Lung cancer epidemiology based on bronchoscopic and imaging findings from newly diagnosed patients in Central Greece

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ABSTRACT

INTRODUCTION There is a current lack of epidemiological data regarding lung cancer in Greece. The aim of this study was to record and analyze pertinent data regarding demographic, clinical, radiological, bronchoscopic and histological findings in lung cancer cases over a ten-year period collected from a hospital in Central Greece, and to investigate potential specific features of lung cancer in Greek patients.

METHODS This was a retrospective cohort study. The data collected were obtained from newly diagnosed lung cancer patients with fiberoptic bronchoscopy during a ten-year period (2009–2018). From the database, we have extracted the demographic data, the tumor location based on the computed tomography (CT) scans, bronchoscopy report with associated images and the histopathology/cytology reports that yielded the diagnosis.

RESULTS A total number of 637 patients were diagnosed with primary lung cancer during the decade 2009–2018 from the authors in a major tertiary hospital in Athens, Greece. Most of the patients were aged 50–69 years (57.6%) and the majority were men (77.1%) and active smokers (74.1%). The most common histological type was adenocarcinoma (31.7%). In the majority of cases, the patients presented initially at advanced stages. At the time of diagnosis, the most common finding was a lung mass or nodule in computed tomography and an endobronchial mass in fiberoptic bronchoscopy. The patients' lesions were detected most frequently in the upper lobes.

CONCLUSIONS The results show a trend in ADLC histology, an increase in the proportion of women with lung cancer and highlight the significant percentage of patients diagnosed in advanced stages. This reflects the need for effective tobacco control strategies to reduce the incidence of lung cancer and a comprehensive national screening program for the purposes of early detection.

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INTRODUCTION

Lung cancer is currently the leading cause of death from neoplastic diseases worldwide. During the preceding decades, it was the most commonly occurring malignant disease, both in terms of impact and mortality. According to Globocan, it is estimated that for the year 2020 there were more than 2 million new cases and 1.7 million deaths from lung cancer, making lung cancer the most common and deadly malignant disease. In Greece, during 2020, almost 9000 new lung cancer cases were diagnosed[1]. Though lung cancer is the leading cause of death in most areas, the incidence rates vary significantly between countries, as they reflect the smoking habits, the socioeconomic status and cultural differences of each country as they evolve over time[2]. In Greece, in 13.8% of all newly diagnosed cancer cases during 2020, the primary location of the malignancy was the lung[2]; though, no further information on the specific features of the patients or their cancer characteristics was available. It is well known that available data for lung cancer epidemiology and specific features of lung cancer patients in Greece are scarce, as there is no official registry for lung cancer. It is unquestionable that epidemiology is the key to understanding the specific features of a disease in a local population, so every scientific information available is important to be collected in order to achieve an insightful perspective on the disease burden in the Greek population. The aim of the study was to record the epidemiological characteristics of patients newly diagnosed with lung cancer, from January 2009 to December 2018 at the Bronchoscopy Unit of a large tertiary Hospital of Greece and

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to compare them with similar data from previous years from the international literature, in order to investigate potential differences in the features of the local population.

METHODS

This was a retrospective epidemiological cohort study. For this study we used data retrieved from the Bronchoscopy Unit database of the Pulmonology Department of the General Hospital 'Evangelismos', which is one of the largest tertiary hospitals in Greece. The Bronchoscopy Unit follows yearly a large number of patients which undergo bronchoscopy for diagnostic or therapeutic purposes.

The aforementioned database contained the retrospective data obtained from all patients diagnosed with neoplastic disease via fiberoptic bronchoscopy (FOB) from January 2009 to December 2018. From the database, we have extracted the demographic data (gender, age, smoking habit), the tumor location based on the computed tomography (CT) scans, bronchoscopy report with associated images, and the histopathology/cytology reports that yielded the diagnosis. The report from the CT performed before the initial bronchoscopy was studied, providing further information regarding staging. The diagnosis in each patient was established by the histopathological examination and/or assessment of the tissue biopsy of transbronchial needle biopsy (TBNB), from the cytology of bronchoalveolar lavage (BAL), washing fluid and brushing.

In this study we only included patients with primary lung cancer and we excluded patients that were diagnosed with a prior history of lung cancer, secondary lung cancer of extra-pulmonary origin, lymphoma or atypia without the confirmation of at least in situ carcinoma.

All the patients of the study had received an initial chest CT, and under the suspicion of a primary lung cancer, further investigation with FOB was scheduled. The results were stratified according to demographics, patient symptoms, CT imaging findings, FOB findings, and histology/cytology. The smoking status of the patients has been recorded based on the information they provided. The exposure has been measured as pack-years, meaning how many cigarettes they have smoked in their lifetime, with a pack equal to 20 cigarettes. A cut-off of 30 pack-years has been used to stratify heavy and light smokers. The current smoking status has been recorded as current smokers for those who continued smoking during the time of diagnosis, ex-smokers for those that had quit at least a year before diagnosis, and never smokers for those that have never been smokers.

