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Lung cancer patients' journey from first symptom to treatment: Results from a Greek registry

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ABSTRACT

Background: To map the patients' journey from symptoms onset to treatment initiation for the most frequent histological types of lung cancer in Greece and describe the initial treatment that patients receive.
Methods: The primary data source was a Greek hospital-based registry. Demographic, anthropometric, lifestyle, and diagnostic-related characteristics as well as treatment-related data were extracted from the registry for patients diagnosed with Adenocarcinoma, Squamous and Small Cell Lung Cancer (SCLC). The time intervals from symptoms onset to diagnosis (StD), diagnosis to treatment initiation (DtT), symptoms onset to treatment initiation (StT) and surgery to post–surgery treatment (SRGtT) were estimated.
Results: 231, 120 and 122 patients were diagnosed with Adenocarcinoma, SCLC and Squamous, respectively. The percentage of patients diagnosed at stage III/IV ranged from 75% in Adenocarcinoma to 97.5% in SCLC ($p < 0.001$). The median (IQR) StD was 52 (28–104) days and no difference was detected across the three histological types ($p = 0.301$). Cough as first symptom was the only determinant of StD ($p = 0.001$). The median (IQR) DtT was 23 (13–36) days, with this time interval being shorter among patients with SCLC compared to patients with Adenocarcinoma and Squamous ($p < 0.001$). The median (IQR) StT was 81 (51–139) days. Almost one third of patients with Adenocarcinoma and Squamous were subjected first to surgery and the median (IQR) SRGtT was 42 (34–55) days.
Conclusions: Our results indicate that time interval from symptoms onset to treatment initiation in Greece is substantially prolonged, highlighting the need for strategies to expedite lung cancer diagnosis and access to evidence-based treatment.

1. Introduction

Lung cancer is a major public health problem worldwide since it accounts for 17% and 9% of all cancers in men and women, respectively, and constitutes 19% of all cancer-related deaths [1]. It is estimated that the number of lung cancer deaths worldwide will have increased from 1.6 million in 2012 to 3 million in 2035 [1]. In Europe, in 2012, 410,000 new cases of lung cancer were reported, and the estimated number of lung cancer deaths was 353,000 (one fifth of the total deaths caused by cancer) indicating that lung cancer was the 4th most common cancer site and the most frequent cause of cancer death [2]. In Greece lung cancer was the first and third most common cancer disease among men and women, respectively, in 2012, with approximately 6800 new cases [2]. Moreover, lung cancer was the first and third most common cause of death among men and women, respectively, in 2012, with 6434 deaths [3].

The poor prognosis of patients with lung cancer is highly related to the stage of disease at the time of diagnosis [1,4]. The vast majority of patients are diagnosed with locally advanced or metastatic disease [1,5] mainly due to the fact that they experience symptoms such as cough, dyspnea, chest pain, hemoptysis; symptoms having low predictive value for cancer diagnosis [6–8]. This leads to longer time between onset of symptoms and diagnosis because general practitioners seem to face difficulties in recognizing symptoms suspicious of lung cancer [8,9]. There is evidence indicating that lung cancer patients are ten times more likely to have three or more pre-referral consultations compared with patients diagnosed with breast cancer [10]. In addition to the delay in diagnosis from physicians, patients also play a part in late diagnosis. A delay in seeking medical advice from patients has been detected, because they may attribute their symptoms to other co-morbidities, ageing and lifestyle (i.e. smoking habits) [5,11,12]. Apart from late diagnosis, the delay in treatment initiation has also been

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associated with worse health outcomes [13].

The time taken to diagnose and initiate treatment of patients with lung cancer has been documented in many studies across different countries [14–20], the majority of which revealed substantial delays in the time from symptoms onset to diagnosis and treatment [13]. These time intervals could be shortened by optimizing clinical management, but this is not possible without measurements of these times.

In Greece, although the burden of lung cancer is substantial as mentioned above, to the best of our knowledge, data regarding the time intervals from symptoms onset to diagnosis and treatment, considered vital to improve patients' outcomes, are completely lacking. In this context, the primary objective of this study was to map the patients' journey from symptoms onset to treatment for the most frequent histological types of lung cancer; data that may inform the development of strategies to expedite lung cancer diagnosis and access to evidence-based treatment in Greece. The secondary objective was to present the initial treatment to which lung cancer patients in Greece are subjected.

2. Methods

2.1. Study population

The primary data source was a hospital-based registry of all new lung cancer cases treated in the Oncology Unit of Sotiria Hospital, in Athens, in Greece from the year 2015 until 2017. The histological types of interest were Adenocarcinoma and Squamous cell carcinoma, the two most common types of Non-Small Cell Lung Cancer (NSCLC), and Small Cell Lung Cancer (SCLC). As such, patients with any other histological type of cancer were excluded from the analysis. Information stored in this cancer registry concerned demographic, anthropometric and lifestyle characteristics, medical history, diagnostic-related characteristics, cancer therapy and follow-up. These data had been obtained from patients' medical records.

