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ORIGINAL ARTICLE

Predicting delays in lung cancer diagnosis and staging

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Keywords
Alert radiology system; delay; diagnosis; lung cancer; rapid lung cancer diagnostic unit.

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Abstract

Background: Despite growing interest in increasing the efficiency and speed of the diagnosis, staging, and treatment of lung cancer (LC), the interval from signs and symptoms to diagnosis and treatment remains longer than recommended. The aim of this study was to analyze the factors that cause delays in the LC diagnosis/staging process and, consequently, delays in making therapeutic decisions.

Methods: We analyzed audit data from a prospective dataset of 1330 patients assessed at The Lung Cancer Rapid Diagnostic Unit from 26 June 2013 to 26 March 2016. The number and type of procedures and medical tests and the times of all procedures were recorded. Clinical and epidemiological variables and whether the diagnosis was performed on an inpatient or outpatient basis were also recorded.

Results: Malignancy was confirmed in 737 (55.4%) of the 1330 patients, with LC in 627 of these (85.2%). The mean interval to final diagnosis was 19.8 ± 13.9 days. Variables significantly related to a longer diagnostic time were the number of days until computed tomography (CT) was performed (odds ratio [OR], 95% confidence interval [CI] 1.347, 1.103–1.645; $P = 0.003$), until a histology sample was obtained (OR 1.243, 95% CI1.062–1.454; $P = 0.007$), and the total number of tests performed during the diagnostic and staging process (OR 1.823, 95% CI 1.046–3.177; $P = 0.03$).

Conclusions: A greater number of tests and more days to CT and histology led to longer delay times. Optimization of these factors should reduce delays in the LC diagnosis process.

Introduction

Lung cancer (LC) is a major cause of morbidity and mortality, accounting for more than 1 400 000 (13%) annual cancer deaths.[1,2] It is the third most common cancer, and the most frequent when considering both genders.[3] Its incidence is increasing in women, probably as a result of greater tobacco exposure, labor integration, and hormonal factors.[1,4,5] Tobacco consumption is the main risk factor for LC, given that more than 85% of cases occur among current or former smokers.[6] Residential radon exposure is the second highest risk factor, and the first highest in never smokers.[7]

Approximately 80% of LC cases are non-small cell lung cancer, and adenocarcinomas are the most frequent histological type, followed by squamous cell carcinoma. These two types account for 60% of LC cases. Traditionally, squamous cell carcinoma was the most frequent type, but the incidence of adenocarcinoma has increased in the last decades.[8,9] Most cases of LC are diagnosed in symptomatic patients. Consequently, the majority of diagnoses are made in advanced stages in patients with a poor prognosis. Tumors are identified in localized stages in only 16–22% of cases, although some series have demonstrated that the proportion of patients diagnosed with localized LC is increasing.[9,10] Therefore, it is of paramount importance reduce the time from the onset of LC signs and symptoms to diagnosis to increase the number of patients identified in early stages.

Our area has a unit dedicated to LC, the Lung Cancer Rapid Diagnostic Unit (LCRDU), with an alert system based on electronic warnings from radiologists after suspicious chest results are detected. These radiological findings usually belongs from patients seen in a general practice, hospital, or preoperatively.[11] Around 90% of patients assessed at the LCRDU are sent through the Radiological Alert System because of their LC radiological findings.[11] Current guidelines have established paths for the correct diagnosis and staging of LC, recommending a final decision from a multidisciplinary committee.[12,13] Nevertheless, the increase in new diagnostic and therapeutic techniques and the constant need for diagnostic accuracy may lead to an increase in diagnostic tests, delaying the LC diagnosis.[14]

