Lung cancer symptoms at diagnosis: results of a nationwide registry study

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ABSTRACT

Background Lung cancer is currently the leading cause of cancer death. Despite its high incidence and mortality, there are few studies describing its symptoms at diagnosis broken down by tumour stage and tobacco use. Accordingly, this study was proposed to describe the frequency of the most common symptoms of non-small cell lung cancer and small cell lung cancer (SCLC) at diagnosis, with a breakdown by stage and tobacco use.

Patients and methods Cases were collected from the Spanish Thoracic Tumour Registry, a nationwide registry sponsored by the Spanish Lung Cancer Group. More than 50 hospitals recruited histologically confirmed lung cancer cases and information was gathered through personal interview plus data contained in the electronic clinical record. There were no data available on the lag between the appearance of the first symptoms and diagnosis of lung cancer.

Results A total of 9876 patients (74% male, median age 64 years) were recruited from 2016 to 2019. Of these, 12.5% presented with SCLC. Stage IV was the most frequent stage at diagnosis (46.6%), and the most frequent symptom was cough (33.9%), followed by dyspnoea (26.7%). No symptom was present in 59% of patients diagnosed in stage I; 40% of stage I patients presented with at least one symptom, while 27.7% of patients in stage IV had no symptoms at diagnosis. Cough was the most frequent symptom in SCLC (40.6%), followed by dyspnoea (34.3%). The number of symptoms was similar across the respective smoking categories in SCLC, and differences between the symptoms analysed did not exceed 7% in any case.

Conclusion The absence of the most frequent symptoms (ie, cough, pain, dyspnoea) should not lead to a decision to rule out the presence of lung cancer. A relevant percentage of stage IV patients displayed no symptoms at diagnosis.

Key messages

What is already known about this subject?

► All available case series describing lung cancer symptoms at diagnoses have a limited sample size. Furthermore, there is little research showing how lung cancer symptoms may differ between stage at diagnosis, smoking status or non-small cell lung cancer (NSCLC) and small cell lung cancer. We aim to describe lung cancer symptoms broken down according to these characteristics using the highest sample size published to date.

What does this study add?

► The most frequent symptom in NSCLC patients was cough (33%), followed by chest pain (25%). There is no clear predominant symptom, even in advanced stages. The presence of symptoms increases across stages. However, less than 50% of all stage IV patients have only one or two symptoms at diagnosis. There were no differences between smokers and never smokers in terms of presence of symptoms, or in the number of symptoms present at diagnosis

How might this impact on clinical practice?

► This information confirms the lack of specificity of lung cancer symptoms and the fact that the absence of the most frequent symptoms (ie, cough, pain and dyspnoea) should in no case lead to a decision to rule out the presence of this disease.

INTRODUCTION

Lung cancer is a serious public health problem worldwide. Although its incidence is falling in some countries, it continues to rise in others, particularly due to women's late incorporation into the smoking habit. In the USA, incidence of lung cancer accounts for 13% and 12% of all cancer cases in men and women, respectively, and is the second leading cancer overall.[1] It is also the leading cause of cancer-related deaths in both sexes, with one in four cancer-related deaths. In Spain, lung cancer is the third most incident tumour in both sexes; it is the most lethal cancer in men and the second in women.[2]

Lung cancer survival is very low and has hardly improved in recent decades despite important advances in immunotherapy and targeted therapies. Even so, over half of cases are diagnosed in stage IV. In the USA, the

5-year survival stands at 19.4%.[3] The CONCORD-3 study, based on cases diagnosed from 2000 to 2014, indicates a 5-year survival of 13.5% in Spain, similar to the UK rate but lower than that of Switzerland and Sweden (around 20%).[4]

