Original Article

Lung cancer in Spain: information from the Thoracic Tumors Registry (TTR study)

Mariano Provencio[1], Enric Carcereny[2], Delvys Rodríguez-Abreu[3], Rafael López-Castro[4], María Guirado[5], Carlos Camps[6], Joaquim Bosch-Barrera[7], Rosario García-Campelo[8], Ana Laura Ortega-Granados[9], José Luis González-Larriba[10], Joaquín Casal-Rubio[11], Manuel Domine[12], Bartomeu Massutí[13], María Ángeles Sala[14], Reyes Bernabé[15], Juana Oramas[16], Elvira del Barco[17]

[1]Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain; [2]Instituto Catalán de Oncología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain; [3]Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain; [4]Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [5]Hospital de Elche, Elche, Spain; [6]Hospital General de Valencia, Valencia, Spain; [7]Instituto Catalán de Oncología, Girona, Spain; [8]Hospital Universitario de la Coruña, La Coruña, Spain; [9]Complejo Hospitalario de Jaen, Jaen, Spain; [10]Hospital Universitario Clínico San Carlos, Madrid, Spain; [11]Complejo Hospitalario Universitario de Vigo, Pontevedra, Spain; [12]Hospital Fundación Jiménez Díaz, Madrid, Spain; [13]Hospital Universitario General de Alicante, Alicante, Spain; [14]Hospital de Basurto, Bilbao, Spain; [15]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [16]Hospital Universitario de Canarias, Santa Cruz Tenerife, Spain; [17]Hospital Universitario de Salamanca, Salamanca, Spain

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Correspondence to: Mariano Provencio, MD, PhD. Oncology Department, Hospital Universitario Puerta de Hierro, Manuel de Falla 1, Majadahonda, 28222 Madrid, Spain. Email: mprovenciop@gmail.com.

Background: Lung cancer remains a leading cause of cancer incidence and mortality worldwide. Although Spain contributes to global statistics related to cancer, it is difficult to discern aspects linked to clinical presentation of the disease or molecular testing. The Thoracic Tumor Registry (TTR) was created with the aim of filling this gap.

Methods: Observational cohort multicenter study performed in Spain, including patients with lung cancer or other types of thoracic tumors undergoing active treatment or palliative care only. Enrollment took place between August 2016 and December 2018. The evaluation included a review of demographic, epidemiological, clinical and molecular data.

Results: A total of 6,600 patients diagnosed with non-small cell lung cancer (NSCLC) were recruited at 56 Spanish hospitals. The mean age at diagnosis was 64 years. The majority of patients (80%) presented with advanced disease, being adenocarcinoma the most frequent histological type. Up to 86% of patients were current- or ex-smokers, with men starting to smoke earlier than women (average age 17.9 *vs.* 19.2 years). Sixty-seven percent of patients underwent some type of molecular testing. Mutations in *EGFR* and *KRAS* genes were found in 18% and 28% of patients, respectively.

Conclusions: Our findings suggest that the TTR study accurately describes the clinical reality of lung cancer in Spain, including useful information on smoking status as well as molecular profiling and tumor histology, and can therefore be used to drive improvements in health care. Social and political pressure to reduce tobacco consumption among the population should be reinforced, particularly among youth.

Keywords: Lung cancer; smoking status; molecular profiling; cancer registry; Spain.

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Introduction

Lung cancer remains a leading cause of cancer incidence and mortality worldwide among both men and women, with more than 2 million newly diagnosed cases and 1.8 million deaths in 2018, accounting for close to 1 in 5 (18.4%) cancer deaths (1). Lung cancer is broadly divided into two categories according to its histological characteristics: small cell lung cancer (SCLC, ~15% of all lung cancers) and non-small cell lung cancer (NSCLC, ~85%). The latter comprises several histological subtypes, mainly squamous cell carcinoma, adenocarcinoma and large-cell lung cancer; adenocarcinoma is the most common subtype of NSCLC (~40%) (2,3).

