Delays in lung cancer diagnosis and treatment: real-life assessment in a tertiary care center

Bernardo Teixeira[a,*], Telma Sequeira[b], Maria Isabel Gomes[c], Filipe Ferreira da Silva[a], José Pedro Boléo-Tomé[a,b]

[a] CEFITEC – Centro de Física e Investigação Tecnológica, Physics Department, Faculdade de Ciências e Tecnologia, NOVA University of Lisbon, Almada, Portugal
[b] Pulmonology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal
[c] Center of Mathematics and Applications, Faculdade de Ciências e Tecnologia, NOVA University of Lisbon, Almada, Portugal
* bd.teixeira@campus.fct.unl.pt

ABSTRACT

Introduction: Clinical guidelines recommend rapid evaluation of patients with suspected lung cancer. There are few data concerning delays in the diagnostic process of lung cancer in Portugal and adherence to recommendations. The aim of this work is to review and analyze the different phases in the process of diagnosis, staging, therapeutic decision and treatment within a pulmonology department.
Methods: Retrospective, single-center cohort study, with identification and analysis of the different stages of the pathway taken by patients with suspected lung cancer. The study contemplates the flow design and characterization related to waiting times. Descriptive statistical analysis of waiting times in each step and total waiting times and comparison with available guidelines.
Results: 77 patients included, predominantly male (72.7%), mean age of 66. Mean time from admission to start of treatment was 68 days (±55.2). Most patients underwent bronchoscopy (71.4%), which was conclusive in 54.6%; 39 patients (50.6%) needed a second exam and 14 (18.2%) a third one. Mean time from multidisciplinary decision to treatment was 14 days (±25.6). There were great differences between modalities: 6 days (±8) to chemotherapy, 5 days (±2) to radiation therapy and 63 days (±33) to surgery. Adherence to guidelines varied between 36.4% and 50.6% concerning total time and between 44.2% and 58.4% for time from diagnosis to treatment.
Conclusion: Total time of the process exceeded main guidelines in 6 to 26 days; however, there was considerable heterogeneity and results do not differ greatly from other published data. Proposing an optimized workflow may shorten critical stages and improve global performance, allowing for improvements in doctor and patient's expectations.

Keywords: lung cancer; waiting time; diagnosis; staging; delays

INTRODUCTION AND OBJECTIVES

Lung cancer is the main cause of death by cancer throughout the world. In 2018, 2,09 million new cases were diagnosed, there were 1,76 million deaths due to lung cancer, and these numbers continue to rise steadily[1]. In Portugal, incidence among men is 41.9/100 000 inhabitants and 11.04/100 000 among women, putting it in fourth place. Each year incidence has been rising around 0.5%[2]. Mortality remains high: in 2015 there were 4015 deaths by lung cancer in Portugal, 3035 of which in men; amongst women, mortality rates have raised from 9.2 to 10.7% between 2011 and 2015 and this growing trend is consistent[3].

Early diagnosis and precise staging of the disease is crucial for better outcomes, and this is well established through large randomized trials and international guidelines[2,4–6]. Less than 30% of patients have early stage cancer eligible for surgery or other radical therapy. Delays in diagnosis and time until start of treatment have been reported as responsible for increases in tumor size and stage[5], but these findings are not completely consistent.

Some authors defend the clinical importance of obtaining a quick tissue diagnosis has been demonstrated, as patients with more than four months delay from imaging to diagnosis have significantly worse survival[6] and may miss the opportunity to undergo curative intent procedure[7].

Also, some studies showed that longer time to treatment was a significant negative prognostic factor in patients with stage III disease, but others have demonstrated that shorter delays are associated with shorter survival[5]. Recently, a review of 693 554 patients diagnosed with non-small cell lung cancer in the United States showed that shorter wait times were associated with a decreased risk of death in early-stage patients, but poorer survival in patients with advanced disease[8].