This high percentage of late diagnoses is largely due to the non-specificity of most of the symptoms, to the fact that they are not as frequent as would be expected or to patient's delay in consulting their physician. Lung cancer symptomatology may be manifestly present in the diagnosis or consist of a general constitutional syndrome in which there is no clearly predominant specific lung cancer symptom.[5] The most frequent symptoms described in the literature (although with variations according to the study in question) are persistent cough, haemoptysis, chest pain, dyspnoea, cervical or supraclavicular lymphadenopathies, weight loss, metastatic pain, fatigue and fever.[6] While many of these symptoms can manifest jointly, something that facilitates diagnosis, a good number are also associated with the extent of disease at diagnosis. The presence of symptoms has been associated with prognosis of lung cancer[7] but few studies have analysed this symptomatology by reference to disease stage at diagnosis. In addition, there are few studies that compare the presence of symptomatology in smokers versus non-smokers. Furthermore, published studies, despite having sample sizes of over 1000 patients in some instances, continue to have insufficient-sized samples that accurately describe the presence of the symptoms which, though manifested less frequently, have a high pre-test probability, as is the case of superior vena cava syndrome and haemoptysis. Indeed, a systematic review published in 2014[8] concluded that, "Prospective studies are now needed that systematically record symptoms and explore their predictive values for lung cancer diagnosis."

Accordingly, this nationwide, multicentre, and retrospective analysis of prospectively and retrospectively collected information describes lung cancer symptoms in a recently diagnosed and representative case series, analysing separately non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); and specifically assess whether symptomatology might differ by stage at diagnosis and tobacco use.

MATERIALS AND METHODS
Design and setting
In terms of epidemiological design, this was a retrospective analysis of prospectively and retrospectively collected information from cases drawn from the Thoracic Tumour Registry managed by the Spanish Lung Cancer Group (SLCG), an independent cooperative group made up of more than 500 members, fundamentally medical oncologists.[9]

In 2015, we decided to initiate a nationwide multicentre epidemiological study aimed at ascertaining the characteristics of lung cancer cases, their treatments and survival, in an effort to offset the existing lack of information

caused by the absence of a national cancer registry. The study was designed to be opened to all Spanish hospitals; the first patient was enrolled in August 2016 and the recruitment is still ongoing. For study purposes, patients were drawn from 58 hospitals distributed throughout the country's Autonomous Regions, and other results from this Registry have recently been published.[9] The Registry was approved by the SLCG and is registered in the ClinicalTrials.gov database (NCT02941458). The protocol approval was obtained from the institutional review board of the Puerta de Hierro University Teaching Hospital (Majadahonda, Madrid) (no. PI 148/15).

All patients included presented with histologically confirmed lung cancer, without age or gender restrictions, and were systematically recruited at the participating hospitals by clinicians involved in the Registry.

Data retrieval
A purpose-designed electronic questionnaire was completed for all participants. This common data format was divided into the following sections: (a) demographic data (gender, age and so on); (b) detailed history of tobacco use; (c) lung cancer characteristics at diagnosis (including symptoms); (d) treatments received (with detailed information on each); (e) presence of specific mutations in driver genes at diagnosis; (f) disease progression; and, (g) survival data.

With respect to symptom presentation, the electronic questionnaire included information on the date and presence/absence of the following symptoms before the first consultation with the oncologist: cough; pain; dyspnoea; haemoptysis; weight loss; anorexia; asthenia; and others. Space was also provided for the inclusion of additional symptoms. Further categories were 'no symptoms' or 'unknown'.

Statistical analysis
Both univariate and bivariate analyses were performed: the univariate analysis described the sample characteristics, and the bivariate analysis compared the presence of different symptoms for NSCLC and SCLC respectively. For NSCLC, we performed a bivariate analysis describing the presence of specific symptoms and the total number of symptoms by tumour stage. We tested for the presence of trend using the Jonckheere-Terpstra non-parametric test (ie, to ascertain whether there was a trend for presence of cough by stage). A similar analysis was performed for SCLC but, in this case, we compared if there was any association between specific symptoms and limited or extended disease. To test this association, we used the χ^2 test. Finally, we compared the presence of different symptoms by smoking status, classified as never smoker (smoked less than 100 cigarettes over his/her lifetime), ex-smoker (stopped smoking more than 1 year before diagnosis) or current smoker (reported smoking during the year before diagnosis). Here we applied the same analysis that was used for NSCLC. All analyses were performed

using the SPSS V.24.0 computer software programme. Results were considered statistically significant at p<0.05.