2.2. Data collection

The data regarding demographic, anthropometric, and lifestyle characteristics extracted from the registry, for the purposes of this study, included: gender, education, date of birth, geographic area of residence, body mass index (BMI), smoking status at the time of diagnosis (i.e. current, former or non- smoker), and smoking pack-years. Patients were classified according to their BMI as normal weight when BMI was lower than 25 kg/m^2, overweight when BMI was between 25 kg/m^2 and 30 kg/m^2 and obese when BMI was more than 30 kg/m^2.

Information extracted from the registry also included comorbidities (i.e. diabetes mellitus, cardiovascular disease, respiratory conditions etc), lung cancer related symptoms that patients experienced as well as the date that these symptoms firstly were noticed, as had been reported by patients or their caregivers during an interview performed by the oncologist, the source of referral to an oncologist (i.e. pulmonologists, internists, thoracic surgeons etc) as well as the date of referral to an oncologist were extracted from the registry. For patients diagnosed with lung cancer without having experienced any symptoms, the diagnosis was defined as incidental since a finding in a routine chest x-ray or routine check-up for an existing chronic disease led to the diagnosis.

Regarding diagnosis-related characteristics, the method used for diagnosis (i.e. histological, cytological or both), the procedure used to receive the sample for diagnosis (i.e. bronchoscopy, surgery, etc) and the date of cytological or/and histological diagnosis (date on which the pathology report was sent to the oncologist), as well as cancer related characteristics at the time of diagnosis like the histological type, the stage and the performance status were also extracted. The diagnosis date was defined as the date of cytological diagnosis for patients with only cytological examination, the date of histological diagnosis for those with only histological examination, and the earliest of these dates for patients with both examinations. The age at the time of diagnosis was calculated by subtracting the date of birth from the date of diagnosis. As for the staging, the 7^{th} edition of TNM classification for patients diagnosed earlier than 1/1/2017 was used, while the 8^{th} edition was used for those with a diagnosis after this date. Patients were categorized into those diagnosed at an early [from 7^{th} edition: IA, IB, IIA, IIB; from 8^{th} edition: IA1, IA2, IA3, IB, IIA, IIB] or locally advanced/ metastatic stage [locally advanced: (IIIA, IIIB from 7^{th} edition; IIIA, IIIB, IIIC from 8^{th} edition); metastatic: (IV from 7^{th} edition; IVA, IVB from 8^{th} edition)].

Finally, the type of treatment that these patients received (i.e. surgery, radiotherapy, systemic therapy/ immunotherapy) along with the corresponding dates was also extracted from the registry. The date of treatment initiation was defined as the earliest date among all treatments received. For patients subjected to surgery as first treatment, the date of post–surgery treatment was defined as the earliest among all other treatments received.

In Greece, patients firstly seek medical advice to an internist or another physician depending on the symptoms they are experiencing. Laboratory and imaging testing (i.e. blood tests, computed tomography etc) is then required for diagnosis. After diagnosis, patients are referred to the corresponding specialist (an oncologist in case of cancer) for treatment initiation. The time intervals considered in the present study are: (i) time from symptoms onset to diagnosis (StD), (ii) time from diagnosis to referral (DtR), (iii) time from diagnosis to treatment initiation (DtT), (iv) time from symptoms onset to treatment initiation (StT) and (v) time from surgery to post–surgery treatment (SRGtT). The time points of date of first symptom, date of referral and date of diagnosis were in accordance with the Aarhus Statement [21].

2.3. Statistical analyses

All continuous variables were summarized as median and interquartile range (IQR: 3rd quartile minus 1 st quartile) as their distributions were skewed, except for time intervals for which the 90^{th} centile was also presented. All categorical variables were summarized as frequencies (n) and percentages (%).

Pearson's chi square test and likelihood ratio chi square test were used to assess the association between categorical variables. Kruskal-Wallis rank test was used to assess the association between continuous variables and the histological type of cancer. For statistically significant associations identified after Kruskal-Wallis, a Dunn's Test with Bonferroni correction was performed [22,23]. In the cases in which only two histological types were compared, a Mann – Whitney Test was used.

For all time intervals of interest, the inversed Kaplan Meier curves were generated for the variable of histological type of cancer and of disease stage. The log-rank test was used to determine statistically significant differences in curves across histological types. In order to determine the patients' or cancer characteristics that may affect (i) DtT and (ii) StD, univariate and multivariate parametric survival models were conducted. More specifically, the Weibull and exponential models were tested and the AIC (Akaike's Information Criterion) goodness of fit statistic was used to select the model with the best fit. A semi-parametric model of Cox could not be used as the proportionality assumption was violated. In the univariate analysis, gender, age at diagnosis, histological type of cancer, method of diagnosis, disease staging, geographic area of residence and incidental diagnosis were considered as potential determinants of DtT, while gender, age at diagnosis, geographic area of residence, smoking habits, educational status, comorbidities and the most frequent symptoms were assessed as potential determinants of StD. Only factors found to be significantly associated with these time intervals at the level of 0.1 qualified for the multivariate analysis. Interaction effects were not assessed. A complete case analysis was conducted. A probability value of 5% was considered as statistically significant. All analyses were conducted using STATA v13.0.

