic lymph-node dissection was performed,[6] and the postoperative TNM stage was determined. We considered differences to be statistically significant for $P \leq .05$.

## Results

A total of 678 patients were attended in the LC-RDU and in 371 cases (54.7%), a final diagnosis of neoplasia was confirmed. In 19 cases in which the diagnostic tests for obtaining samples were contraindicated, the diagnosis was made based only on clinical and radiologic criteria (5.1%). In 352 patients, the diagnosis was based on one or more confirming histopathological samples, three-quarters of which were obtained by endoscopic techniques. In half of the patients with histopathologic diagnosis, this was obtained by fiberoptic bronchoscopy, using biopsy and/or cytology samples. The EBUS-guided TBNA was also an essential endoscopic technique for

diagnosis, as its use confirmed the clinical suspicion of LC in almost one-fifth of diagnosed patients, in which diagnostic fiberoptic bronchoscopy and other procedures had not produced any definitive results. It was far more useful than the rest of the sampling procedures used (Table 1).

The proportion of patients with chest neoplasia referred to the LC-RDU from their primary health care centre was slightly above 20% and similar to the percentage of patients referred from emergency services. The majority of patients had been initially assessed by a specialist before being tested at the LC-RDU. The median time lapse between the first consultation to the LC-RDU and the diagnosis was less than 2 weeks (Table 2), and it was lower when diagnosis was confirmed using an endoscopic procedure, whether fiberoptic bronchoscopy (median, 8 d; IQR, 4-14 d), or EBUS-guided TBNA (median, 14 d; IQR, 2-30 d), Figure 1. Time until diagnosis was inversely proportional to the extent of the disease in the subgroup of patients with NSCLC ($P$<.001, chi-squared test), Figure 2.

Of the 280 patients with NSCLC, a total of 166 EBUS-guided TBNA were performed for lymph node staging (59.3%); this technique was the most widely used for evaluating the extent of the disease in the LC-RDU. In over 40% of patients, TNM staging was based on clinical and radiological criteria because the disease was already advanced or the age/comorbidity of the patient contraindicated using invasive

**Table 1**
Patients diagnosed with chest neoplasia (No.=352)

| Social and demographical data | |
| --- | --- |
| Age, mean (SD) | 63.3 (10.5) |
| Sex (females), No. (%) | 46 (13.1) |
| | |
| Tobacco use | |
| Non-smoker, No. (%) | 31 (8.8) |
| Smoker, No. (%) | 321 (90.6) |
| Pack-years, median (IQR)* | 50 (40-75) |
| Initial complementary examinations, No. (%) | |
| Chest CT-scan | |
| Nodule/lung mass | 221 (62.7) |
| Pathologic hilum | 32 (9.1) |
| Multiple lung nodules | 31 (8.8) |
| Mediastinal presence | 15 (4.3) |
| Normal lung areas | 4 (1.1) |
| Other | 49 (14) |
| | |
| Fiberoptic bronchoscopy, No. (%) | |
| Bronchial tumor | 72 (20.4) |
| Irregular mucous | 31 (8.8) |
| Other bronchial anomaly | 110 (31.2) |
| | |
| Diagnostic examination, No. (%)** | |
| Sputum cytology | 4 (1.1) |
| Fiberoptic bronchoscopy | 170 (48.2) |
| Thoracocentesis | 8 (2.2) |
| Transthoracic puncture | 30 (8.5) |
| Extrathoracic puncture | 16 (4.5) |
| EBUS-guided TBNA | 70 (19.9) |
| Surgery | 54 (15.4) |
| Mediastinoscopy | 2 (0.6) |
| Thoracotomy | 52 (14.8) |
| | |
| Histopathologic diagnosis, No. (%) | |
| Adenocarcinoma | 118 (33.5) |
| Epidermoid carcinoma | 88 (25.0) |
| Large cell carcinoma | 9 (2.5) |
| Undifferentiated non-small cell carcinoma | 65 (18.5) |
| Small cell carcinoma | 44 (12.5) |
| Mesothelioma | 3 (0.8) |
| Lymphoma | 4 (1.1) |
| Other primary chest neoplasia | 2 (0.6) |
| Extrathoracic metastasis of the neoplasia | 19 (5.4) |

CT indicates computed tomography; EBUS, endobronchial ultrasound; SD, standard deviation; TBNA, transbronchial needle aspiration.