All the patients consented to FOB (Olympus video bronchoscope) in our Bronchoscopy Unit. The findings of the bronchoscopy were reported right after the procedure and in most cases pictures of the endoscopic findings were taken.

The pathological types of the tumors had been classified according to the 2021 WHO classification for lung tumors[3] as: 1) Adenocarcinoma (ADLC), 2) Squamous cell carcinoma (SqCLC), and neuroendocrine tumors divided into: 3) Small cell lung cancer (SCLC), 4) Large cell neuroendocrine carcinoma (LCNEC), and 5) Adenosquamous carcinoma (combined type). Some non-small cell lung cancer types (NSCLC) that could not be further specified were classified as: 6) Not otherwise specified (NOS), and finally 7) Other, all the rare types found that cannot be classified in one of the previous categories.

Statistical analysis

Categorical variables are presented as mean and standard deviation (SD), and qualitative variables as absolute and relative frequencies. For comparisons of proportions, chi-squared and Fisher's exact tests were used. Student's t-tests were computed for comparison of mean values when the distribution was approximately symmetric. All p values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS 23.0 software.

RESULTS

A total of 637 patients were diagnosed with primary lung cancer between January 2009 and December 2018 at the Bronchoscopy Unit of the Pulmonary Department of the 'Evangelismos' Hospital. In all cases, the diagnosis was made through Fiberoptic Bronchoscopy, after the endoscopic acquisition of endobronchial sampling, transbronchial sampling, bronchial washing fluid, bronchial brushing and/or bronchoalveolar lavage (BAL), and the subsequent histopathological and/or cytological examinations.

Epidemiology

The patients' age ranged 36–91 years, but the majority (57.6%) of patients were aged 50–69 years at the time of diagnosis. Very few patients (3.3%) were aged <49 years. The mean age of the patients was 66 years and the median age of the patients was also 66 years. The majority of patients were men (77.1%) and only 22.9% were women (Table 1). In terms of smoking history, there is a significant percentage of missing data, but most of the patients were active smokers at the time of diagnosis (74.3%). Less than 10% had never been smokers and the majority had over 30 pack-years (Table 1).

At the time of diagnosis distant metastases were confirmed in 389 (61%) patients and 450 (70%) had enlarged lymph nodes in the mediastinum or other locations, as detected by the CT chest. Thirteen patients were classified as stage I or II, identified by CT scan and bronchoscopy, without further investigation. Even though the location of the primary tumor was the lungs for all patients, 48.7% had main symptoms from the respiratory system. The most common initial complaint of the patients was persistent cough (15.4%), symptoms from distant metastases (15.1%), and general symptoms (e.g. fatigue, fever, weight loss) (14%). A significant proportion of the patients (14.9%) had no symptoms at the time of diagnosis and the detection of the

Table 1. Demographic data, main symptom, computed tomography images and endobronchial findings from fiberoptic bronchoscopy of the patients at the time of diagnosis with primary lung cancer

	n (%)
Age (years)	
<40	2 (0.3)
40–49	19 (3.0)
50–59	128 (20.2)
60–69	238 (37.5)
70–79	184 (29.0)
≥80	64 (10.1)
Missing	2
Gender	
Male	491 (77.1)
Female	146 (22.9)
Smoking habit (pack-years)	
No	35 (8.2)
<29	17 (4.0)
≥30	376 (87.9)
Missing	209
Smoking status	
Never	35 (7.7)
Current smoker	338 (74.3)
Ex-smoker (quit >1 year)	82 (18.0)
Missing	181
Symptoms	
Cough	98 (15.4)
Distal metastases	96 (15.1)
Random finding	95 (14.9)
General symptoms	89 (14.0)
Hemoptysis	82 (12.9)
Dyspnea	71 (11.1)
Chest pain	56 (8.8)
Other/no data	50 (7.9)
Computed tomography findings	
Mass/nodule	368 (57.8)
Distal metastases	136 (21.4)
Pleural effusion	56 (8.8)
Mediastinal lymph node enlargement	32 (5.0)
Atelectasis	28 (4.4)
Consolidation–ground glass opacity	15 (2.4)
Other	2 (0.3)
Endobronchial findings (FOB)	
Endobronchial mass	235 (36.9)
Submucosal infiltration	215 (33.8)
No visible lesion	112 (17.6)
External pressure	73 (11.5)
Other	2 (0.3)

FOB: fiberoptic bronchoscopy.

malignancy was an incidental finding (Table 1).