There are official recommendations for the maximum delays during an LC diagnosis.[12–17] Some studies that assessed the delay to an LC diagnosis showed median diagnostic intervals between the first symptomatic presentation and diagnosis of LC of approximately 180 days, and in some cases exceeding 300 days.[18] In a systematic review, the median delays to therapeutic care after symptom appearance varied from 47 to 138 days.[19] Some studies have focused on the differences in ambulatory versus hospitalized management of LC, others on tumor size or comorbidities, with different results.[20,21] Nevertheless, the links between prolonged delays to diagnosis and therapeutic management and outcomes are still unclear. It does seem clear that treatment delays increase the risk of poor clinical outcomes and are associated with poorer patient experiences in subsequent cancer care.[18] The identification of factors related to the clinical evaluation, diagnosis, and staging times in LC is crucial to avoid delays to treatment. Therefore, the aim of this study was to determine the factors that influence the time to diagnosis in patients with suspected LC.

Methods

Study Design

This is a clinical audit of LCRDU performance. It can be formally considered a cohort study where all patients included have a positive radiological sign. The cohort was followed until LC diagnosis and treatment or the radiological finding was considered false positive. All clinical records from all patients with a high suspicion of LC who were seen at the LCRDU from 26 June 2013 to 26 March 2016 were included. The LCRDU operates daily and is staffed by a pulmonary physician and a clinical oncology nurse who monitors clinical progress, assists with the coordination of care, and provides patients with the necessary psychosocial support. All variables were collected from a prospective database (electronic health records) where all interventions and tests are registered, from blood analysis results to positron emission tomography (PET) imaging (if performed). No personal information that could be used directly or indirectly to identify an individual was extrapolated from the database. Only the clinical oncology nurse was aware of the link between the audit code and the clinical history number.

Patients and variable selection

All patients seen at the LCRDU were included. Epidemiological and clinical variables were recorded. Smokers were defined as participants who had smoked ≥ 100 cigarettes in their lifetime. Current smokers were those who smoked more than one cigarette in the month prior to enrollment or quit within one year of enrollment. The remaining ever smokers were classified as ex-smokers. Never smokers were defined as having smoked < 100 cigarettes in their lifetime.[22] Whether diagnostic study was performed on an inpatient or outpatient basis and how patients entered the LCRDU, according to the service (general practice, hospital, or pre-surgery consultation, or hospitalization) that requested the radiological test with the suspicious finding were also recorded. The diagnosis of LC was made after suggestive radiological findings and pathologic confirmation. The histological type was obtained by reviewing the

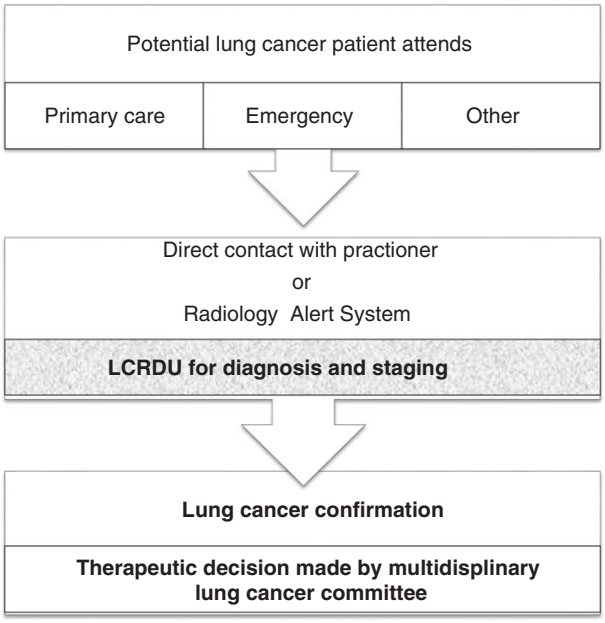

Figure 1 Route of a patient who entered the Lung Cancer Rapid Diagnostic Unit (LCRDU).