Available data from studies in the United States shows that time from suspicion of cancer to beginning of treatment ranges from 45 to 90 days, largely surpassing recommendations[9]. One of these studies, with a large sample of 2 372 patients, showed considerable differences between stages – 90 days for patients with stages I and II, and 52 days in those with more advanced disease[10]. A study in Canada found median time from presentation to specialist referral was 27 days and a further 23 days to complete investigations. The overall time from development of first symptoms to starting treatment was 138 days[11]. The Canadian Strategy for Cancer Control recommends that the maximum time to diagnose most cancers should not exceed four weeks[11], as do other guidelines[13-15]. However, recommendations about waiting times are largely empirically based, and there is a lack of strong evidence about differences in outcomes.

There remains questioning whether delays in diagnosis depend on organizational factors or on patients' variability. Missed opportunities can happen at three different stages of the process: at the initial assessment, at diagnostic test performance and interpretation (imaging, biopsies, staging work-up), and follow-up and coordination[12]. It is therefore crucial to identify these different opportunities at different steps and find out what are the key factors that delay the process.

Several strategies have been proposed to improve timely diagnosis. In the United Kingdom, the National Health Service proposes new standards for a timely diagnosis of lung cancer, with fast-track diagnostic and assessment pathways that allow for a communication of a diagnosis within 28 days or 14 days[13–15]. Other countries have published guidelines concerning recommen-

ded timeframes[2,15–20]. A recent scoping review found that most published studies show non-compliance with existing guidelines, although with considerable regional differences; treatment interval median was 27 days, with only 6 studies (in a total of 52) showing adherence to guideline timeframes[21].

Within this context, the present study tries to shed some light in the current situation in a Portuguese scenario. To our knowledge, there is very few data concerning delays in the diagnostic process of lung cancer in Portugal and adherence to recommendations. Despite the existence of a universal access health service that can provide state-of-the-art therapy to cancer patients in our country, that are still considerable organizational problems that can impact access, timely diagnosis and timely start of therapy. The national health authorities recommend maximum response times for some diseases, such as cancer[20]. For lung cancer, referral to a specialist should happen between 7 and 15 days; multidisciplinary team (MDT) meeting should happen 8 days after diagnosis, and treatment should start in 15 days; some treatments waiting times are defined by law, such as radiotherapy (15 days) and oncological surgery (15 to 45 days)[22].

The present work is part a project designed to assess and optimize the process of diagnosis, staging and therapeutic decision in patients with suspected lung cancer (DiaSTOP).