Table 1
Demographic, anthropometric and lifestyle characteristics as well as comorbidities of patients, overall and by histological type.

Demographic, anthropometrics and lifestyle characteristics and comorbidities	Overall	Histological Type			p-value
	N = 473	Adenocarcinoma N = 231	Squamous N = 122	SCLC N = 120	
Gender, n (%)					
Male	370 (78.2)	163 (70.6)	107 (87.7)	100 (83.3)	< 0.001[a]
Female	103 (21.8)	68 (29.4)	15 (12.3)	20 (16.7)	
Age at diagnosis, years	**N = 472**	**N = 231**	**N = 121**	**N = 120**	
Median (IQR)	66.8 (60.6 – 73)	65.5 (58.9 – 72.2)	68.5 (64.7 – 72.5)	69 (62.7 – 75.8)	0.002[b]
Residence, n (%)					
Country	164 (34.8)	66 (28.7)	51 (41.8)	47 (37.2)	0.069[a]
Suburban	82 (17.4)	40 (17.4)	19 (15.6)	23 (19.2)	
Urban	226 (47.9)	124 (53.9)	52 (42.6)	50 (41.7)	
Education, n (%)					
≤6 years	35 (7.5)	14 (6.2)	12 (10)	9 (7.6)	0.308[c]
6 to 12 years	416 (89.5)	203 (89.8)	107 (89.2)	106 (89.1)	
Higher	14 (3.0)	9 (4)	1 (0.8)	4 (3.4)	
BMI status					
Normal weight	155 (41.3)	78 (43.6)	44 (49.4)	33 (30.8)	
Overweight	139 (37.1)	67 (37.4)	31 (34.8)	41 (38.3)	0.028[a]
Obese	81 (21.6)	34 (19)	14 (15.7)	33 (30.8)	
Number of comorbidities per patient	**N = 473**	**N = 231**	**N = 122**	**N = 120**	
Median (IQR)	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	
Comorbidities, n (%)					
Respiratory comorbidity	115 (24.3)	49 (21.2)	30 (24.6)	36 (30)	0.190[a]
Cardiovascular comorbidity	282 (59.6)	122 (52.8)	76 (62.3)	84 (70)	0.006[a]
Diabetes mellitus	105 (22.2)	40 (17.3)	30 (24.6)	35 (29.2)	0.031[a]
Renal insufficiency	3 (0.6)	1 (0.4)	1 (0.8)	1 (0.8)	0.862[c]
Previously treated malignancy	22 (4.7)	11 (4.8)	5 (4.1)	6 (5)	0.939[c]
Dyslipidemia	110 (23.3)	52 (22.5)	27 (22.1)	31 (25.8)	0.739[a]
Autoimmune diseases	9 (1.9)	3 (1.3)	3 (2.5)	3 (2.5)	0.637[c]
Other comorbidities	287 (60.7)	140 (60.6)	74 (61.7)	73 (59.8)	0.958
Patients without comorbidities	64 (13.5)	38 (16.5)	17 (13.9)	9 (7.5)	0.109[a]
Smoking, n (%)					
Current smoker	223 (49.2)	98 (45)	65 (54.2)	60 (52.2)	
Former smoker	211 (46.6)	101 (46.3)	55 (45.8)	55 (47.8)	< 0.001[c]
Non smoker	19 (4.2)	19 (8.7)	0 (0)	0 (0)	
Pack-years	**N = 388**	**N = 176**	**N = 105**	**N = 107**	
Median (IQR)	80 (49.5 – 100)	66.5 (40 – 100)	80 (60 – 100)	80 (50 – 100)	0.020[b] *

IQR: interquartile range; a) Pearson's chi square; b) Kruskal – Wallis equality of populations rank test with correction for ties; c) Likelihood ratio chi square test.
* $p < 0.05$ for comparison between Adenocarcinoma and Squamous; Dunn's Test was used with Bonferroni corrections.