The most important risk factor for lung cancer is tobacco smoking, along with other environmental pollutants (4,5). Nevertheless, only approximately 10% of smokers develop lung cancer, and the disease also occurs in the absence of exposure to cigarette smoke (6); in this sense, several studies have identified a genetic susceptibility locus for lung cancer carcinogenesis and prognosis (7). Since these risk factors are highly preventable, mortality rates can be largely reduced through tobacco control and other population-based preventive strategies (8). Global numbers show a declining trend in the incidence and mortality rates in men, primarily due to decreased cigarette consumption. Among women, the tobacco epidemic is less advanced, and most countries are still observing a rising trend in incidence; only relatively few populations (e.g., the US and possibly the UK) are showing signs of decline among recent birth cohorts (1,9).

Information from European registries, including treatments for lung cancer and their efficacy, as well as data on tobacco consumption and mutational profiles of tumors, is somewhat scarce. Many countries collect data on a national level, with the majority using a national registry for all cancers, but few have a data collection program for lung cancer in addition to a cancer registry (10). However, this information is of particular interest, not only because of the need for deeper understanding of the characteristics of lung cancer, both in its presentation and during treatment, but also to evaluate certain aspects related to health care quality. In this sense, information from a country like Spain, with universal health coverage, can provide valuable data from a more realistic scenario, with no bias related to private health insurance or patient socioeconomic status.

According to recent data from the Spanish National Institute of Statistics (INE), lung cancer was responsible for the highest number of deaths among the Spanish population in 2017, and for the first time was the second cause of cancer mortality among Spanish women, especially due to smoking (11); the number of deaths in 2017 increased by 6.4% compared to the previous year, and doubled compared to 2003 (12).

Until recently, the coverage of the population by cancer registries in Spain was limited, with no official, unified database for lung cancer and other thoracic tumors. To obtain a better picture of the epidemiology of these diseases in Spain, in 2016 the Spanish Lung Cancer Group (GECP) created the first Thoracic Tumor Registry (TTR), an observational, prospective cohort multicenter study that included patients treated for lung cancer and other thoracic tumors. To our knowledge, this is the first registry of its kind in Europe. In this paper, we present the methodology of the registry and the results from 6,600 patients with NSCLC recruited in 56 Spanish hospitals until December 2018.

Methods

Study design

The TTR is an observational (patient registry), non-post-authorization, prospective cohort multicenter study. Enrolment started in August 2016 and is still ongoing (as of April 23, 2019, 10,145 patients from 58 centers had been included in the study, 8,653 of whom had been diagnosed with NSCLC). The study was conducted in accordance with the provisions of the Declaration of Helsinki. Protocol approval was obtained from the institutional review board at each study site. The registry was approved in 2016 by the Spanish Agency for Medicines and Medical Devices (AEMPS) and is registered on the ClinicalTrials.gov database (NCT02941458). Protocol approval was obtained from the institutional review board of Hospital Universitario Puerta de Hierro Majadahonda (No. PI 148/15).

Study sponsor

This registry was sponsored by the GECP, an independent, cooperative and multidisciplinary oncology group established in 1991, whose purpose is to promote the study and research of lung cancer and incorporate advances in the treatment of the disease into routine clinical practice. The GECP consists of more than 400 specialists from all over Spain associated with treatment and research in lung cancer,

mostly medical oncologists. It brings together a network of more than 160 public and private hospitals distributed throughout the Spanish territory that conduct their research in a coordinated manner. This infrastructure was the basis for establishing the TTR registry, proposed by the steering committee.

Eligibility

Eligible patients included those with lung cancer or other types of thoracic tumors (NSCLC, SCLC, mesothelioma, thymic carcinoma, carcinoid cancer) undergoing active treatment or not treated (palliative care only), with no sex or age restrictions. Patients with other types of tumors and healthy volunteers were not admitted.

Information retrieval

Data was collected from patient medical records using an electronic data capture system (EDC), where each research team included the information on all patients with lung carcinoma attended by the healthcare personnel of their hospital. Sociodemographic, epidemiological, clinical, molecular/genetic and treatment outcome (e.g., response rate, current status, date of death) variables were recorded. The information collected was classified into different sections: (I) patient personal history, which included the performance status (PS), tobacco consumption (including environmental exposure to tobacco smoke), and comorbidities; (II) family history of cancer; (III) diagnosis, which included the histological type and detailed TNM classification of the tumor (including the location of metastases when appropriate); (IV) treatment, which included information on all treatments received, including dates and specific characteristics (surgery, chemotherapy, radiotherapy); (V) disease progression; and (VI) genetic information (alterations of driver genes).