* In smokers (No=321). IQR, interquartile range.

** First diagnostic sample.

procedures for mediastinal staging. Of the patients who underwent EBUS, the pre-operative staging showed only local disease in 105 cases (37.5%) (Table 3), and therapeutic surgery was performed in 83 of these patients with adequate lung function. This procedure confirmed the local disease and was radical in 73 cases (87.9%). In only 10 patients (12.0%) with a pre-operative staging of I/II systematic lymph node dissection during the surgery provided evidence of metastasis in the mediastinal lymph nodes, indicating a postoperative stage III.

## Discussion

In our study, over half of the patients referred to the LC-RDU were

**Table 2**
Patient origin and time elapsed, median (interquartile range) (No.=352)

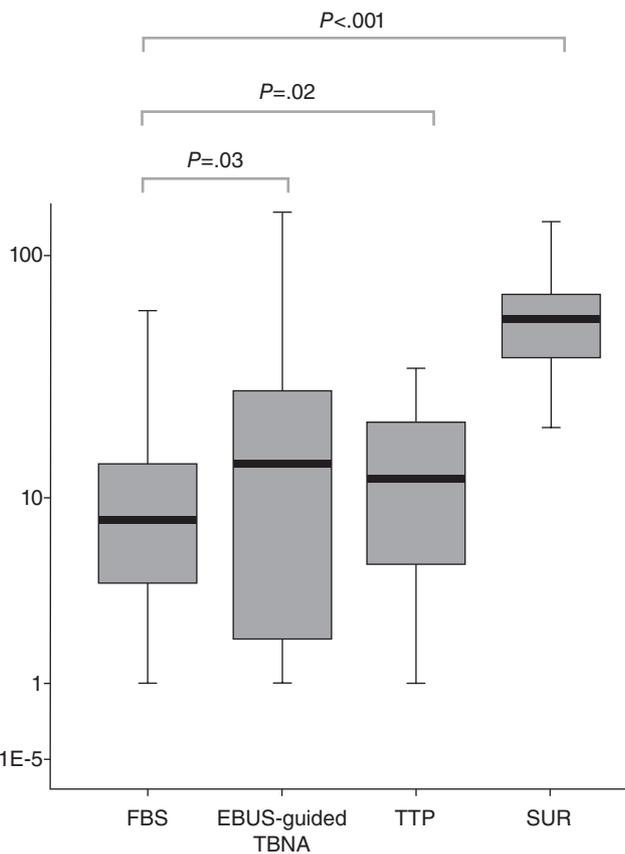| | |
|---|---|
| Patient origin, No. (%) | |
| Primary health care | 72 (20.4) |
| Specialised outpatient centre | 209 (59.4) |
| Emergency service | 71 (20.2) |
| | |
| Time lapse, median (interquartile range) | |
| Request from family doctor – first pneumology consultation | 5 (3-7) |
| First pneumology consultation– diagnosis | 11 (5-22) |
| Diagnosis – start of treatment | 28 (15-43) |



**Figure 1.** Time lapse between first consultation to LC-RDU to diagnosis, according to diagnostic examination. A) Conventional bronchoscopy (FBS). B) EBUS-guided TBNA. C) Transthoracic puncture (TTP) (thoracocentesis or CT-guided transthoracic puncture) or extrathoracic puncture. D) Surgery (SUR) (mediastinoscopy or thoracotomy, excluding the group of patients who underwent CT follow-up and therapeutic surgery). EBUS indicates endobronchial ultrasound; TBNA, transbronchial needle aspiration.
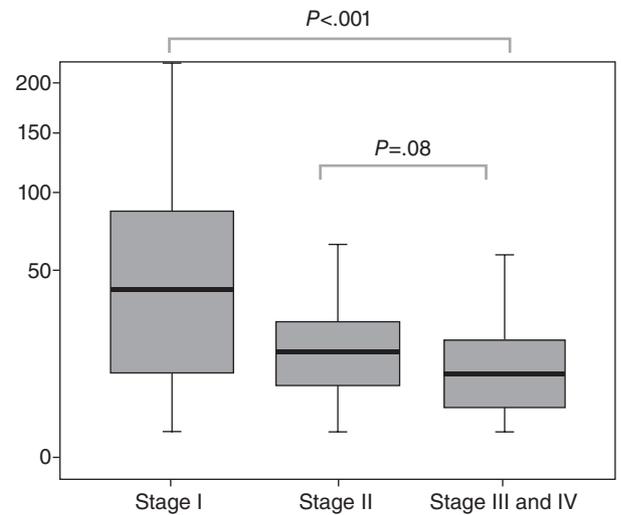


**Figure 2.** Non-small cell lung carcinoma (No=280). Time lapse between first LC-RDU consultation to diagnosis, based on tumor staging (median and interquartile range).