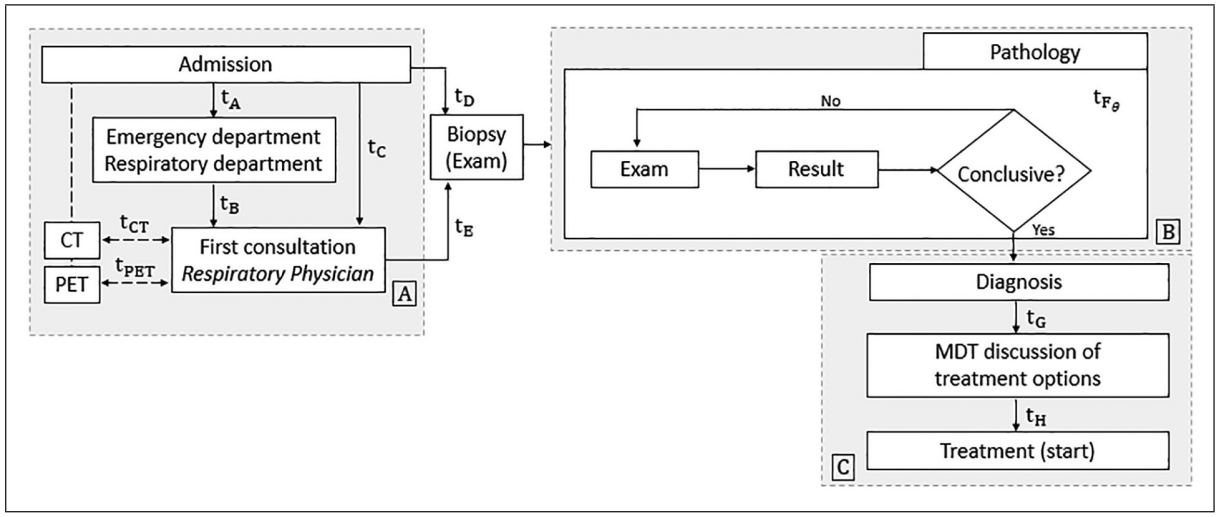
METHODS

The present study is a retrospective, single-center cohort study focused on the analysis the different stages of the pathway taken by patients with lung cancer through the flow design and characterization of the waiting times on each stage. The pathway starts when a patient is referred to specialist consultation to be investigated and includes pathological diagnosis (through biopsy or cytology), adequate staging (using 8th edition TNM classification criteria), MDT assessment and treatment decision and finishes when the patient begins treatment. All the key phases of the process were assessed, in order to build a diagnostic work-up pathway reflecting the reality seen in clinical practice within the department.

We included patients followed-up at the Pulmonology department of a tertiary care hospital in suburban Lisbon, serving a population of around 700 000 people. Inclusion criteria were: adult patients admitted or referred to the Department in the period comprised between January 2016 and December 2017, in whom a diagnosis of malignant lung neoplasm was made. Patients that were found to have other diagnosis or that had significant missing data concerning times were excluded. Data was extracted from the hospital information system Soarian® and collected in a database covering the key stages of the process. Phases were organized in three time regions and time between each phase was registered (Figure 1). Region A starts with patient admission and includes the main imaging investigations necessary prior to invasive biopsy studies. Region B includes the investigations necessary to obtain and confirm histological diagnosis; for practical purposes, a pathological exam (including biopsy or cytology) will be called “biopsy”. Each biopsy procedure performed (bronchoscopy, thoracentesis, etc.) can be either conclusive or inconclusive, leading to a second exam. Region C starts when a pathological diagnosis is confirmed includes MDT discussion and ends when any kind of cancer treatment is started.

We performed descriptive statistical analysis of each individual waiting time, of total waiting

Figure 1. schematic diagram of the pathway taken by patients with suspected lung cancer admitted or referred to the pulmonology department.



t_i represents time at phase i (A, B, C, …H); CT: thoracic computed tomography; PET: positron emission tomography; MDT: multidisciplinary team; θ represents the number of iterations (number of exams).

times within each region and of global waiting times, using measures of central tendency (mean and median), measures of dispersion (standard deviation) and measures of position (quartiles and extremes). RStudio® version 3.5.1 was used for data analysis and graphing. Through software packages it was possible to include and exclude outliers in the analysis under study in order to focus results on reality. Time results were then compared with selected available national and international guidelines, including Portuguese regulations.

RESULTS

Demographics

From a pool of 161 medical records, we extracted a sample of 77 patients with considerable data and admitted according to the defined criteria, with male predominance (56; 72.7%) and a mean age of 66 ± 12 years. Patients were referred either from outside the hospital (33.8%), mainly from primary care, or from inside the hospital (66.2%) – mainly from the pulmonology outpatient (32.5%), the emergency department (14.3%) and other outpatient clinics (11.6%). In some patients a lung cancer suspicion arose while they were already admitted to a ward (7.8%).

From admission to consultation

Assessment of the diagnostic process allowed us to build a schematic diagram reflecting the work-up pathway taken by the majority of patients within the department (Figure 1). Concerning Region A, most patients (57) had a prior thoracic CT scan; for the remainder 20, a CT scan was ordered. In 37 patients (49.4%) a PET scan was also scheduled according to international guidelines, for diagnostic and/or staging

purposes; this exam is performed at another institution in Lisbon.

Pathologic diagnosis pathway

Concerning Region B, represented in Table 1, bronchoscopy was the first exam performed in the majority of patients, but it was conclusive in 54.6% of cases. In total, 39 patients (50.6%) needed a second exam and 14 (18.2%) needed a third one. Transthoracic needle aspiration was more frequently performed as second or third exam. In our institution this technique is performed by a dedicated interventional radiologist. EBUS was not available in our center until mid-2016, so not all patients benefited from this technique.