In the initial CT scan performed before the FOB that set the diagnosis, the most common finding was one or more nodules or masses in the lungs. Although in most cases the chest CT scan showed findings located in the lung parenchyma or bronchi, about one-fourth of the patients had only findings outside of the lungs, most commonly from metastatic locations. In less than 10% of the cases, the main finding was a pleural effusion, atelectasis, ground glass opacities, consolidation or mediastinal lymph node enlargement (Table 1). A FOB has been performed in all patients and the histological/cytological examinations of collected specimens established the diagnosis. Though, 36.9% of the patients presented a visible endobronchial lesion, the remainder featured the presence of a submucosal lesion, external pressure at the bronchi, or no pathological

Table 2. Histopathological type of the tumor and location of the primary lung cancer lesion at the time of diagnosis

Diagnosis	n (%)
Histopathological type of tumor	
ADLC	202 (31.7)
SqCLC	169 (26.5)
SCLC	165 (25.9)
NSCLC NOS	67 (10.5)
LCNEC	9 (1.4)
Combined	5 (0.8)
Other	20 (3.1)
Location	
Right lung (RL)	252 (39.6)
Right upper lobe (RUL)	163 (25.9)
Right middle lobe (RML)	29 (4.6)
Right lower lobe (RLL)	60 (9.4)
Left lung (LL)	140 (22.0)
Left upper lobe (LUL)	82 (12.9)
Lingula	7 (1.1)
Left lower lobe (LLL)	51 (8.0)
>1 lobe ipsilateral	132 (27.0)
>1 lobe contralateral	40 (6.3)
Outside lung parenchyma/bronchi	29 (4.6)
Mediastinum	12 (1.9)
Trachea	17 (2.7)
Unidentified primary location	44 (6.9)

ADLC: adenocarcinoma. SqCLC: squamous cell carcinoma. SCLC: small cell lung cancer. NSCLC: non-small cell lung cancer. NOS: no otherwise specified. LCNEC: large cell neuroendocrine carcinoma.

Table 3. Correlation of the location of the primary lesions with the symptoms of the patients, the presence of lymphadenopathy, the endobronchial findings from fiberoptic bronchoscopy and computed tomography findings at the time of diagnosis

Factors	Location										
	RUL	RML	RLL	LUL	LLL	LG	MS	TR	>1 lesion ipsilateral	>1 lesion contralateral	UPL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Symptoms (p<0.001)											
Hemoptysis	20 (12.3)	7 (24.1)	9 (15.0)	11 (13.4)	9 (17.6)	1 (14.3)	0 (0)	2 (11.8)	16 (12.1)	7 (17.5)	0 (0)
Cough	36 (22.1)	5 (17.2)	9 (15.0)	9 (11.0)	6 (11.8)	0 (0)	0 (0)	2 (11.8)	21 (15.9)	7 (17.5)	1 (4.8)
Dyspnea	13 (8.0)	2 (6.9)	7 (11.7)	9 (11.0)	3 (5.9)	0 (0)	2 (16.7)	4 (23.5)	20 (15.2)	8 (20.0)	0 (0)
Chest pain	11 (6.7)	3 (10.3)	8 (13.3)	8 (9.8)	5 (9.8)	0 (0)	1 (8.3)	0 (0)	10 (7.6)	4 (10.0)	4 (19.0)
General symptoms	19 (11.7)	4 (13.8)	7 (11.7)	15 (18.3)	7 (13.7)	1 (14.3)	5 (41.7)	5 (29.4)	19 (14.4)	3 (7.5)	1 (4.8)
Secondary locations	26 (16.0)	4 (13.8)	10 (16.7)	10 (12.2)	8 (15.7)	1 (14.3)	0 (0)	2 (11.8)	16 (12.1)	6 (15.0)	8 (38.1)
Random finding	26 (15.9)	3 (10.3)	6 (10.0)	14 (17.1)	13 (25.5)	2 (28.6)	3 (25.0)	0 (0)	12 (10.3)	3 (7.5)	4 (19.0)
Other/No data	12 (7.4)	1 (3.4)	4 (6.7)	6 (8.3)	0 (0)	2 (28.6)	1 (8.3)	2 (11.8)	15 (11.4)	2 (5.0)	3 (14.3)
Lymphadenopathy (p<0.001)											
Yes	119 (73)	17 (58.6)	44 (73.3)	42 (51.2)	32 (62.7)	3 (42.9)	10 (83.3)	12 (70.6)	92 (69.7)	39 (97.5)	21 (100)
No	44 (27)	12 (41.4)	16 (26.7)	40 (48.8)	19 (37.3)	4 (57.1)	2 (16.7)	5 (29.4)	40 (30.3)	1 (2.5)	0 (0)
Endobronchial findings (FOB) (p<0.001)											
No visible lesion	16 (9.8)	2 (6.9)	14 (23.3)	11 (13.4)	12 (23.5)	3 (42.9)	7 (58.3)	0 (0)	5 (3.8)	3 (7.5)	19 (90.5)
Endobronchial mass	75 (46.1)	12 (42.4)	23 (38.4)	38 (46.3)	19 (37.2)	3 (42.9)	2 (16.6)	8 (47.1)	0 (0)	1 (2.5)	0 (0)
Submucosal infiltration	50 (30.7)	12 (41.4)	12 (20.0)	26 (31.7)	13 (25.5)	1 (14.3)	0 (0)	8 (47.1)	73 (55.3)	20 (50.0)	0 (0)
External pressure	22 (13.5)	3 (10.3)	11 (18.3)	7 (8.5)	6 (11.8)	0 (0)	3 (25.0)	1 (5.9)	13 (9.8)	3 (7.5)	1 (4.8)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
Computed tomography findings (p<0.001)											
Mass/nodule	101 (62)	14 (48.3)	33 (55.0)	52 (63.4)	38 (74.5)	5 (71.4)	5 (41.7)	9 (52.9)	73 (55.3)	17 (42.5)	5 (23.8)