**Table 3**
Non-small cell lung carcinoma staging (No.=280)

| | |
|---|---|
| Staging technique, No. (%) | |
| Clinical/radiological | 112 (40.0%) |
| EBUS-guided TBNA | 166 (59.3) |
| Mediastinoscopy | 2 (0.7) |
| | |
| Preoperative staging, No. (%) | |
| Stage I | 79 (28.2) |
| Stage II | 26 (9.3) |
| Stage III | 112 (40.0) |
| Stage IV | 63 (22.5) |
| | |
| Postoperative staging, No. (%)* | |
| Stage I/II | 73 (87.9) |
| Stage III | 10 (12.0) |

EBUS indicates endobronchial ultrasound; TBNA, transbronchial needle aspiration.
*In 83 patients who underwent therapeutic surgery.

diagnosed with LC, a higher percentage than that previously observed in other studies.[10] In three-quarters of the patients with a final diagnosis of neoplasia, diagnosis was made using endoscopic techniques. The EBUS-guided TBNA established itself as an essential endoscopic technique, since its use confirmed the clinical suspicion of LC in one-fifth of the patients diagnosed in which previous diagnostic fiberoptic bronchoscopy had not provided decisive results. The median time between the first visit to the LC-RDU and diagnosis was less than 2 weeks and was shorter when the diagnosis was confirmed using endoscopic procedures. In over half of the 280 patients with NSCLC, EBUS-guided TBNA was performed for staging, this being the most frequently used technique for evaluating the extent of the disease. In one-quarter of these patients, preoperative staging only showed local disease, which was confirmed in close to 90% of patients who underwent therapeutic surgery in consequence.

Although 75% of patients with LC consulted their family doctor for symptoms compatible with this disease, such as cough, dyspnea, hemoptysis, and thoracic pain,[11] the positive predictive value of these symptoms remains low, and requires complementary tests for diagnosis. The greater accessibility to CT in basic health centers has led to a higher rate of identification of lung opacities. Consequently, this has led to a slight decrease in the proportion of patients with unconfirmed diagnostic suspicion of the disease,[11] and to an increase in referrals to pneumologists due to suspicion of LC. In the majority

of hospitals, this increase has meant transfer to the LC-RDU. The LC-RDU staff that examined the patients was made up of pneumologists and nurses who performed the endoscopic examinations required for the diagnosis and participated in the multidisciplinary chest tumor committee at the centre.

In our study, three-fourths of the patients with a final diagnosis of LC that were referred to the LC-RDU were attended to within one week, diagnosed within 3 weeks since the first pneumology consultation, and treated within 45 days following diagnosis. These time periods show better results than in other studies performed in similar populations,[12,13] and falls within the range recommended by the British Thoracic Society, in which LC patients should start treatment within 2 months of their first consultation.[14]

The need to reduce the time to diagnosis and treatment in LC is based on the importance of reducing the anxiety associated with a diagnostic suspicion of a neoplastic disease,[4] or when the patient is diagnosed in an initial stage and may be successfully treated.[15] Kashiwabara et al analyzed the survival of a sample of LC patients who were not treated within 1 year after identifying the disease because of rejection of treatment by the patient or an erroneous initial diagnosis, demonstrating the worse prognosis associated with this situation as opposed to the LC being treated immediately following initial identification of the disease. In this cases the worse patient evolution correlated to an increase in tumor size.[16,17] Although early treatment of LC has not been shown to improve survival in various studies focused on the time lapse between the first hospital consultation and the diagnosis and surgical treatment of the disease,[3,18] this lack of evidence has been influenced to some degree by the fact that patients in advanced stages of the disease seek treatment sooner than those in initial stages,[19] a phenomenon that was also observed in our study. On the other hand, several studies have shown improved prognosis in patients that are quickly referred to a specialist by the family doctor, suggesting that the effect of early diagnosis and treatment is only beneficial in the earliest stages of the disease. Buccheri et al[20] demonstrated decreased survival in patients with a longer time lapse between the appearance of symptoms and their referral to the specialist and Bozcuk et al[3] showed that, when diagnostic suspicion exists, direct referral to a specialist improves prognosis by reducing the time to first evaluation by a specialist in patients with LC still in its initial stages. Because the duplication time of non-small cell LC (the most prevalent form of the disease) is estimated at 4 months, the time lapse between the first symptoms and treatment should not be greater than this period by reducing the total number of days between the appearance of symptoms and the first evaluation by a specialist.[20]