Statistical analysis

Descriptive statistics were performed and quantitative data were summarized as mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum. Qualitative variables were summarized as frequencies in the entire population and percentages. Characteristics of two groups (early and advanced) were compared using the χ^2 test for categorical variables. The significance level was established at a value of α=0.05.

Results

Patient characteristics

A total of 6,600 patients diagnosed with NSCLC were enrolled between August 2016 and December 2018 in 56 hospitals of 12 Spanish autonomous regions. The median number of patients/month (patients/year) recruited in 2017 and 2018 was 162 [1,900] and 402 [4,423], respectively. Enrolled patients were diagnosed with NSCLC from before 2010 to 2018, with approximately 50% of them diagnosed in the last 3 years [2016–2018].

Baseline patient characteristics are shown in *Table 1*. There were significantly more males (73.4%) than females (26.6%). Median age at diagnosis was 64.0 years, with approximately 30% of patients being younger than 55 or older than 75 years. Regarding tobacco use, more than 85% of the patients diagnosed (n=5,650) were current smokers (n=2,611, 39.6%) or ex-smokers (n=3,039, 46.0%), and only 13.1% (n=866) had never smoked. The most frequent histological type was adenocarcinoma (n=4,208, 63.8%), followed by squamous cell carcinoma (n=1,826, 27.7%) and large cell carcinoma (n=202, 3.1%). More than 85% of patients presented a good PS [Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1].

Patient characteristics according to disease stage

Median age at diagnosis was 64 years for patients with advanced disease and 65 for those with early-stage disease. As expected, most patients presented with advanced stage III (n=1,874, 28.4%) or IV (n=3,446, 52.2%) disease at diagnosis, independently of sex (63.1% and 70.6% in males and females, respectively). Interestingly, among those diagnosed with advanced disease, a progressive growth in the percentage of adenocarcinoma was observed over the years of diagnosis: 11% in ≤2012, 16% in 2013/2014, 28% in 2015/2016 and 32% in 2017/2018. There was a higher number of patients with no comorbidities at diagnosis among those with advanced disease than among those with early-stage disease (63.4% *vs.* 36.6%, P<0.001), although among patients who presented comorbidities, the prevalence was much higher, in general, in those with advanced disease. Significant differences (P<0.001, unless otherwise indicated) were observed between the two groups in the prevalence of cardiopathy, dyslipidemia (P=0.043), chronic obstructive pulmonary disease (COPD), hypercholesterolemia (P=0.026), hypertension, nephropathy (P=0.012), obesity (P=0.007), and vasculopathy (*Table 2*).

Table 1 Baseline characteristics of the patients

Characteristic	n	%
Sex		
Male	4,847	73.4
Female	1,753	26.6
Age at diagnosis		
Mean (SD), years	63.9 (10.2)	
Median [range], years	64 [21–98]	
Distribution		
<55 years	1,046	15.8
55–64 years	1,838	27.8
65–74 years	1,956	29.6
≥75 years	907	13.7
Unknown	853	12.9
Race		
Caucasian	6,507	98.6
Other	93	1.4
Smoking status		
Never smoker	866	13.1
Ex-smoker	3,039	46.0
Current smoker	2,611	39.6
Unknown	84	1.3
ECOG PS		
ECOG PS 0	2,396	36.3
ECOG PS 1	3,342	50.6
ECOG PS 2	650	9.8
ECOG PS 3	158	2.4
ECOG PS 4	19	0.3
ECOG PS 5	18	0.3
Unknown	17	0.3
Stage		
I	662	10.0
IA	312	4.7
IB	348	5.3
Ix	2	0.0
II	592	9.0
IIA	248	3.8
IIB	344	5.2
III	1,874	28.4
IIIA	1,041	15.8
IIIB	765	11.6
IIIC	68	1.0
IV	3,446	52.2
IVA	18	0.3
IVB	26	0.4
IVx	3,402	51.5
Other	26	0.4
Histology		
Adenocarcinoma	4,208	63.8
Adenosquamous carcinoma	68	1.0
Squamous cell carcinoma	1,826	27.7
Large cell carcinoma	202	3.1
Sarcomatoid carcinoma	18	0.3
NOS/undifferentiated	151	2.3
LC neuroendocrine carcinoma	75	1.1
Carcinoid tumor	5	0.1
Other	47	0.7

ECOG PS, Eastern Cooperative Oncology Group performance status; LC, large cell; NOS, not otherwise specified; SD, standard deviation.