Staging and treatment

Region C corresponds to therapeutic decision in a MDT, after obtaining a final diagnosis. Histological classification of lung cancer is described in Table 2, as well as staging according to TNM classification (8th edition). Patients initially staged using the previous TNM classifications were re-classified according to the more recent one. Four cases lacked a final clinical staging: two were transferred to other hospitals before finishing work-up, one had a poor performance status to further investigation, and one died before finishing work-up.

The MDT met weekly and therapeutic modalities were discussed and proposed to the patients. Chemotherapy was the treatment modality in 37 patients (48,1%); 12 (15,6%) were sent for surgery, 8 (10,4%) started chemoradiation, 4 (5,2%) radiation alone and 10 (13%) were offered best supportive care. Surgery and radiation therapy are not available at our hospital, so these patients were referred to pre-determined centers if this was the case.

Waiting times

Table 3 represents the results of waiting times, according to the diagram in figure 1. Mean total time from admission to start of therapy was 69 days (±55.2), with a median of 59 days (8 – 370 days). Mean time to first biopsy was 12 days

Table 1. Exams performed to obtain pathologic diagnosis.

		1st Exam		2nd Exam		3rd Exam	
		n(%)	Conclusive(%)	n(%)	Conclusive(%)	n(%)	Conclusive(%)
Bronchoscopy	Br	55 (71.4)	54.6	13 (33.3)	85.6	3 (21.4)	33.3
	Br + EBUS	2 (2.6)	0	0	---	0	---
	EBUS	5 (6.5)	60.0	8 (20.5)	50.0	3 (21.4)	0.0
Interventional Radiology	TTNA	10 (13.0)	70.0	13 (33.3)	92.3	5 (35.7)	80.0
Pleural Exams	Thora	1 (1.3)	100.0	0	---	0	---
	PB	2 (2.6)	0	3 (7.7)	0	2 (14.3)	---
Surgery	Mediastinoscopy	0	---	1 (2.6)	---	1 (7.1)	---
	Surgery	2 (2.6)	100	0	---	0	---
Other exams	STB	0	---	1 (2.6)	0	0	---
	n	**77**		**39**		**14**	

Br – Bronchoscopy, EBUS – Endobronchial ultrasound; TTNA – Transthoracic needle aspiration; Thora – Thoracentesis; PB – Pleural Biopsy; STB – soft tissue biopsy

Table 2. Histological classification and staging (according to TNM system 8th ed.); Undefined represents patients with incomplete or unavailable staging; n is the number of patients.

		Male n (%)	Female n (%)	Total n (%)
Histology	Adenocarcinoma	23 (41.8)	13 (61.9)	36 (46.8)
	Squamous cell carcinoma	19 (34.5)	4 (19.1)	23 (29.9)
	Small cell carcinoma	9 (16.0)	2 (9.5)	11 (14.3)
	Large cell carcinoma	1 (1.8)	2 (9.5)	3 (3.9)
	Poorly differentiated / undifferentiated carcinoma	3 (5.5)	0	3 (3.9)
	Undefined	1 (1.8)	0	1 (1.3)
Stage	IA	2 (3.6)	3 (14.3)	5 (6.5)
	IB	2 (3.6)	5 (23.8)	7 (9.1)
	IIA	1 (1.8)	0	1 (1.3)
	IIB	1 (1.8)	1 (4.8)	2 (2.6)
	IIIA	8 (14.3)	1 (4.8)	9 (11.7)
	IIIB	10 (17.9)	2 (9.5)	12 (15.6)
	IV	30 (53.6)	7 (33.3)	37 (48.1)
	X	2 (3.6)	2 (9.5)	4 (5.2)

Table 3. Statistical analysis of waiting times; t represents waiting time (in days) spent in each phase, according to Figure 1.