pathology information. All patients were assigned tumor node metastasis (TNM) stages according to the current classification at the time of the study after completing staging processes. The decision to proceed with oncologic and/or surgical treatment was made by a multidisciplinary committee, including pulmonologists, surgeons, radiotherapeutic and medical oncologists, radiologists, and pathologists.[23] The diagnostic pathway is shown in Figure 1. Tumor staging was obtained following established guidelines.[8] All procedures performed for diagnosis and staging were recorded for each patient, including imaging, as well as the number of invasive tests performed to obtain histological samples. We used the following variables for analysis: the total number of radiological studies, the total number of invasive techniques, the total number of lung functional tests necessary for therapeutic evaluation, and the total number of tests needed (imaging, functional, and for histology). The recorded radiological techniques were all imaging tests and included computed tomography (CT), PET-CT, magnetic resonance, bone scintigraphy, and abdominal ultrasound. The recorded techniques for tissue biopsy and/or cytology were all endoscopic, pleural, transthoracic puncture, or thoracic diagnostic surgery procedures and included: conventional bronchoscopy, endobronchial or endoscopic ultrasound (EBUS, EUS), diagnostic thoracocentesis, closed transparietal pleural biopsy, pleural biopsy through medical thoracoscopy, transthoracic puncture guided by CT or ultrasound, and thoracic surgery for diagnosis. We did not take the accuracy of the invasive techniques into account in the analysis. Cardiopulmonary exercise testing and lung perfusion scintigraphy were performed to test lung function. The total number of tests performed for the diagnosis/staging included the radiological tests, the tests necessary to obtain histopathological confirmation of malignancy, and other tests necessary for therapeutic/functional evaluation. The time variables used for the analysis were: the time until the first patient consultation (the days between the radiological alert and when the patient was seen in the LCRDU; time until CT (the days between the request and its performance); time until PET-CT (the days between the request and its performance); time until histological sampling (the days between the request and the first sample); time until the pathology report (the days between obtaining the pathological sample and the pathology diagnosis); total study time (the days since the alert was issued to the final therapeutic decision by the tumor committee or when the patient was discharged from the care circuit with any diagnosis of malignancy); and the time until the Lung Cancer Committee decision (total study time for patients discussed at the tumor committee, specifically LC patients). We did not record delays to treatment initiation, as they do not influence the effectiveness of the LCRDU.

Ethical aspects

The LCRDU protocol was approved by the Direction of Hospital Care Processes according to the Integrated Health Care Project in Lung Cancer of the Galician Health Service (SERGAS) under the Conselleria de Sanidade (Galician and Spanish Health Care System). Current research laws in Spain (Ley de Investigación Biomédica de 2007 and Ley de Protección de datos de 1999) explicitly state that ethic review board approval or individual consent is not required for retrospective assessments of data obtained from usual clinical care for audit and research purposes, such as in this study.

Statistical analysis

Quantitative variables were expressed as percentages and frequencies, and numerical variables as the mean and standard deviation. Bilateral tests were used and $P < 0.05$ was considered significant. χ^2 and Fisher's exact tests were used for the statistical analysis of qualitative variables. For the comparative analysis of numerical variables, the Student's *t*-test was used for normal distribution and nonparametric techniques if not for abnormal distribution. Normal distribution was checked with the Kolmogorov–Smirnov test. Univariate analysis included epidemiological variables (gender, age, smoking status); location of patient care (ambulatory or hospitalized); final diagnosis of malignancy

and LC; TNM stage categorized as localized (stages I–IIIA) or advanced (stages IIIB–IV); PET-CT result; EBUS result; EBUS as the initial diagnosis procedure; number of imaging studies needed per patient; number of invasive procedures needed per patient; total number of tests per patient; and the durations until the patient's first consultation, CT, PET-CT, and histological sample was obtained, and the pathology report. The significant variables from univariate analysis were included in a multivariate logistic regression model, with the dependent variable being a delay time > or ≤ the median time to diagnosis, as assessed by the multidisciplinary committee. Analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

In this clinical audit, 1330 patients were included; 1106 (83.2%) were managed as outpatients. The patient characteristics are listed in Table 1. Most patients (718, 54.8%) entered the LCRDU after a radiological alert from radiologists because of a suspicious image of a thoracic malignancy (Fig 2). Patients came mainly from primary care, the pulmonology department (and other medical pulmonary subspecialties), and the emergency department. Most patients (936, 70.4%) were male and the mean age was 66.5 ± 12 years. There were 528 former smokers (39.7%), 445 current smokers (33.4%), and 314 never smokers (23.6%). Among these smokers, the mean pack-year rate was 46.7 ± 30.7.