Likewise, the prevalence of symptoms, including cough, pain, dyspnea, hemoptysis, weight loss, anorexia, and asthenia was much higher (P<0.001) among patients with advanced disease (*Table S1*).

Although no association was found between the professional occupation of patients (recorded in only 20% of cases) and the disease stage at diagnosis (data not shown), differences were found according to previous exposure to potential carcinogenic compounds. Compared to the total population, a higher percentage of patients with advanced disease was observed among those who had been exposed to arsenic compounds (87.5% *vs.* 65.1%, P=0.020) and, to a lesser extent, acrylonitrile (75.0% *vs.* 65.1%, P=0.020); on the other hand, early-stage disease was more prevalent among patients exposed to asbestos (47.5% *vs.* 34.9%, P=0.020), radon/silica (47.4% *vs.* 34.9%, P=0.020) and, to a lesser extent, paint (38.1% *vs.* 34.9%, P=0.020) and diesel

Table 2 Patient characteristics and comorbidities according to the initial stage of the disease

Characteristic	Total (n=6,574)		Early disease (n=2,295)		Advanced disease (n=4,279)		P value
	n	%	n	%	n	%	
Sex							<0.001
Male	4,830	73.5	1,782	36.9	3,048	63.1	
Female	1,744	26.5	513	29.4	1,231	70.6	
Age							<0.001
Mean (SD), years	63.9 (10.2)		65.0 (9.7)		63.3 (10.4)		
Median [P25–P75], years	64 [57–71]		65 [59–72]		64 [56–71]		
Comorbidities							<0.001
Unknown	765	11.6	219	28.6	546	71.4	
No	1,072	16.3	342	31.9	730	68.1	
Yes	4,737	72.1	1,734	36.6	3,003	63.4	
Asthma	96	1.5	29	30.2	67	69.8	0.388
Cardiopathy	834	12.7	342	41.0	492	59.0	<0.001
Diabetes mellitus	1,081	16.4	400	37.0	681	63.0	0.116
Dyslipidemia	1,590	24.2	589	37.0	1,001	63.0	0.043
COPD	1,221	18.6	579	47.4	642	52.6	<0.001
Ex alcoholism	346	5.3	115	33.2	231	66.8	0.524
Hepatitis	100	1.5	30	30.0	70	70.0	0.342
Hypercholesterolemia	485	7.4	192	39.6	293	60.4	0.026
Hypertension	2,394	36.4	923	38.6	1,471	61.4	<0.001
Nephropathy	152	2.3	68	44.7	84	55.3	0.012
Obesity	261	4.0	112	42.9	149	57.1	0.007
Depressive syndrome/anxiety	409	6.2	139	34.0	270	66.0	0.708
Tuberculosis	92	1.4	35	38.0	57	62.0	0.511
Vasculopathy	362	5.5	156	43.1	206	56.9	0.001
Other	2,457	37.4	867	35.3	1,590	64.7	0.630

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

engine smoke (38.2% *vs.* 34.9%, P=0.020) (*Table S2*).

More patients with a previous history of cancer had early-stage disease at diagnosis than those with advanced disease (47.6% *vs.* 34.9%, P<0.001); no differences were found in the disease stage at diagnosis according to family history of prostate cancer (*Table S3*).

Smoking status

The majority of patients included in the study, 86.7%, were current smokers or ex-smokers (40.1% and 46.6%, respectively). Only 13.3% had never smoked (*Table 3*). In addition, almost 16% of patients were passive smokers (i.e., those who lived with active smokers in the last 20 years), with proportionally higher percentage among women (*Table S4*).

Smoking status according to sex

Comparing smoking status by sex, significant differences were observed between males and females in all groups, non-smokers, ex-smokers and current smokers (P<0.001).