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Table 3. Continued

Factors	Location										
	RUL	RML	RLL	LUL	LLL	LG	MS	TR	>1 lesion ipsilateral	>1 lesion contralateral	UPL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Atelectasis	7 (4.3)	4 (13.8)	1 (1.7)	5 (6.1)	1 (2.0)	0 (0)	0 (0)	0 (0)	10 (7.6)	0 (0)	0 (0)
Pleural effusion	6 (3.7)	2 (6.9)	7 (11.7)	6 (7.3)	3 (5.9)	0 (0)	0 (0)	3 (17.6)	19 (14.4)	5 (12.5)	3 (14.3)
Consolidation-GGO	7 (4.3)	0 (0)	2 (3.3)	2 (2.4)	0 (0)	0 (0)	0 (0)	1 (5.9)	2 (1.5)	0 (0)	0 (0)
Lymph node enlargement	7 (4.3)	3 (10.3)	2 (3.3)	1 (1.2)	1 (2.0)	1 (14.3)	4 (33.3)	2 (11.8)	5 (3.8)	1 (2.5)	3 (14.3)
Metastatic lesions	35 (21.5)	6 (20.7)	14 (23.3)	16 (19.5)	8 (15.7)	0 (0)	3 (25.0)	2 (11.8)	23 (17.4)	17 (42.5)	10 (47.6)
Other	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

RUL: right upper lobe. RML: right middle lobe. RLL: right lower lobe. LUL: left upper lobe. LLL: left lower lobe. LG: lingula. MS: mediastinum. TR: trachea. UPL: unidentified primary lesion. CT: computed tomography. GGO: ground glass opacity. FOB: fiberoptic bronchoscopy.

findings (Table 1).

As far as endoscopic inspection at the time of diagnosis, the most commonly observed finding was an endobronchial mass (36.9%), but in only 2.4% of the patients the endobronchial mass caused signs of bronchial obstruction. In a significant proportion (17.6%), no visible lesion had been detected during bronchoscopy and the diagnosis was made without direct visualization of the lesion under the guidance of CT images and endobronchial ultrasound (EBUS).

The most common histopathological diagnosis was adenocarcinoma (ADLC) (31.7%), followed by squamous cell carcinoma (SqCLC) and small cell carcinoma (SCLC) (26.5% and 25.9%, respectively). A less commonly observed diagnosis was non-small-cell-lung carcinoma non-otherwise-specified (NSCLC-NOS). Various not commonly observed histopathological diagnoses had appeared in a very small percentage and were grouped under the term 'Other', and 57.8% of the patients had a solitary lesion in the lungs and only in a small percentage the lesion was not identified inside the lung parenchyma or the bronchi. In the majority of patients, the lesion was located in the right lung (39.6%) and more specifically in the right upper lobe (RUL) (25.9%). The upper lobes in both lungs were generally a common location for a primary lesion (35.6%) (Table 2).

Correlation of the primary tumor location with other characteristics of the patients and tumor features

The location of the primary tumor correlated with statistical significance to specific characteristics of the patients' symptomatic presentation during the initial assessment ($p<0.001$); this p-value applies to the general category of symptoms, meaning that the symptoms of the patients were statistically significant related to the location of the tumor (Table 3). When the location of the primary tumor was in the right middle lobe (RML), they presented most frequently with hemoptysis (24.1%). The patients with a primary lesion in the RUL experienced cough more often (22.1%) and the patients with findings only in the mediastinum had mainly general systemic symptoms (41.7%).

The patients presented more often with lymph node enlargement, as detected at the initial CT assessment when their primary tumor was located in the RUL, right lower lobe (RLL), mediastinum or when they presented with multiple ipsilateral or contralateral lesions ($p<0.001$) (Table 3).