After completing diagnostic and staging assessments, malignancy was confirmed in 737 (55.4%) of the initial 1330 patients; 627 (85%) with LC (Fig 2). In the other 110 (15%) patients, the pulmonary involvement corresponded to metastatic colorectal disease (24%), otorhinolaryngological disease (14.5%), lymphomas (12.7%), and neoplasms originating in the breast (11%.) The most frequent histological type among LC patients was adenocarcinoma (49%); followed by squamous (24%); small-cell LC (12.5%); and others (14.5%), such as carcinoid or undifferentiated types. The prevalence of tobacco exposure in LC patients was high: 260 (42.3%) were smokers, 266 (43.3%) former smokers, and 89 (14.5%) never smokers. Regarding radiological tests, CT was performed in 1278 (96%) and PET-CT in 650 (47.8%) patients. Only two imaging tests were required in 84% of patients. Overall, 1124 tests were performed to obtain a cytohistological sample, including: conventional bronchoscopy in 708 (57.8%) patients, EBUS in 276 (22.5%), EBUS as the first diagnostic procedure in 179 (13%), biopsy or pleural cytology in 110 (9%), transthoracic needle biopsy in 123 (10%), and other tests in 44 (3.5%) patients. Only one diagnostic test was needed to obtain a diagnostic histological sample in 73.7% of patients, while the remaining 26.3% required more than two tests. In patients who underwent EBUS as the initial procedure, only 16.6% (28/169) required more than one procedure compared to 28.4% (215/756) of the other patients ($P = 0.01$). One to three tests were performed in 76.3% of patients, while the remaining 23.7% required four or more.

The audit results of the measured times of the most important phases of the LCRDU are shown in Table 2. It was possible to determine global and split times for the diagnostic study in 1244 patients. The total study time, defined as the days since the alert was issued to the final therapeutic decision, was 19.8 ± 14 days. Therefore, the cutoff value for a delay in study time (dependent variable in univariate analysis and in the multivariate regression model) was defined as ≥ 20 days. We developed different univariate analyses of variables influencing the diagnostic delays of patients seen at the LCRDU for all of the time periods recorded. The number of participants included in the univariate and multivariate analyses was 1244. The significant variables related to a longer diagnosis interval after univariate analysis were male gender, being an outpatient, diagnosis of malignancy, diagnosis of LC, more localized LC stages (I–IIIA), EBUS results, number of tests per

Table 1 Patient characteristics

Characteristics	Patients
N	1330
Gender, male (%)	936 (70.4%)
Age (mean ± SD)	66.5 ± 12
Smoking, current/former (%)	973 (75.6%)
Access by Radiologists Alert System	726 (54.6)
Patient origin	
Primary care	367 (27.7%)
Pulmonology Department	410 (31%)
Emergency Department	186 (14%)
Oncology Department	85 (6.4%)
Others	198 (15%)
Preoperative	78 (5.9%)
Ambulatory study (%)	1106 (86.2%)
Malignant (%)	737 (55.4%)
LC diagnosis (%)	627 (47.1%)
Colorectal	27 (25%)
Otorhinolaryngological	16 (14.8%)
Breast	11 (10.2%)
Gynecological	5 (4.6%)
Lymphoma	14 (13%)
Mesothelioma	1 (0.9%)
Other	33 (3%)
Stage I–IIIA (%)	252 (41.6%)†
PET-CT performance (%)	659 (49.5%)
Number of pathology samples (mean ± SD)	1.3 ± 0.6
Number of radiological studies (mean ± SD)	1.6 ± 0.7
Total studies (mean ± SD)	2.5 ± 1.2

†Data available in 606 LC cases. LC, lung cancer; PET-CT, positron emission tomography-computed tomography; SD, standard deviation.