3. Results

3.1. Baseline profile

In our analysis, 231, 120 and 122 patients diagnosed with Adenocarcinoma, SCLC and Squamous, respectively, were included, while 70 patients with other types of cancer were excluded. The demographic and anthropometric characteristics as well as the smoking habits and comorbidities of patients, overall and by histological type are presented in Table 1. Most patients were male (78.2%) and the median (IQR and range) age was 66.8 (60.6–73 and 36.8–88.1, respectively) years. Patients diagnosed with Adenocarcinoma were younger compared to those diagnosed with SCLC and Squamous ($p = 0.002$). The prevalence of overweight/obesity was higher in patients with SCLC (˜ 70%) compared to those with Adenocarcinoma (˜ 56%) or Squamous (˜ 51%) ($p = 0.028$). The most frequent comorbidities were cardiovascular disease (59.6%) and respiratory conditions (24.3%), as well as dyslipidemia (23.3%) and diabetes mellitus (22.2%). At least 95.8% of patients were smokers at the time of diagnosis or used to be smokers and the median (IQR) pack-years of smoking was 80 (49.5–100). More patients with SCLC or Squamous were currently smokers compared to patients with Adenocarcinoma ($p < 0.001$), while patients with SCLC had a longer smoking history, as expressed by pack-years, compared to patients with Adenocarcinoma ($p = 0.020$).

3.2. Profile at diagnosis

Almost half of patients (52.7%) were diagnosed at metastatic stage (IV) and 28.1% at locally advanced stage (III) [data not shown]. Patients with SCLC were more likely to be diagnosed at stage III or IV compared to the rest of patients ($p < 0.001$). The most frequent symptoms that patients experienced in the overall sample were cough (33.6%), dyspnea (18.2%) and pain (17.3%). The symptoms mentioned above were the most frequent among patients diagnosed with Adenocarcinoma or SCLC, while cough, weight loss and hemoptysis were the three most frequently reported symptoms among those diagnosed with Squamous. The vast majority of patients (˜93%) had histological diagnosis with or without cytological diagnosis and only 7.2% of patients had cytological diagnosis only, with no difference detected among the three histological types. Regarding the sampling method used for diagnosis, most patients were diagnosed with bronchoscopy and this percentage ranged from 39.8% among patients with Adenocarcinoma to 79.2% among those with SCLC ($p < 0.001$). A total of 31.9% of the patients had restricted activity with ability for light work. For another 31.7% of patients the performance status was not reported. The distribution of performance status differed across the histological types of cancer. Patients with Adenocarcinoma or Squamous were associated with better performance (66.7% and 70.5% of patients had normal activity or restricted but light work availability, respectively) compared with patients with SCLC (57.5%) ($p < 0.001$) (Table 2).

Table 2
Diagnosis-related characteristics of patients, overall and by histological type.

Diagnosis-related characteristics	Overall	Histologic type of cancer			p-value
	N = 473	Adenocarcinoma N = 231	Squamous N = 122	SCLC N = 120	
Reasons which led to diagnosis of cancer, n (%)					
At least one symptom	372 (78.7)	166 (71.9)	97 (79.5)	109 (90.8)	0.001[a]
Finding in a routine chest x-ray with no other symptom	47 (9.9)	32 (13.9)	12 (9.8)	3 (2.5)	
Patients with finding at a routine check for an existing chronic disease	54 (11.4)	33 (14.3)	13 (10.7)	8(6.7)	
Number of symptoms per patient, median (IQR)	1 (1 – 2)	1 (0 – 2)	1 (1 – 2)	2 (1 – 2)	< 0.001
Patients with 1 symptom, n (%)	189 (40)	96 (28.1)	42 (35)	51 (41.8)	
Patients with 2 or more symptoms, n (%)	183 (28.7)	70 (30.3)	46 (37.7)	67 (55.8)	
Most common symptoms reported, n (%)					
Cough	159 (33.6)	61 (26.4)	42 (34.4)	56 (46.7)	0.001[a]
Haemoptysis	71 (15)	30 (13)	22 (18)	19 (15.8)	0.432[a]
Dyspnea	86 (18.2)	37 (16)	18 (14.8)	31 (25.8)	0.040[a]
Pain	82 (17.3)	39 (16.9)	14 (11.5)	29 (24.2)	0.032[a]
Weight loss	50 (10.6)	14 (6.1)	23 (18.9)	13 (10.8)	0.001[a]
Fever	37 (7.8)	19 (8.2)	10 (8.2)	8 (6.7)	0.862[a]
Fatigue	32 (6.8)	8 (3.5)	11 (9)	13 (10.8)	0.017[a]
Any other symptom	7 (1.5)	4 (1.7)	1 (0.8)	2 (1.7)	
Cancer staging, n (%)					
Early stage (I, II)	90 (19.2)	57 (25)	30 (24.6)	3 (2.5)	< 0.001[a]
Locally advanced/metastatic stage (III, IV)	379 (80.8)	171 (75)	92 (75.4)	113 (97.5)	
Source of referral to oncologists, n (%)					
Pulmonologist	281 (64.7)	118 (57.8)	67 (59.3)	96 (82.1)	
Thoracic surgeon	110 (25.4)	61 (29.9)	39 (34.5)	10 (8.5)	< 0.001[a]
Other	43 (9.9)	25 (12.3)	7 (6.2)	11 (9.4)	
Patients with histological or cytological test, n (%)					
Only histological	332 (70.2)	154 (66.7)	83 (68)	95 (79.2)	
Only cytological	33 (7)	16 (6.9)	9 (7.4)	8 (6.7)	0.120[a]
With both exams	108 (22.8)	61 (26.4)	30 (24.6)	17 (14.2)	
Sampling method, n (%)					
Bronchoscopy	245 (51.8)	92 (39.8)	58 (47.5)	95 (79.2)	
CT-Guided biopsy	71 (15)	38 (16.5)	24 (19.7)	9 (7.5)	
Open biopsy	17 (3.6)	9 (3.9)	8 (6.6)	0 (0)	< 0.001[a]
Surgery	99 (20.9)	67 (29)	27 (22.1)	5 (4.2)	
Other method	41 (8.7)	25 (10.8)	5 (4.1)	11 (9.2)	
Performance status, n (%)					
Normal activity	113 (23.9)	69 (29.9)	21 (17.2)	23 (19.2)	< 0.001[a]
Restricted but light work	196 (41.4)	85 (36.8)	65 (53.3)	46 (38.3)	
Self-caring. Unable to work. Mobile > 50% working hours	68 (14.4)	26 (11.3)	13 (10.7)	29 (24.2)	
Limited self-care only. Mobile > 50% working hours OR Completely disabled. Immobile	39 (8.3)	15 (6.5)	10 (8.2)	14 (11.7)	
Not reported	57 (12.1)	36 (15.6)	13 (10.7)	8 (6.7)	