In the patients included in our study, the diagnosis was performed in a median of 11 days, a period shorter than described in other published studies.[13] We should also point out that, although the samples obtained by fiberoptic bronchoscopy facilitated accurate diagnosis in almost half of the cases, EBUS-guided TBNA was the diagnostic technique used in 20% of patients, with only slightly longer periods of time from the first consultation to diagnosis than those achieved using fiberoptic bronchoscopy.

Independently of their size, EBUS-guided TBNA allowed for approaching lung tumors close to the trachea and large bronchi and those in the mediastinal and lobar lymph nodes into which the neoplastic disease could have spread. The use of this technique facilitates diagnosis in the majority of referred patients in whom no clear diagnosis was obtained using other techniques.[21,22] In accordance with this assessment, the patients from our study in which the diagnosis depended on nonendoscopic techniques required over 3 weeks for confirmation, similar to results from other studies.[23] Therefore, the combined use of two endoscopic techniques, fiberoptic bronchoscopy and EBUS-guided TBNA, was the main factor confirming the diagnosis of each patient within the time period established by the clinical guidelines

In our study, EBUS-guided TBNA was the technique used for tumor staging in over half of the patients, and so only a small number of mediastinoscopies were performed with this objective in mind. Positron emission tomography is also currently used for LC staging, and has been incorporated into the diagnostic algorithm for this disease.[24] However, at the start of this study, this technique was not systematically used in patients referred to the LC-RDU, and was therefore not considered in our analysis. EBUS-guided TBNA is a noninvasive technique that does not require hospitalization and has a low risk of complications.[9,25] In our experience it provides sensitivity and specificity of over 90%,[26] equivalent to the values obtained using mediastinoscopy and clearly superior to positron emission tomography if the mediastinum sampling is sufficient to obtain representative samples of the right and left paratracheal and subcarinal lymph nodes.[25] The proportion of patients (12%) who underwent radical surgery in which the post-operative staging demonstrated that the disease had spread to the mediastinum is similar to the proportion found in other studies in which mediastinoscopy was the technique used for tumor staging.[27] Furthermore, it confirms the benefits of using this nonsurgical technique for evaluating the extent of the disease, which also simplifies the evaluation of the disease once the diagnosis has been confirmed.

The patients referred to the LC-RDU had a single lung nodule in 20.4% of cases, and the preoperative staging indicated a resectable disease in one-third of cases, confirming that the existence of an LC-RDU leads to a high rate of identification of potentially curable cases. Therapeutic surgery was the first treatment used in one-third of the patients with non-small cell lung carcinoma (a greater figure than in previous studies[12,28]), and the disease was confirmed not to have spread to the mediastinum in 90% of patients who underwent systematic lymph node dissection.

When symptoms appear that lead to a diagnostic suspicion of LC, a direct referral of the patient to an LC-RDU reduces the length of time needed to confirm the diagnosis[29] and increases the proportion of patients in initial stages for whom surgery is indicated.[30] Furthermore, it has been shown to have an effect on survival when the disease is identified in the initial stages,[3] with a reduction in health costs.[2] Therefore, the care given to patients with suspected LC in an LC-RDU can contribute to improving the prognosis of the disease by favoring early detection, which was achieved in nearly one-third of cases in our study.

In conclusion, direct referrals to an LC-RDU of patients in which the suspicion of LC has been established has been associated with diagnosis in the initial stages of the disease in one-third of cases. The use of EBUS-guided TBNA within the diagnosis and staging system has allowed for diagnosis in one-fifth of patients, and staging in over half of patients, with results equivalent to those obtained using mediastinoscopy and without the need for hospitalization and the risk of morbidity.

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