		Number of observations	Measures of Central Tendency		Measures of Dispersion	Measures of Position				
			Mean (day)	Median (days)	Standard Deviation (days)	Min (days)	Q_1	Q_2	Q_3	Max (days)
Zone A	t_A	77	1.9	0	5.9	0	0	0	0	26.0
	t_B	77	0.2	0	1.4	0	0	0	0	12.0
	t_C	77	2.1	0	6.0	0	0	0	0	26.0
	t_D	70	12.7	4.0	24.2	0	1.0	4.0	9.0	124.0
	t_E	56	12.0	4.0	23.7	0	1.0	4.0	9.0	124.0
Zone B	t_{F1}	75	8.3	7.0	5.0	0	5.0	7.0	12.0	22.0
	t_{F2}	40	11.5	10.0	7.4	0	6.0	10.0	14.3	42.0
	t_{F3}	14	12.3	11.0	6.7	4.0	7.5	11.0	14.0	31.0
Exams	t_{PET}	36	40.8	20.5	33.4	2.0	19.8	29.5	50.8	138.0
	t_{TC}	20	16.0	14.0	13.5	2.0	5.5	14.0	20.0	53.0
Zone C	t_G	63	11.2	0	18.3	0	0	0	17.0	74.0
	t_H	50	7.0	0	21.5	0	0	0	2.1	131.0
t_{Total}		**77**	**68.6**	**58.5**	**55.2**	**8.0**	**37.3**	**58.5**	**84.0**	**370.0**

Table 4. Adherence of sample patients to selected guidelines[15–19,22]. Time (days) represents proposed maximum waiting time for each phase; number of patients and percentage in adherence to each guideline.

Institution / Country	Time (days)	Admission → First Consultation → Diagnosis → Treatment (start)
NHS – National Health Service (UK)[16]	14	71 (92.2%)
	62	39 (50.6%)
	31	45 (58.4%)
NOLCP-National Optimal Lung Cancer Pathway (UK)[15]	49	34(44.2%)
	28	44 (57.1%)
SLCG-Swedish Lung Cancer Study Group[17]	42	40 (51.9%)
	14	34 (44.2%)
Australia Optimal Care Pathway for People with Lung Cancer[18]	14	71 (92.2%)
	42	28 (36.4%)
	14	34 (44.2%)
Ontario (Canada)[19]	42	28 (36.4%)
Portugal[22]	7-15	68-72 (88.3%-93.5%)
	23	40 (51.9%)

(±23.7). Mean time spent in the pathologic loop (from ordering of the first exam to the results of the last diagnostic biopsy) was 41,3 days (3-327). There is considerable deviation caused by outliers (mostly due to non-clinical reasons, like patient refusal to proceed the investigation); mean time was 27 days (3-124) excluding outliers and median was 27 days for both cases.

Mean time from MDT decision to start of first-line therapy (t_H) was 7 days (±21.5 days), but with considerable differences according to the chosen modality: mean time to chemotherapy was 6 days (±8 days), mean time to radiation therapy was 5 days (±2 days), mean time to surgery was 63 days (±33).

We compared these results with existing guidelines; adherence represents the percentage of patients that are concordant with recommended times in the UK (NHS and NOLCP), Sweden, Australia, Canada and Portuguese recommendations and legislation (Table 4).

DISCUSSION

Our results show that global waiting times in the process of diagnosis and staging in this sample are significantly longer than most recommended times in international clinical guidelines and national recommendations, and only 36.4% to 51.9% patients are adherent when considering total time. However, there is considerable heterogeneity in specific times of the process. Considering the first stage of the process, time from admission or referral to specialist consultation, most patients adhere to guidelines (> 88%). The same is true with time to first biopsy, which is within accepted times. Considering the second phase, region B, representing the “pathological loop”, it is important to note that about half of the patients needed to undergo a second biopsy, adding an average 11.5 days to this phase, and a smaller proportion needing a third biopsy. This is an acceptable situation in a complex diagnostic

process like lung cancer, as clinical presentation is variable and numerous patient, operator and system factor can affect the results of each diagnostic exam. However, it is crucial that the first-line test should be chosen considering best cost--effectiveness and that is not always the case. In our center, bronchoscopy is more readily available than transthoracic needle aspiration, and this can affect diagnostic conclusiveness and add delay if a second test is needed. Local availability of exams affects both effectiveness and delay; in our center, EBUS was not available in 2016 and that could affect diagnosis and staging in some patients, costing more time. Also, PET scan is dependent of other institutions, and we found a mean delay of 41 days, when Portuguese guidelines recommend 30 days[20]..