IQR: Interquartile range; a) Pearson's chi square test; b) Likelihood ratio chi square test.

3.3. Cancer diagnostic pathway

Median (IQR) for each interval, as well as the treatment modalities received, for the overall sample and for each histological type separately are presented in Table 3. The median (IQR) StD was 52 (28–104) days and no statistically significant differences were detected among the three histological types (p = 0.301). The median (IQR) DtT was 23 (13–36) days, with no significant differences detected among those starting their treatment with systemic therapy, radiotherapy or surgery (p = 0.623; data not shown). This time interval was shorter among patients with SCLC compared to the other two histological types (p < 0.001). Among Adenocarcinoma patients, the median (IQR) DtT was higher in those who started their treatment with systemic therapy (30 (20–41) days) compared to those subjected first to surgery (23 (12–41) days), although this difference did not reach statistically significance (p-value = 0.373; data not shown). The median (IQR) StT was 81 (51–139) days, ranging from 64 (40–115) days to 90 (60–154) days for SCLC and Adenocarcinoma, respectively (p = 0.007) (Table 3). The time interval of StD was shorter among patients with locally advanced/metastatic disease compared to those with early disease (p < 0.05), with a median (IQR) equal to 50 (27–101) days and 73 (46–134) days, respectively. Stratified analysis by histological type showed similar findings between Adenocarcinoma patients and Squamous cell carcinoma patients (Table S1 at Supplementary).

A statistically significant difference was observed in the distribution of first treatment received after diagnosis among the three histological types (p-value < 0.001): the majority of patients with adenocarcinoma or squamous received systemic therapy (52.5% and 59.8%, respectively) and surgery with or w/o neoadjuvant (37.2% and 34.2%, respectively), while those with SCLC were mainly treated with systemic therapy (92.5%) (Table 3). The distribution of first treatment differed between early and locally advanced/metastatic stages (p-value < 0.05): patients in early stages were mainly subjected to surgery with or w/o neoadjuvant (96.6%), while the majority of those in locally advanced/metastatic stages were subjected to systemic therapy (79.4%) (Table S1 at Supplementary).

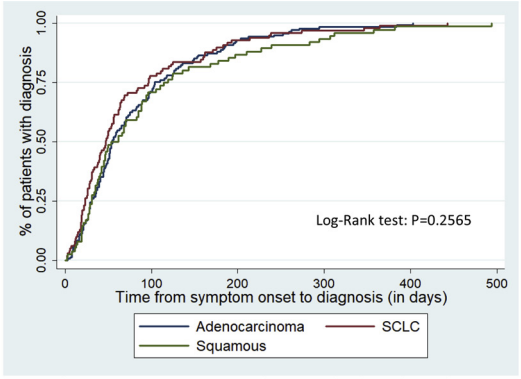
For patients firstly subjected to surgery, the median (IQR) SRGtT was found to be 42 (34–54) days, with no statistically significant deference detected between Adenocarcinoma and Squamous. More than three quarters of patients received adjuvant therapy post-surgery irrespective of histological type (Table 3).