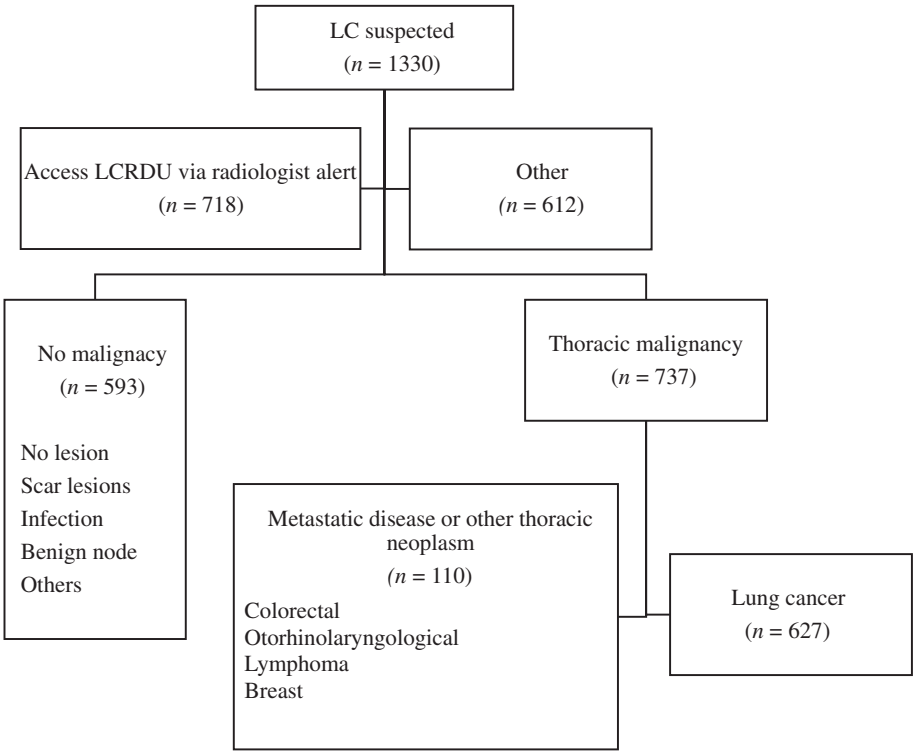

Figure 2 Diagram of study participants.

patient for pathology and radiology, total tests per patient, the days until the patient's first consultation, days until CT, days until PET-CT, days until histology sample, and days until the pathology report (Table 3). Significant variables in the univariate analysis were included in a multivariate logistic regression model (Table 4). The variables significantly related to a diagnostic delay were the number of days until CT was performed (odds ratio [OR] 1.347, 95% confidence interval [CI] 1.103–1.645; $P = 0.003$), the days until a histology sample probe was performed (OR 1.243, 95% CI 1.062–1.454; $P = 0.007$), and the total number of tests per patient for diagnosis and staging (OR 1.823, 95% CI 1.046–3.177; $P = 0.03$) (Table 4).

Table 2 Audit times until different phases of the LCRDU

Process	Mean ± SD (days)
First pulmonary consultation	3.5 ± 4
CT performance	5.8 ± 3.1
Histology sample performance	4.9 ± 4.8
Histology sample results (since its performance)	4.3 ± 2.7
PET-CT performance	9.4 ± 5
Total study time (all patients)	19.8 ± 14
Time until Lung Cancer Committee decision (only lung cancer)	20.6 ± 13.1

PET-CT, positron emission tomography-computed tomography; LCRDU, Lung Cancer Rapid Diagnostic Unit; SD, standard deviation.