The patients smoking history showed no statistically significant correlation with the location of the tumor ($p=0.222$). Submucosal infiltration was the most commonly observed endoscopic sign for multiple lung lesions, as seen in 55.3% of cases with more than one ipsilateral lesion and 50% of cases with multiple contralateral lesions. When the lesion was located in the RUL or RML, it was most commonly visualized endobronchially ($p<0.001$), with exception in lesions located in the lingula and thus not easily accessible. Distant metastases were identified more often when the patients had multiple pulmonary contralateral lesions (42.5%) on their initial CT scan, and pleural effusions were present most commonly in patients who had multiple ipsilateral lesions (14.4%). When the main lesion was located in the left lung, the CT showed a mass or nodule in almost all cases but in the right lung we often had other findings, such as consolidations, ground glass opacities (GGOs), atelectasis or distant metastases ($p<0.001$) (Table 3).

Correlation of the primary tumor pathology with other characteristics of the patients and tumor features

The majority of patients were smokers, a finding independent of the histological type of the tumor (Table 4). Among the thirty-five non-smoker patients, seventeen of them had an ADLC, there was though a small number of five non-smokers with SCLC ($p=0.028$); this p-value and all relevant p-values apply to the general categories compared and not to an individual characteristic. Half of the patients with ADLC or neuroendocrine tumors had recognizable distant metastases at the time of diagnosis, but this percentage was significantly lower for patients with SqCLC (27.2%) ($p<0.001$) (Table 4). Comparing the histological type of the tumor with the CT findings, patients with neuroendocrine tumors had a higher rate of metastatic disease (27.3%) than other histological types, and patients with SqCLC had more often a solitary mass or nodule at initial imaging (65.1%) ($p<0.001$). The evidence of lymph node involvement from the CT was not correlated with statistical significance to the histologic diagnosis ($p=0.063$) (Table 4).

Correlation of the patients' symptoms with other characteristics of the patients and tumor features

Irrespective of the main presenting symptom, the most common radiological sign was a mass or nodule located in the lungs. Though, in patients who presented with symptoms attributable to distant metastases, the main radiological finding was evidence of metastatic disease (59.4%) (Table 5). Also, patients presenting with dyspnea had an associated pleural effusion (36.6%) and patients with disease located only in the mediastinum presented more often with generalized systemic symptoms (11.2%) ($p<0.001$); this p-value and all relevant p-values apply to the general categories compared and not to an individual characteristic.

Patients presenting with dyspnea, chest pain or generalized symptoms had an associated lymphadenopathy with a prevalence of approximately 70%, but when presenting with hemoptysis this percentage was lower (53.7%). Almost all the patients who presented with symptoms from distant metastases had pathologically enlarged lymph nodes at the CT scan at the time of diagnosis (92.7%) ($p<0.001$).

Finally, when comparing the endobronchial findings during the FOB that established the diagnosis with the existence of distant metastases, a lower rate of metastases was observed when the main finding was an endobronchial mass (30.2%)

Table 4. Correlation of histopathologic type of the cancer with the smoking habit of the patients, the existence of distal metastases and the computed tomography findings

Factors	Histopathological type						
	ADLC	SqCLC	SCLC	NSCLC NOS	Combined	LCNEC	Other
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Smoking habit (p=0.028)							
Yes	130 (88.4)	114 (94.2)	106 (95.5)	29 (93.5)	2 (100)	5 (100)	7 (63.6)
No	17 (11.6)	7 (5.5)	5 (4.5)	2 (6.5)	0 (0)	0 (0)	4 (36.4)
Distal metastases (p=0.007)							
Yes	91 (45.0)	46 (27.2)	71(43.0)	26 (38.8)	3 (60.0)	5 (55.6)	6 (30.0)
No	111 (55.0)	123 (72.8)	94 (57.0)	41 (61.2)	2 (40.0)	4 (44.4)	14 (70.0)
Computed tomography findings (p<0.001)							
Mass/nodule	114 (56.4)	110 (65.1)	84 (50.9)	37 (55.2)	4 (80.0)	5 (55.6)	14 (70.0)
Atelectasis	5 (2.5)	16 (9.5)	4 (2.4)	2 (3.0)	0 (0)	0 (0)	1 (5.0)
Pleural effusion	24 (11.9)	12 (7.1)	14 (8.5)	5 (7.5)	0 (0)	0 (0)	1 (5.0)
Consolidation-GGO	3 (1.5)	5 (3.0)	3 (1.8)	2 (3.0)	0 (0)	0 (0)	2 (10.0)
Lymph node enlargement	7 (3.5)	2 (1.2)	15 (9.1)	5 (7.5)	0 (0)	3 (33.3)	0 (0)
Metastatic lesions	49 (24.3)	23 (13.6)	45 (27.3)	15 (22.4)	1 (20.0)	1 (11.1)	2 (10.0)
Other	0 (0)	1 (0.6)	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)

ADLC: adenocarcinoma. SqCLC: squamous cell carcinoma. SCLC: small cell lung cancer. NSCLC: non-small cell lung cancer. NOS: no otherwise specified. LCNEC: large cell neuroendocrine carcinoma. CT: computed tomography. GGO: ground glass opacity.