The inversed Kaplan Meier curves for the intervals StD, DtR, DtT and SRGtT by histological type of cancer are presented in Fig. 1. The DtR and DtT varied statistically significantly across the three histological types (p < 0.001). No statistically significant differences were detected in intervals StD or SRGtT across the three histological types. Patients with SCLC experienced the shortest elapsed time from diagnosis to referral or treatment initiation compared with those with

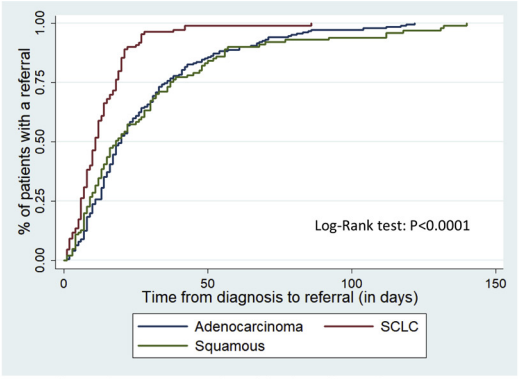
Table 3
Lung cancer patients' journey from symptoms onset to treatment initiation and first treatment that patients receive in Greece.

	Overall	Histological type of cancer			p-value
	N = 473	Adenocarcinoma N = 231	Squamous N = 122	SCLC N = 120	
Time passed (in days) from:					
Symptom onset to diagnosis	**N = 317**	**N = 142**	**N = 76**	**N = 99**	
Median (IQR)	52 (28 – 104)	55 (31 – 104)	58 (31 – 117)	47 (23 – 97)	0.3011[b]
90th quartile	193	184	239	183	
Diagnosis to referral [a]	**N = 401**	**N = 190**	**N = 101**	**N = 110**	
Median (IQR)	16 (9 – 30)	20 (11 – 36)	18 (9 – 37)	11 (6 – 18) [*,¥]	< 0.001[b]
90th quartile	52	63	57	24	
Diagnosis to treatment initiation	**N = 353**	**N = 150**	**N = 87**	**N = 116**	
Median (IQR)	23 (13 – 36)	29 (18 – 41)	26 (18 – 39)	13 (8 – 21) [*,¥]	< 0.001[b]
90th quartile	54	58	59	33	
Surgery to post – surgery treatment	**N = 86**	**N = 63**	**N = 23**		
Median (IQR)	42 (34 – 55)	42 (34 – 54)	43 (35 – 56)	–	0.891[e]
90th quartile	66	66	62	–	
Symptom onset to treatment initiation	**N = 261**	**N = 107**	**N = 58**	**N = 96**	
Median (IQR)	81 (51 – 139)	90 (60 – 154)	89 (43 – 161)	64 (40 – 115) [*,¥]	0.0068[b]
90th quartile	220	219	304	201	
First treatment received after diagnosis, n (%)					
Systemic therapy	298 (64.8)	117 (52.5)	70 (59.8)	111 (92.5)	
Radiotherapy	36 (7.8)	23 (10.3)	7 (6)	6 (5)	< 0.001[c]
Surgery with or w/o neoadjuvant	126 (27.4)	83 (37.2)	40 (34.2)	3 (2.5)	
First post – surgery treatment, n (%)					
Systemic therapy	16 (15.7)	12 (16.7)	4 (14.8)	0 (0)	
Radiotherapy	8 (7.8)	6 (8.3)	2 (7.4)	0 (0)	0.787[d]
Adjuvant	78 (76.5)	54 (75)	21 (77.8)	3 (100)	

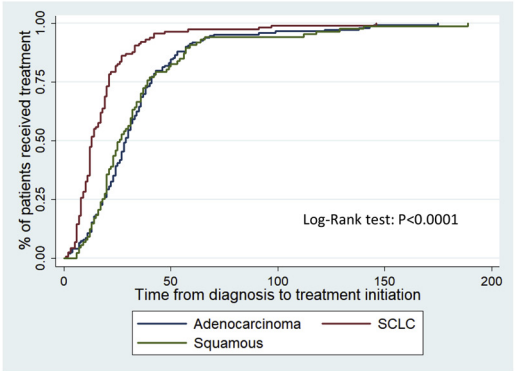
IQR: Interquartile range; Results for time intervals are presented with median (IQR), in days.
a) 8% of patients seem to be referred to an oncologist before the day of diagnosis, due to the delay of the histological or cytological exam; b) Kruskal – Wallis equality of populations rank test with correction for ties; c) Pearson's chi square test; d) Likelihood ratio chi square test; e) Mann – Whitney Test (patients with SCLC excluded due to very small sample size).
* $p < 0.05$ for comparison between SCLC and Adenocarcinoma; Dunn's Test was used with Bonferroni corrections.
¥ $p < 0.05$ for comparison between SCLC and Squamous; Dunn's Test was used with Bonferroni corrections.



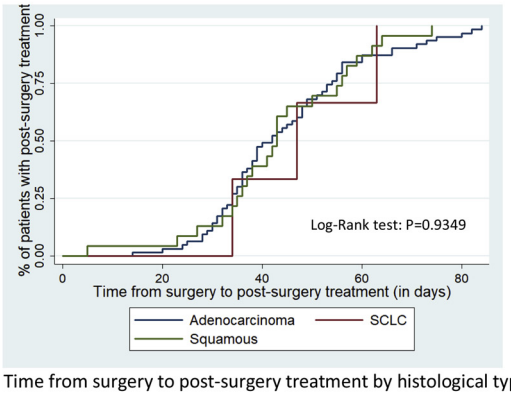
(a) Time from symptom onset to diagnosis by histological type



(b) Time from diagnosis to referral by histological type



(c) Time from diagnosis to treatment initiation by histological type



(d) Time from surgery to post-surgery treatment by histological type

Fig. 1. Inversed Kaplan Meier graphs of (a) StD, (b) DtR, (c) DtT and (d) SRGtT time intervals.