RESULTS

The study covered 9876 patients recruited until June 2019. A breakdown of the sample showed the following; 74% male; median age 64 years; IQR 57 to 72 years; 12% never smokers. The most frequent histological type was adenocarcinoma (52%), with 12.5% of patients presenting with SCLC. The most frequent stage at diagnosis was stage IV (46.6%), followed by stage III (24.2%). In SCLC, extended disease was more common (63.5% vs 36.5%). The following symptoms all had a frequency of over 20% at diagnosis: cough (33.9%); dyspnoea (26.7%); pain (23.8%); and weight loss (21%). While 31.5% of patients displayed no symptoms at diagnosis, 7.5% had four or more. A detailed description of participants is shown in table 1.

table 2 shows a description of symptoms by tumour stage and number of symptoms at diagnosis. The frequency of all symptoms analysed increased with tumour stage (p for trend was <0.01, except for superior vena cava syndrome). It was noteworthy that no symptoms were present in 59% and 42% of patients diagnosed in stages I and II, respectively. The most frequent symptom for all stages was cough, with the exception of stage IV in which pain was slightly more frequent (18.5% vs 17.9%). In terms of the number of symptoms present, the percentage of patients with no symptoms decreased with stage, that is, while 40% of stage I patients presented with at least one symptom, 27.7% of stage IV patients had no symptoms at diagnosis and 28.3% of stage IV patients had only one symptom. This figure was quite similar for patients in stage III. The trend for number of symptoms across stages was statistically significant, except for one symptom, with no differences across stages.

In the case of SCLC, the most frequent symptom was cough (40.6% of patients), followed by dyspnoea (34.3%). Other symptoms with frequencies higher than 20% were pain and weight loss. Dyspnoea was the most frequent symptom in both limited and extended disease (11% and 23.3%, respectively). The following symptoms were associated with extended as opposed to limited disease: pain; dyspnoea; weight loss; anorexia; and asthenia. A description of SCLC symptoms can be seen in table 3.

Table 4 shows symptom distribution by smoking status. The presence of symptoms was not very different across smoking status. Cough was the most frequent symptom in never smokers, ex-smokers and current smokers (ranging from 31.7% to 34.5%), followed by pain and dyspnoea. The presence of haemoptysis was twice as frequent in ever smokers than in never smokers (12% vs 6%, respectively). There was a significant p trend for most of the symptoms but the magnitude of the differences was not relevant. When it came to the number of symptoms, never smokers had a similar frequency to that of ex-smokers and current smokers. In no case did the difference between the

Table 1	Sample description
Variable	**N (%)***
Gender	
Men	7338 (74.3)
Women	2538 (25.7)
Age	
Mean	64
Median (pct 25 to 75)	65 (57 to 72)
Smoking status*	
Never smoker	1177 (11.9)
Ex-smoker	4636 (46.9)
Current smoker	3965 (40.1)
Histological type	
Adenocarcinoma	5138 (52.1)
Squamous cell carcinoma	2394 (24.3)
Small cell	1234 (12.5)
Other histological types	1110 (11.2)
Stage at diagnosis	
I	824 (8.3)
II	723 (7.3)
III	2394 (24.2)
IV	4600 (46.6)
Small cell limited	449 (4.5)
Small cell extended	783 (7.9)
Other/unknown	103 (1.1)
Main symptoms	
Cough	3344 (33.9)
Pain	2743 (23.8)
Dyspnoea	2638 (26.7)
Haemoptysis	1116 (11.3)
Weight loss	2073 (21.0)
Anorexia	601 (6.1)
Asthenia	983 (10.0)
Superior vena cava syndrome	53 (0.5)
Aphonia or voice alterations	313 (3.2)
Number of symptoms at diagnosis	
0	3112 (31.5)
1	2710 (27.4)
2	2077 (21.0)
3	1231 (12.5)
four or more	502 (7.6)

*1% of participants had unknown smoking status.