Table 5. Correlation of the symptoms of the patients with the computed tomography findings and the presence of lymphadenopathy

Factors	Symptoms							
	Hemoptysis	Cough	Dyspnea	Chest pain	General symptoms	Secondary locations	Random finding	Other/ no data
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Computed tomography findings (p<0.001)								
Mass/nodule	61 (74.4)	72 (73.5)	26 (36.6)	34 (60.7)	49 (55.1)	25 (26.0)	66 (78.6)	10 (71.4)
Atelectasis	5 (6.1)	6 (6.1)	2 (2.8)	2 (3.6)	5 (5.6)	2 (2.1)	1 (1.2)	0 (0)
Pleural effusion	4 (4.9)	5 (5.1)	26 (36.6)	6 (10.7)	4 (4.5)	3 (3.1)	2 (2.4)	1 (7.14)
Consolidation–GGO	0 (0)	2 (2.0)	1 (1.4)	2 (3.6)	5 (5.6)	4 (4.2)	1 (1.2)	0 (0)
Lymph node enlargement	3 (3.7)	1 (1.0)	4 (5.6)	1 (1.8)	10 (11.2)	5 (5.2)	3 (3.6)	2 (14.3)
Metastatic lesions	9 (11.0)	12 (12.2)	12 (16.9)	11 (19.6)	16 (18.0)	57 (59.4)	11 (13.1)	1 (7.14)
Lymphadenopathy (p<0.001)								
Yes	34 (53.7)	67 (68.4)	55 (77.5)	41 (73.2)	62 (69.7)	89 (92.7)	42 (62.2)	31 (62.0)
No	38 (46.3)	31 (31.6)	16 (22.5)	15 (26.8)	27 (30.3)	7 (7.3)	37 (37.8)	19 (38.0)

GGO: ground glass opacity.

or external pressure at the bronchi (38.4%). In the rest of the cases, this percentage was close to 50% (p<0.001) (Table 5).

DISCUSSION

Epidemiological data concerning the distribution and determinants of lung cancer in Greece are scarce, as there is no official registry for lung cancer. The objective of this study was to record and analyze basic epidemiological, clinical, radiological, bronchoscopic and histopathological/cytological data of lung cancer cases in Greece. During the aforementioned period, the diagnosis of primary lung cancer was established in 637 patients. As the exact number of lung cancer cases diagnosed in Greece during the same period is unknown, we cannot safely assume if the number of cases diagnosed in our Center is representative of the total cases in Central Greece. We can only compare our results with previous studies conducted in other Greek regions.

The mean age of the patients in our study was 66 years and the median age was 66 years, with a high proportion (57.6%) of patients aged 50–69 years. The majority of patients were men (77.1%) and active smokers at the time of diagnosis (74.3%). Two previous studies have also recorded lung cancer cases in larger populations, similarly to our study. Kontakiotis et al.[4] analyzed 9981 patients from northern Greece with bronchoscopic specimens positive for lung cancer over two decades (1986–2005). The mean age of all patients was 63.6 ± 9.3 years, while men represented the vast majority of the patients (92%). A second more recent study by Sifaki-Pistolla et al.[5] analyzed 5509 primary lung cancer cases diagnosed from 1992 to 2013 on the Greek island of Crete. Patients were mostly males (87.3%), aged >55 years (20.4% aged 55–64; and 35.2% aged 65–74). A positive smoking history was present in 75.1% of the cases[5]. One could hypothesize that in Greek populations the obvious predominance of males amongst lung cancer patients may be attributed, at least partly, to their smoking patterns[6,7]. Nevertheless, non-smoking related risk factors may also be important for the sex disparities in lung cancer incidence[8,9].

In our cohort study the most common radiological finding was the presence of one or more nodules or masses in the lungs. Less commonly (<10%), the initial radiological examination revealed pleural effusion, atelectasis, ground glass opacities, consolidation or mediastinal lymph node enlargement. Concerning patients with pulmonary lesions, two-thirds of them presented with a solitary lesion, most commonly located in one of the upper lobes and predominantly in RUL. This finding is in line with previous published results in Greek lung cancer patients by Kontakiotis et al.[4]. Other earlier studies have also reported a preference of lung cancer for the upper lobes[10,11]. This predilection of lung tumors to the upper lobes could be attributed to various anatomical and physiological factors that render the upper lobe vulnerable[12], including a more prolonged and intense contact with tobacco smoke inhalation[10]. It should be noted that in one-quarter of our cases, extrapulmonary metastatic lesions represented the only visible finding.