Discussion

Despite growing interest in increasing the efficiency and speed of the diagnosis, staging, and treatment of LC, the interval from the first signs until the diagnosis and treatment of this disease is longer than recommended by international guidelines. The 2011 National Institute for Health and Clinical Excellence guidelines recommend that rapid access clinics should be provided, where possible, for the investigation of patients with suspected LC. They suggest an acceptable delay of two months from an urgent general practitioner referral to the beginning of treatment.[12] The most recent American College of Chest Physicians LC guidelines suggest that efforts should be made to deliver "timely" care.[13] Most recommendations emphasize a maximum delay of 7–14 days between visits with a general practitioner and specialist. In our series, the mean time until the multidisciplinary committee made a final LC diagnostic decision was 20.6 ± 13.1 days. This result is more than acceptable according to current recommendations. A review including 65 papers published between 2007 and 2016 measuring the timeliness of LC diagnosis and treatment in 21 countries found that the most commonly reported wait-time intervals were from diagnosis to treatment, first visit with a specialist to a confirmed diagnosis, and symptom onset to the first physician visit.[19] This systematic review reported a median delay of 14 days

Table 3 Univariate analysis of variables influencing diagnostic times

Variables	Time (< 20 days)	Time (≥ 20 days)	*P*
Gender, Male (%)	452 (66.8%)	414 (73%)	0.01
Age (mean ± SD)	65.9 ± 11.3	66.7 ± 10.9	0.32
Smoking, current/former (%)	470 (73%)	437 (77.6%)	0.07
Ambulatory (%)	555 (86.7%)	530 (93.6%)	< 0.0001
Malignant (%)	306 (45.2%)	359 (63.3%)	< 0.0001
LC diagnosis (%)	261 (38.6%)	299 (52.7%)	< 0.0001
Stages I–IIIA (%)	77 (30.3%)	156 (54.4%)	< 0.0001
PET-CT performance (%)	197 (29.1%)	438 (77.2%)	< 0.0001
EBUS performance (%)	68 (10%)	170 (30%)	< 0.0001
EBUS performance as the first diagnosis procedure	52 (7.7%)	105 (21.5%)	< 0.0001
†Number of pathology samples (mean ± SD)†	1.2 ± 0.5	1.4 ± 0.6	< 0.0001
†Number of radiological studies (mean ± SD)†	1.3 ± 0.6	2 ± 0.7	< 0.0001
†Total studies (mean ± SD)†	2 ± 1.1	3.3 ± 1	< 0.0001
Time until patient first consultation (mean ± SD)	3.3 ± 3.3	3.8 ± 4.8	0.04
Time until CT performance (mean ± SD)	5.3 ± 2.8	6.4 ± 3.3	< 0.0001
Time until PET-CT performance (mean ± SD)	8.5 ± 4.6	9.8 ± 5.1	0.003
Time until histological sample (mean ± SD)	3.8 ± 4.1	5.8 ± 5.1	< 0.0001
Time until pathology report (mean ± SD)	4.1 ± 2.6	4.4 ± 2.7	0.06

†Per patient. EBUS, endobronchial ultrasound bronchoscopy. LC, lung cancer; PET-CT, positron emission tomography-computed tomography; SD, standard deviation.

Table 4 Multivariate analysis of audit variables influencing diagnosis

Variables	OR (95% CI)	*P*
Time until CT performance	1.347 (1.103–1.645)	0.003
Time until histology sample performance	1.243 (1.062–1.454)	0.007
Total number of diagnostic studies per patient	1.823 (1.046–3.177)	0.034

Cutoff value of increased diagnostic time ≥ 20 days CI, confidence interval; CT, computed tomography; OR, odds ratio.