Table 2 Symptom description by stage and number of symptoms present at diagnosis of non-small cell lung cancer*

Symptoms at diagnosis	Not present	Stage at diagnosis				P for trend
		I	II	III	IV	
Cough	5723 (67.0)	158 (1.8)	208 (2.4)	919 (10.7)	1533 (17.9)	<0.001
Pain	6203 (72.6)	88 (1.0)	131 (1.5)	535 (6.3)	1584 (18.5)	<0.001
Dyspnoea	6352 (74.4)	121 (1.4)	133 (1.5)	620 (7.2)	1315 (15.4)	<0.001
Haemoptysis	7561 (88.5)	58 (0.6)	99 (1.1)	399 (4.7)	424 (5.0)	<0.001
Weight loss	6778 (79.4)	41 (0,5)	83 (1.0)	466 (5.4)	1173 (13.7)	<0.001
Anorexia	8059 (94.4)	11 (0.1)	27 (0.3)	121 (1.4)	323 (3.4)	<0.001
Asthenia	7767 (90.9)	28 (0.3)	48 (0.6)	194 (2.3)	504 (5.9)	<0.001
Superior vena cava syndrome	8517 (99.7)	0	0	11 (0.1)	13 (0.2)	0.419
Aphonia or voice alterations	8304 (97.2)	5 (0.0)	14 (0.2)	77 (0.9)	141 (1.6)	0.004
Number of symptoms	n/a n/a n/a n/a n/a	489 (59.3)	307 (42.5)	724 (30.2)	1276 (27.7)	<0.001
0		202 (24.5)	201 (27.8)	669 (27.9)	1300 (28.3)	0.127
1		102 (12.4)	131 (18.1)	538 (22.5)	983 (21.4)	<0.001
2		23 (2.8)	63 (8.7)	304 (12.7)	625 (13.6)	<0.001
3		5 (1.0)	21 (2.9)	159 (6.6)	416 (9.0)	<0.001
4 or more						

*Tumours with unknown status excluded.

symptoms analysed exceed 7% across the various smoking categories.

DISCUSSION

This nationwide study of lung cancer symptoms at diagnosis has observed that the most frequent symptom in NSCLC was cough (33%), followed by chest pain (25%). Nevertheless, there is no clearly predominant lung cancer symptom, even in advanced stages: while 28% of patients diagnosed in stage IV had no symptoms, 30% of patients diagnosed in stage II had two or more symptoms. The presence of symptoms increases across stages; however, less than 50% of all stage IV patients have only one or two symptoms at diagnosis. There were no differences between smokers and never smokers in terms of presence of symptoms, or in the number of symptoms present at diagnosis. To our knowledge, our study has the largest sample size of any study to date that has exclusively analysed lung cancer symptoms at diagnosis.

The distribution of symptoms in our study was similar to that observed by Athey et al.[7] These authors observed that the most frequent symptom in stage IV was chest pain (44%), followed by cough (25%), while the most frequent symptom in stage III was cough (35%). Similarly, a British study reported that cough was the most frequent symptom, followed by dyspnoea, as did a further two Swedish and Greek studies.[10 11] A Chinese study of more than 7000 patients recruited from 2005 to 2014 found that the most frequent symptom was cough (65%), followed by haemoptysis (33%). In this study, 39% of stage I patients had no symptoms compared with 28.7% of stage IV patients. The frequency of haemoptysis, cough and chest pain was much higher across all stages than in

our sample; however, dyspnoea was less frequent in the Chinese study.[6]

With regard to the number of symptoms at diagnosis, a study published by Walter et al showed that 19% of lung cancer patients had two or more symptoms and 8.8% had three or more symptoms at diagnosis,[12] figures very similar to ours (21% and 12%, respectively). Unfortunately, this study did not break down the number of symptoms by tumour stage at diagnosis.