Table 4
Potential determinants of time interval from symptoms onset to diagnosis and from diagnosis to treatment initiation.

From diagnosis to treatment initiation	Crude		Adjusted [a]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender				
Female	Ref	–	Ref	–
Male	1.03 (0.79 – 1.33)	0.833	1.09 (0.84 – 1.43)	0.505
Age at diagnosis	0.99 (0.98 – 1.00)	0.142	0.99 (0.98 – 1.00)	0.093
Histological type of cancer				
Adenocarcinoma	Ref	–	Ref	–
SCLC	2.18 (1.70 – 2.79)	< 0.001	2.17 (1.69 – 2.8)	< 0.001
Squamous	0.96 (0.74 – 1.25)	0.756	1 (0.76 – 1.31)	0.983
Diagnosis with…				
Cytological exam	Ref	–	Ref	–
Histological exam	1.37 (0.94 – 1.99)	0.102	1.19 (0.81 – 1.74)	0.367
Both exams	0.97 (0.65 – 1.45)	0.878	0.92 (0.61 – 1.39)	0.693
Staging of cancer				
Early stage	Ref	–		
Locally advanced/metastatic stage	1.37 (0.86 – 2.17)	0.184		
Residence				
Country	Ref	–		
Suburban	1.13 (0.82 – 1.55)	0.447		
Urban	1.13 (0.89 – 1.42)	0.315		
Incidental diagnosis				
No	Ref			
Yes	1.17 (0.88 – 1.57)	0.283		
From symptoms onset to diagnosis	**Crude**		**Adjusted [b]**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Gender				
Female	Ref	–	Ref	–
Male	1.09 (0.82 – 1.44)	0.570	1.03 (0.75 – 1.41)	0.870
Age at diagnosis	1.00 (0.99 – 1.01)	0.951	1 (0.98 – 1.01)	0.784
Residence				
Country	Ref	–		
Suburban	0.86 (0.62 – 1.19)	0.356		
Urban	0.97 (0.76 – 1.24)	0.832		
Smoking				
Current smoker	Ref	–		
Former smoker	0.97 (0.76 – 1.22)	0.636		
Non smoker	1.05 (0.6 – 1.81)	0.870		
Cough	0.68 (0.54 – 0.85)	0.001	0.64 (0.50 – 0.83)	0.001
Dyspnea	1 (0.77 – 1.29)	0.680		
Pain	0.87 (0.66 – 1.13)	0.294		
Haemoptysis	0.88 (0.67 – 1.16)	0.366		
Education				
≤6 years	Ref	–		
6 to 12 years	0.88 (0.59 – 1.31)	0.536		
Higher	0.75 (0.37 – 1.52)	0.427		
BMI status				
Normal	Ref	–	Ref	–
Overweight	0.77 (0.59 – 1.02)	0.069	0.83 (0.63 – 1.1)	0.187
Obese	0.74 (0.54 – 1.02)	0.064	0.84 (0.6 – 1.17)	0.298
Respiratory comorbidity	0.85 (0.66 – 1.10)	0.207		
Cardiovascular comorbidity	1.02 (0.82 – 1.28)	0.862		
Diabetes mellitus	0.79 (0.6 – 1.04)	0.089	0.80 (0.58 – 1.11)	0.179
Dyslipidemia	0.9 (0.69 – 1.18)	0.434		

Parametric survival models with Weibull distribution were performed for the analysis; a] Adjusted for gender, age at diagnosis, histologic type of cancer, diagnosis examination; b] Adjusted for gender, age at diagnosis, cough symptom, BMI and diabetes mellitus comorbidity.
HR < 1 is interpreted as "less hazard to have the event" indicating delays in diagnosis and treatment.

Adenocarcinoma or Squamous.

Analysis using a multivariate parametric model revealed that the histological type was the only determinant of DtT, cough the only determinant of StD (Table 4) and patients' age the only factor associated with SRGtT (data not presented). More specifically, patients with SCLC received first treatment earlier than patients with Adenocarcinoma or Squamous, following adjustment for gender, age and method of diagnosis. Patients experiencing cough compared to those who experienced other than cough symptoms delayed asking medical advice as found after adjusting for gender and age. Finally, the time interval between surgery and post-surgery treatment was found to be longer in older patients.

4. Discussion

The current study was conducted based on data extracted from a hospital-based registry for lung cancer and sought to explore prolonged time intervals that may occur in lung cancer diagnosis and treatment in Greece. To the best of our knowledge, this is the first study aiming to measure specific time intervals from symptoms onset to treatment in Greece for lung cancer, the third most common cancer site and the most frequent cause of death in Greece.