According to previous data, a substantial percentage of lung cancer cases in asymptomatic patients are detected upon radiological evaluation[13-15]. In our study, about 15% of our patients were asymptomatic at the time of diagnosis. Unfortunately, it is known that patients with lung cancer usually present late and around 80% of them have stage III or IV disease at presentation[16]. In accordance with this, most of our patients showed distant metastases or lymph node enlargement at the time of the diagnosis. Lymph node enlargement and distant metastases were more common in the presence of multiple pulmonary lesions. Thus, in our study the vast majority of patients were identified at stage III or higher by means of the initial CT scan and bronchoscopy. Similarly in the study of Sifaki-Pistolla et al.[5], most patients (61.6%) were diagnosed at stage IIIA or higher.

Lung cancer may present with non-specific systemic symptoms of fever, weakness, anorexia, and weight loss, or with a wide range of direct signs and symptoms, most commonly dyspnea, cough, hemoptysis, hoarseness, chest and shoulder pain[17,18]. Respiratory symptoms were present in about half of the patients of our study, while general symptoms were very common. Interestingly, our study showed that the frequency of certain symptoms seems to differ depending on the anatomic location of the malignant pathology. Hemoptysis was more frequent in lesions of the RML, while cough was more common in lesions of the RUL. Patients with isolated mediastinal pathology had mainly general symptoms. In patients complaining about dyspnea, the presence of a pleural effusion was more likely. Finally, lymph node enlargement was evident in chest CT scans with a higher frequency in the presence of dyspnea, chest pain, general symptoms or symptoms from distant metastases.

The fiberoptic bronchoscopy (FOB) represents a very valuable tool for the diagnosis and staging of lung cancer patients[19]. In our study, bronchoscopic findings included the presence of an endobronchial mass or submucosal pathology or external pressure at the bronchi. Endobronchial tumors were the most common finding as they were detected in 36.9% of the patients. Nonetheless, bronchial obstruction was rarely noticed. It should be noted that in about 18% of the cases, bronchoscopic examination did not reveal any visible lesion. This can be expected especially in peripheral lung cancers. Hence, the diagnosis was made without direct visualization of the lesion, but based on CT images and the use of EBUS. Submucosal infiltration was more common in the presence of multiple lung lesions, while visible endobronchial masses were more frequently located in RUL or RML. Finally, when the main bronchoscopic finding was an endobronchial mass or external pressure on the bronchial lumen, the presence of distant metastases was less frequent.

In our cohort of patients, ADLC was the most common histopathological type as it appeared in about one-third (31.7%) of cases. SqCLC and SCLC appeared almost equally in about one-quarter of the cases, respectively. This finding

is in line with previous studies reporting NSCLC as the predominant type accounting for 85% of all cases[20]. Other histopathological types appeared in very small percentages. The majority of our patients were smokers, independently of the histological type of the tumor. This seems to be in agreement with previous knowledge linking all histological subtypes with tobacco use[20]. Similarly to previous findings, our results showed a significant frequency of ADLC in non-smokers[21]. Our study provided interesting correlations of the histopathology of lung cancer with radiological characteristics. Recognizable distant metastases at the time of the diagnosis were more frequent when the histopathological diagnosis was ADLC compared with SqCLC. Moreover, when initial imaging revealed a solitary mass or nodule, SqCLC was the most commonly observed diagnosis. Radiologically evident lymph node involvement showed no correlation with any histological diagnosis.

Strengths and limitations

The most important strength of this study is that the data come from a significant number of lung cancer patients over a large period of time and a large amount of information regarding demographic data, tumor and patient features have been recorded. Even though 'Evangelismos' Hospital is one of the largest tertiary Hospitals in Greece, the number of cases diagnosed in our Bronchoscopic Unit is not representative of all Greek cases and this is a significant limitation of this study. Also, there is a significant number of missing data, mainly because we could not follow up the patients after diagnosis, for the information about the exact stage, the course of disease or the treatment followed.

Implications

The information that we have for newly diagnosed lung cancer cases in Greece is limited. The main problem is that there is not an accurate data collection method in every Center and the registry of cases is not mandatory. In the future, a national registry of lung cancer cases in Greece should be established. This includes the cooperation between large reference lung cancer centers and the establishment of a network of lung cancer specialists so a large database of primary lung cancer cases can be formed[22].

CONCLUSIONS

In Greece, the histological distribution of lung cancer has changed over the years showing a trend in increased ADLC percentage. Furthermore, the proportion of women presenting with lung cancer over the last decades has increased, which reflects on the increasing number of female smokers. Patients with lung cancer are diagnosed in more advanced stages, and, as a result, the chances for curative treatment are reduced. All of the above underline the need of more effective tobacco control strategies and for the establishment of official screening programs for the early detection of pulmonary malignancies.

CONFLICTS OF INTEREST

The authors have completed and submitted to ICMJE for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this retrospective study.