The results of our study highlight important information for clinicians when deciding whether a patient may or may not have a lung cancer suspicion. Bearing in mind that approximately 30% of all patients diagnosed in stages III and IV had no lung cancer symptoms at diagnosis, clinicians and general practitioners (GP) in particular, should not rule out the presence of lung cancer in cases where no symptoms are present. Chest imaging (mainly chest X-ray) may prove very helpful in such situations. The application of lung cancer risk calculators might be also helpful to determine the a priori lung cancer risk to patients without any symptoms. It is important to raise awareness of lung cancer among GPs. It has been estimated that, while GPs in the UK can see hundreds of patients who present with lung cancer symptoms, they may only diagnose one or two cases of lung cancer per year.[13] Hence, additional tools for estimating lung cancer risk may be useful for such clinicians.

We were unable to locate studies that compared lung cancer symptoms between ever smokers and never smokers by reference to symptom presentation. This is due to the fact that most available studies targeting symptoms describe current and former smokers, given the low frequency of lung cancer among never smokers. Even landmark reviews of lung cancer in never smokers have

Table 3 Symptom description by stage at diagnosis of small cell lung cancer

Symptoms at diagnoses	N (%)	p-value*
Cough		
No	732 (59.4)	
Yes (limited)	183 (14.8)	0.925
Yes (extended)	317 (25.7)	
Pain		
No	854 (69.3)	
Yes (limited)	104 (8.4)	<0.001
Yes (extended)	274 (22.2)	
Dyspnoea		
No	809 (65.7)	
Yes (limited)	136 (11.0)	0.024
Yes (extended)	287 (23.3)	
Haemoptysis		
No	1105 (89.7)	
Yes (limited)	51 (4.1)	0.359
Yes (extended)	76 (6.2)	
Weight loss		
No	937 (76.1)	
Yes (limited)	87 (7.0)	0.004
Yes (extended)	208 (16.9)	
Anorexia		
No	1120 (90.9)	
Yes (limited)	24 (1.9)	0.001
Yes (extended)	88 (7.1)	
Asthenia		
No	1039 (84.3)	
Yes (limited)	50 (4.0)	0.001
Yes (extended)	143 (11.6)	
Superior vena cava syndrome		
No	1203 (97.6)	
Yes (limited)	12 (1.0)	0.576
Yes (extended)	17 (1.4)	
Aphonia or voice alterations		
No	1159 (94.1)	
Yes (limited)	27 (2.2)	0.921
Yes (extended)	46 (3.7)	

*chi-square values for each symptom (limited and extended).

not addressed the issue of symptoms in this subpopulation.[14 15]

With respect to SCLC, only three symptoms displayed a frequency higher than 20% (cough, dyspnoea and pain, in that order) in patients with extended SCLC, while cough was present in 14.8% and dyspnoea in 11% of patients with limited disease. These results show that limited SCLC is mostly asymptomatic. To our knowledge, this is

the study with the highest SCLC sample size, including more than 1200 patients.

The lack of reliable data on lung cancer symptoms has been recognised by different studies because no standardised information is usually collected and a comparison between different studies is difficult to perform. On the other hand, patients may experience symptoms months before consulting their physician, either because they do not attach importance to them or because they fear a lung cancer diagnosis.[16]