The present study focused on Adenocarcinoma, Squamous and SCLC which are the most frequent histological types of lung cancer. Our results revealed that the time interval from appearance of first symptom to treatment initiation was 81 (51–139) days, ranging from 64 (40–115)

days for SCLC patients to 90 (60–154) days for Adenocarcinoma patients, respectively, suggesting that patients with poorer prognosis (i.e. SCLC) were diagnosed quicker. This time interval has been estimated in a limited number of previously conducted studies [7,24]. Comparing our results for this time interval to those from a study conducted in Canada [median (IQR) StT: 138 (79–175) days] [7], we revealed that it was shorter in Greece, but still long. On the other hand, the time between initial symptoms and treatment initiation in our study was found to be similar to that of other European countries (i.e France [3 (2–5.7) months] and Spain [87.5 (53–139) days]) [24,25].

The time passed till treatment initiation was mainly attributed to the time taken to diagnose lung cancer, since the median (IQR) StD was found to be 52 (28–104) days with no statistically significant differences detected among the three histological types. Comparing our findings with those of previously conducted studies in Europe and the US it was found that this time interval ranges from 41 to 187 days [5,26–29], revealing that this time interval was less prolonged in Greece. This time prolongation from symptoms onset to diagnosis might be attributed to the inability of patients and physicians to appreciate the severity of their symptoms. There is considerable evidence demonstrating that patients diagnosed with lung cancer experience a substantial delay in consulting with their doctor because they thought that their symptoms were not serious [11,12,30]. Moreover, physicians usually attribute these symptoms to respiratory infections hence initial treatment assignment may involve antibiotics, cough syrups or inhalers [10]. In general, the time interval between symptoms onset and diagnosis can be divided into the following: patient delay defined as the time passed from symptoms onset until first doctor's visit, doctor delay defined as the time passed from first doctor's visit to the date of the first diagnostic test request, and system delay defined as the time passed from the start of sign and symptom investigation to final diagnosis [7,14]. Unfortunately, the nature of our data does not allow us to detect the step of diagnostic process in which time prolongation occurs. However, education programs aiming to increase awareness of patients and physicians about lung cancer symptoms might be helpful to shorten the time taken to diagnosis. There is early evidence indicating that approaches to raise symptoms awareness resulted in early-stage lung cancer diagnosis [31]. We further explored the potential determinants of total diagnostic interval and found that cough prolonged this time interval.

In our study, the time passed between confirmed diagnosis and treatment initiation was 23 (13–36) days which is comparable with the corresponding intervals reported in studies conducted in other countries and close to the 1-month NHS National Cancer plan recommendation [32]. The median time between diagnosis and first treatment in other countries ranged from 12.5 days to 52 days [13,19,27,33]. Our results indicate that histological type is the only predictor of time interval between diagnosis and treatment and more specifically this interval seems to be significantly shorter among patients with SCLC, indicating that physicians are aware of the poor prognosis of these patients. Moreover, in the overall sample, no differences were detected in this time interval across different types of first treatment, whereas in a study conducted in Canada this time interval varied, reporting 35 days, 49 days and 52 days for those starting their treatment with radiotherapy, surgery and systemic therapy, respectively [33]. Finally, a median time of 42 days was found for the time interval between surgery and post-surgery treatment, a time prolongation similar to that detected in Canada [33]. Moreover, our data revealed that patient's age was associated with the SRGtT; a finding that is in line with the international literature [33].

The main study limitation is that this is a hospital-based registry and not a national population-based registry. Even though this hospital constitutes a reference center for lung cancer management in Greece, the sample of lung cancer patients is not representative of the whole population. Additionally, the patients admitted to this center are of moderate to low socioeconomic status as indicated by the educational status of our sample. Since sociodemographic characteristics of patients may influence the duration of diagnosis, the results of the present study should be interpreted cautiously. Moreover, the time interval from symptoms onset to diagnosis may be subject to recall bias, since the date of first symptom was self-reported. Finally, it should be mentioned that the fact that certain associations were found to be non-significant, including symptoms other than cough and comorbidities, could be attributed to the small sample size.

Despite some limitations in the present study, our results indicate that patients with lung cancer in Greece experience substantially prolonged time intervals from symptoms onset to diagnosis and treatment, even though shorter than that observed in other countries. Patients with cough as the first symptom experience a longer waiting time until diagnosis and patients diagnosed with NSCLC experience a longer delay in the time elapsed from diagnosis to treatment initiation. These findings provide useful insights in identifying populations at high risk of experiencing delays in the care pathway. Although more studies are needed to describe the lung cancer care pathway in Greece, it is becoming evident that policy initiatives to expedite lung cancer diagnosis and access to evidence-based treatment in Greece are needed.

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Declarations of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.04.014.

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