between the first symptom and the first consultation with a general practitioner, 24 days before consulting a specialist, and a range of 29 to 73 days before treatment. Some studies report median intervals from specialist visit to diagnosis of 15 days and for diagnosis to treatment of 15 days.[24,25] Our series included the time to diagnosis and staging, but did not take into account the time from diagnosis to treatment. We focused on identifying modifiable factors significantly related to an increased diagnostic time. This original approach should have immediate clinical applicability. Our clinical audit of real-life data identified multiple factors to be improved in the diagnosis of LC. More than 50% of patients were seen at the LCRDU as a result of the alert radiology system, which has contributed to reducing the delays in primary care, loss of patients, and inadequate hospitalization. Thus, this selection of patients with suspected LC could improve care at this level and contribute to saving resources. The diagnostic accuracy of clinical and radiological suspicions of malignancy was 55%, which means that more than one out of two patients referred will be diagnosed with a malignancy. More than two thirds of patients required three or fewer tests, suggesting that it was only necessary to perform one biopsy in two thirds of patients and a single imaging procedure in more than 80%. Univariate analysis revealed that many factors were initially associated with a longer interval to diagnosis (Table 3). Yet in multivariate analysis, only the time until CT, the time until a histology sample was obtained, and the total number of diagnostics tests significantly influenced the delay to diagnosis. The number of tests required to diagnose and stage LC is essential when analyzing delay times. In a Spanish study of 415 patients (75.4% with stage IIIB–IV), the delay between the first symptoms and the beginning of treatment was 124 days (82 days before consultation with a specialist, 41 before treatment commenced).[26] Eighty percent of patients with a more evolved disease were treated within the month following the first consultation. An increased time to diagnosis was associated with better survival. More advanced tumors might be more accessible for sampling and this may explain this paradoxical relationship between diagnostic time and survival. According to our data regarding LC stages and the number of tests necessary to make an accurate diagnosis, early stages are often insidious and require more tests to achieve a definitive diagnosis, resulting in longer delays.

The use of EBUS for the initial diagnosis was associated with a significant reduction in the number of invasive procedures. Only 16.6% (28/169) of patients required more than one procedure compared to 28.4% (215/756) of patients who did not initially undergo EBUS. Other studies have shown similar results.[14,27] These studies also showed a

positive correlation between the time to diagnosis and treatment decisions and survival.[15,24,28,29] In our study, we failed to find any significant relationship between performing EBUS (initially or during the study) and the timeliness of diagnosing LC.

Rapid LC diagnostic units have proven to be very useful, although audits are necessary to evaluate them.[11,26,30–32] In some series, a specific rapid diagnosis program has reduced the delay from 128 to 20 days for the entire management process and significantly reduced the delays to access a specialist or undergo a scan, a bronchoscopy, or PET-CT.[17] Nurse navigation has also improved the time from suspicion of LC to treatment with a trend toward diagnosing non-small cell lung cancer at an earlier stage, both in our study and in previous series.[33]

Based on our results, we suggest some areas for improvement. The times to complete the various tests are acceptable. However, given that the number of tests is an important variable influencing delay, we should try to minimize the number of tests performed on each patient via improvements in coordinated healthcare.[34] Most patients in our series were diagnosed as outpatients through LCRDU ambulatory care, indicating that many patients have few or non-specific symptoms at the time of diagnosis, confirming that LC is an insidious disease. This reinforces the need for early detection programs, such as our LCRDU. The radiological alert system has proven effective and could serve as an example for other national and international health systems.

Our study has certain limitations. It was conducted at a single university center, which limits the generalizability of the results. We did not analyze the size of the tumor and the influence that this could have on the ease and time to reach a diagnosis. In addition, we did not record the comorbidities of patients or whether the histological type influenced the delays. The advantages of our study include the large sample size of almost 1300 patients. The loss of patients was minimized as the whole Galician population has public health coverage, meaning that there was no selection bias for our sample as we recruited more than 95% of all LC cases diagnosed in the referral area during the study period. In addition, we included patients managed as both inpatients and outpatients.

Our results reinforce current recommendations, emphasizing the importance of rapid diagnosis units and the efficiency of our radiological alert systems. More standardized definitions and procedures to calculate time intervals for cancer diagnosis and treatment should be implemented to better understand the delays that occur during LC management. In conclusion, wait times to the diagnosis and staging of LC could be improved by reducing the times to CT and biopsy and optimizing the number and order of tests performed during the care process. The results from this study will help to develop strategies to improve these wait times and can be adapted to individual health care systems.

Disclosure

The authors declare no conflicts of interests.

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