DATA AVAILABILITY

The data supporting this research are available from the authors upon reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

REFERENCES

1. Cancer Today. Global Cancer Observatory. 2020. Accessed September 2023. https://gco.iarc.fr/today/home
2. Lung Cancer. World Health Organization. June 26, 2023. Accessed September 2023. https://www.who.int/news-room/fact-sheets/detail/lung-cancer
3. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol. 2022;17(3):362-387. doi:10.1016/j.jtho.2021.11.003
4. Kontakiotis T, Manolakoglou N, Zoglopitis F, et al. Epidemiologic trends in lung cancer over two decades in Northern Greece: an analysis of bronchscopic data. Monaldi Arch Chest Dis. 2009;71(4):147-152. doi:10.4081/monaldi.2009.346
5. Sifaki-Pistolla D, Lionis C, Georgoulias V, et al. Lung cancer and tobacco smoking in Crete, Greece: reflections from a population-based cancer registry from 1992 to 2013. Tob Induc Dis. 2017;15:6. doi:10.1186/s12971-017-0114-2
6. Gikas A, Merkouris P, Skliros E, Sotiropoulos A. Urban-rural differences in smoking prevalence in Greece. Eur J Public Health. 2007;17(4):402. doi:10.1093/eurpub/ckm055
7. Filippidis FT, Vardavas CI, Loukopoulou A, Behrakis P, Connolly GN, Tountas Y. Prevalence and determinants of tobacco use among adults in Greece: 4 year trends. Eur J Public Health. 2013;23(5):772-776. doi:10.1093/eurpub/cks148
8. Hellyer JA, Patel MI. Sex disparities in lung cancer incidence: validation of a long-observed trend. Transl Lung Cancer Res. 2019;8(4):543-545. doi:10.21037/tlcr.2019.04.06
9. Stapelfeld C, Dammann C, Maser E. Sex-specificity in lung cancer risk. Int J Cancer. 2020;146(9):2376-2382. doi:10.1002/ijc.32716
10. Celikoğlu SI, Aykan TB, Karayel T, Demirci S, Göksel FM. Frequency of distribution according to histological types of lung cancer in the tracheobronchial tree. Respiration.

1986;49(2):152-156. doi:10.1159/000194873
11. Pavlovska I, Danilovski D, Orovchanec N, Stefanovski T, Taushanova B, Ivanovska-Zafirova B. An epidemiologic study of some characteristics of lung cancer. Folia Med (Plovdiv). 2004;46(3):23-31.
12. Casha AR, Manché A, Gauci M, Navarro A, Farrugia E. Common Pathophysiological Pathways for Apical and Upper Lobe Lung Disease. J Infect Dis Epidemiol. 2018;4:053. doi:10.23937/2474-3658/1510053
13. Jett JR, Midthun DE. Commentary: CT screening for lung cancer-Caveat Emptor. Oncologist. 2008;13(4):439-444. doi:10.1634/theoncologist.2008-0027
14. In KH, Kwon YS, Oh IJ, et al. Lung cancer patients who are asymptomatic at diagnosis show favorable prognosis: A Korean Lung Cancer Registry Study. Lung Cancer. 2009;64(2):232-237. doi:10.1016/j.lungcan.2008.08.005
15. Alanen V, Koivunen JP. Association of diagnostic delays to survival in lung cancer: single center experience. Acta Oncol. 2019;58(7):1056-1061. doi:10.1080/0284186X.2019.1590635
16. Pearson FG. Current status of surgical resection for lung cancer. Chest. 1994;106(6 Suppl):337S-339S. doi:10.1378/chest.106.6_supplement.337s
17. Hyde L, Hyde CI. Clinical manifestations of lung cancer. Chest. 1974;65(3):299-306. doi:10.1378/chest.65.3.299
18. Collins LG, Haines C, Perkel R, Enck RE. Lung cancer: diagnosis and management. Am Fam Physician. 2007;75(1):56-63. Accessed October 31, 2023. https://www.aafp.org/pubs/afp/issues/2007/0101/p56.pdf
19. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e165S. doi:10.1378/chest.12-2353
20. Belani CP, Marts S, Schiller J, Socinski MA. Women and lung cancer: epidemiology, tumor biology, and emerging trends in clinical research. Lung Cancer. 2007;55(1):15-23. doi:10.1016/j.lungcan.2006.09.008
21. Marquez-Garban DC, Mah V, Alavi M, et al. Progesterone and estrogen receptor expression and activity in human non-small cell lung cancer. Steroids. 2011;76(9):910-920. doi:10.1016/j.steroids.2011.04.015
22. Rich A, Baldwin D, Alfageme I, et al. Achieving Thoracic Oncology data collection in Europe: a precursor study in 35 Countries. BMC Cancer. 2018;18:1144. doi:10.1186/s12885-018-5009-y