In the third phase of the process, region C, we found that it takes an average 13 days from diagnosis to MDT discussion; this is a delay that could easily be shortened and is probably more related to system inefficacies, not patient characteristics. Although mean time to treatment (14 days) was within most guidelines, there are significant differences according to the modality, and surgery waiting times are very high, even considering broader Portuguese norms that state the oncological surgery should take place between 15 and 45 days[22].

Approximately 50% of the patients underwent chemotherapy as first line treatment, which is in line with the diagnosis of locally advanced or metastatic disease. Additionally, when the data was collected back in 2016, immunotherapy as first line treatment was still pending approval.

To our knowledge, this is the first study specifically addressing waiting times in a lung cancer center in Portugal, and this data is important to identify key steps and players and to propose an optimized design.

Improving diagnostic performance in lung cancer within our health system is complex and carries important implications, including more timely access to therapy and to potentially curative therapy. We cannot forget that all the process carries significant patient anxiety and adding delay will contribute to more anxiety and uncertainty[23].

It is expected that future implementation of effective nation-wide screening protocols will increase the number of patients with early stage disease, who will be candidates to curative therapy[24]. This will add pressure to the present system and presumably increase waiting times, if no measures are taken. Increased risk of death due to tumor growth has been implicated in missed opportunities for following-up suspicious lesions detected radiologically[6,25] and underutilization of definitive therapy[26,27]. We also need more data as to wether a a fast-track effective system will contribute to better outcomes and survival. Some authors found that survival may not improve with a fast-track approach due to the "sicker quicker" hypothesis: diagnosis and treatment is made sooner in symptomatic patients, who have a higher likelihood of advanced disease, as opposed to early stage patients, mostly asymptomatic[28]. Impact on survival has been extensively explored in the literature, with mixed results[29–31].

Timely health system performance in lung cancer care presents extensive clinical implications, and multiple international studies have shown a wide range of delays as patients traverse their healthcare systems. A prospective study of 52 patients in Ontario reported a median delay of 138 days from symptom development to treatment[11], while a Swedish study reported a median time of 189 days[32] and a Finish study reported a delay of 112 days[26]. As a result, a recent comparison of lung cancer guidelines in the four most populous Nordic countries (Sweden, Denmark, Finland and Norway) led to the establishment of

shorter recommended times from initial referral to diagnostic conclusion and staging (26 to 30 days) and from staging to start of treatment (7 to 15 days)[33]. A standardized measurement of time intervals and outcome measures may allow more robust analysis in health service research in the future, with potentially better patient outcome.

We acknowledge that our findings may not reflect the present complexity of lung cancer diagnosis and treatment, due to huge advances in the past few years. More precise molecular diagnosis and tailoring of therapy to the patients according to new knowledge will surely impact waiting times in clinical practice.

In conclusion, although only approximately half of our patients met the international recommended timelines, our results are in line with many published international studies. These results leave place for improvement which should always be sought. Additionally, our findings regarding factors responsible for delay in lung cancer care are similar to those seen in the existing literature[28,31,34]. Lack of overt symptoms in patients with early stage lung cancer[34] and recognition of subtle symptoms of lung cancer[35] are other frequently implicated barriers to timely care, not approached in this study. Careful choice of first diagnostic test modality and investigations of comparable standard should be optimal. It is a priority to facilitate access and shorten time to curative treatments, like thoracic surgery, of crucial importance in earlier stages of lung cancer.

Ethics

The project was approved by the ethics committee of Hospital Prof. Doutor Fernando Fonseca (Register N. 63/2018); confidentiality was kept at all times and investigation was carried according to the Declaration of Helsinki principles and to national regulations.

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