This study has some limitations. There was no control group and lung cancer survival was not analysed by reference to its symptoms, though it has to be said that the study was not designed to ascertain the probability of presenting lung cancer, given the presence of a number of symptoms or of certain symptoms. Some studies have observed no effect of symptoms on survival.[16] A further limitation was that there were no data available on the lag between the appearance of the first symptoms and diagnosis of lung cancer. Nevertheless, oncologists retrieving this information were aware of the importance of asking participants about the symptoms present when they first consulted their GP, though the possibility of some degree of memory bias cannot be ruled out. It is, of course, possible that the number of symptoms increased with respect to those initially presented at the first consultation with a GP. Even so, we feel that the impact of such bias might well be small because the time interval between the first medical visit to the GP and data retrieval for study purposes was, on average, less than one and a half months, as the majority of patients entered the fast-track clinical pathway available in most healthcare areas. Some degree of variability when introducing information in large registries is sometimes unavoidable. We tried to reduce this using a previously piloted electronic questionnaire, minimising open questions when possible and not allowing illogical or impossible information introduced.

This study also has a number of advantages, the main one being its sample size and nationwide coverage, two factors which made it possible to obtain an extremely clear and highly representative picture of lung cancer symptoms at diagnosis. A further advantage was its reliance on recently recruited cases, something that ensured up-to-date application of current diagnostic procedures (ie, imaging tests in the form of positron emission tomography (PET) or PET/CT scan). In previous studies, settings where these imaging procedures were either not present or seldom applied might have entailed longer periods between appearance of first symptoms and final diagnosis, thereby increasing the likelihood of information bias with respect to the presence of symptoms. Finally, detailed data were collected on tobacco use, which enabled us to analyse if there were differences in this variable according to symptom presentation. Few studies have analysed tobacco use and lung cancer symptoms in such a large-sized sample.

To conclude, this study provides valuable information on the frequency and type of lung cancer symptoms at

Table 4 Symptom description by tobacco consumption in non-small cell lung cancer

Symptoms at diagnosis*	Never smokers†	Ex-smokers†	Current smokers†	P trend
Cough	387 (34.1)	1310 (31.7)	1099 (34.5)	0.163
Pain	318 (28.0)	990 (24.0)	1008 (31.6)	<0.001
Dyspnoea	330 (29.1)	1014 (24.5)	823 (25.8)	0.365
Haemoptysis	70 (6.2)	511 (12.4)	389 (12.2)	<0.001
Weight loss	223 (19.7)	678 (16.4)	842 (26.4)	<0.001
Anorexia	66 (5.8)	185 (4.5)	226 (7.1)	0.001
Asthenia	114 (10.1)	315 (7.6)	331 (10.4)	0.024
Superior vena cava syndrome	3 (0.3)	6 (0.1)	15 (0.5)	0.039
Aphonia or voice alterations	331 (2.7)	100 (2.4)	104 (3.3)	0.085
Number of symptoms‡	341 (30.1)	1531 (37.0)	879 (27.6)	<0.001
0	252 (31.0)	1121 (27.1)	887 (27.8)	0.263
1	236 (20.8)	812 (19.6)	694 (21.8)	0.113
2	127 (11.2)	427 (10.3)	454 (14.2)	<0.001
3	78 (6.9)	242 (5.8)	272 (8.4)	<0.001
4 or more				

*Percentages calculated as a total of the sample.
†Never smoker: participant smoked less than 100 cigarettes in lifetime. Ex-smoker: stopped smoking more than 1 year before diagnosis. Current smoker: declared smoking during the year before diagnosis. Eighty-nine participants had unknown tobacco consumption.
‡Totals calculated for each smoking category.

diagnosis, with a breakdown by stage and tobacco use. This information is highly relevant to clinicians, given its important representativeness in terms of the study's sample size and nationwide recruitment. The most relevant findings are that 28% of stage IV lung cancers (the most frequent stage) do not present with any symptoms at diagnosis, and that there are no relevant differences in symptom presentation with reference to smoking status. This information confirms the lack of specificity of lung cancer symptoms and the fact that the absence of the most frequent symptoms (ie, cough, pain and dyspnoea) should in no case lead to a decision to rule out the presence of this disease.

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