Table 3 Distribution of smoking status by sex and year of diagnosis

Smoking status by sex	All years (n=6,600)		Unknow (n=845)		<2011 (n=424)		2011–2012 (n=492)		2013 (n=442)		2014 (n=624)		2015 (n=747)		2016 (n=932)		2017 (n=1,289)		2018 (n=805)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Both sexes	6,516	98.7	828	98.0	403	95.0	482	98.0	433	98.0	620	99.4	742	99.3	924	99.1	1,285	99.7	799	99.3
Never-smoker	866	13.3	119	14.4	69	17.1	70	14.5	60	13.9	95	15.3	99	13.3	118	12.8	153	11.9	83	10.4
Ex-smoker	3,039	46.6	394	47.6	204	50.6	232	48.1	204	47.1	289	46.6	379	51.1	437	47.3	577	44.9	323	40.4
Current-smoker	2,611	40.1	315	38.0	130	32.3	180	37.3	169	39.0	236	38.1	264	35.6	369	39.9	555	43.2	393	49.2
Males	4,791	73.5	602	72.7	306	75.9	350	72.6	324	74.8	443	71.5	546	73.6	698	75.5	945	73.5	577	72.2
Never-smoker	216	4.5	34	5.6	16	5.2	12	3.4	17	5.2	18	4.1	27	4.9	32	4.6	37	3.9	23	4.0
Ex-smoker	2,558	53.4	326	54.2	179	58.5	197	56.3	167	51.5	239	54.0	317	58.1	382	54.7	485	51.3	266	46.1
Current-smoker	2,017	42.1	242	40.2	111	36.3	141	40.3	140	43.2	186	42.0	202	37.0	284	40.7	423	44.8	288	49.9
Females	1,725	26.5	226	27.3	97	24.1	132	27.4	109	25.2	177	28.5	196	26.4	226	24.5	340	26.5	222	27.8
Never-smoker	650	37.7	85	37.6	53	54.6	58	43.9	43	39.4	77	43.5	72	36.7	86	38.1	116	34.1	60	27.0
Ex-smoker	481	27.9	68	30.1	25	25.8	35	26.5	37	33.9	50	28.2	62	31.6	55	24.3	92	27.1	57	25.7
Current-smoker	594	34.4	73	32.3	19	19.6	39	29.5	29	26.6	50	28.2	62	31.6	85	37.6	132	38.8	105	47.3
P value	<0.001		–		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

The percentage of non-smokers was much higher in females (37.7%) than in males (4.5%), while the percentage of ex-smokers was much higher in males (53.4%) than in females (27.9%), as was the percentage of current smokers (42.1% *vs.* 34.4%, respectively). These sex differences were maintained throughout all the years of diagnosis. In males, a rapidly growing trend in the number of patients who were active smokers was observed from 2015 to 2018, along with an opposite downward trend in the number of ex-smokers; the low percentage of males who never smoked remained stable throughout the period analyzed. In females, a rapid decline in the number of patients who never smoked was observed from 2011 onwards, along with a continuous rise in the number of current smokers; although much higher than in males, the percentage of ex-smokers remained more or less stable during the period analyzed (*Table 3*).

Age of onset of smoking

The age of onset of smoking was recorded in 2,707 patients (47.9% of total current smokers and ex-smokers), with the average being 18.2 years in the total population. There were significant differences (P<0.001) between males and females, with males being earlier to start smoking (mean age 17.9 years; 95% CI: 17.6–18.2) than females (mean age 19.2 years; 95% CI: 18.5–19.8) (*Figure 1A*). The differences in the average age of onset of smoking between sexes remained more or less stable throughout all the years of diagnosis (*Figure 1B*).

Smoking status according to disease stage

No association was observed between the smoking status, active or passive, and the initial stage of the disease. In all subgroups, the percentage of patients presenting with advanced disease was significantly higher (active smoking, P<0.001; passive smoking, P=0.003) than that of patients with early disease (*Table 4*).

Biomarker profiling of tumors

A total of 4,456 patients (67.5%) underwent some type of molecular testing for biomarker analysis, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Kirsten rat sarcoma viral oncogene homolog (KRAS), B-RAF proto-oncogene, serine/threonine kinase oncogene (BRAF), human epidermal growth factor receptor type 2 (HER2), ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), fibroblast growth factor receptor type 1 (FGFR1),

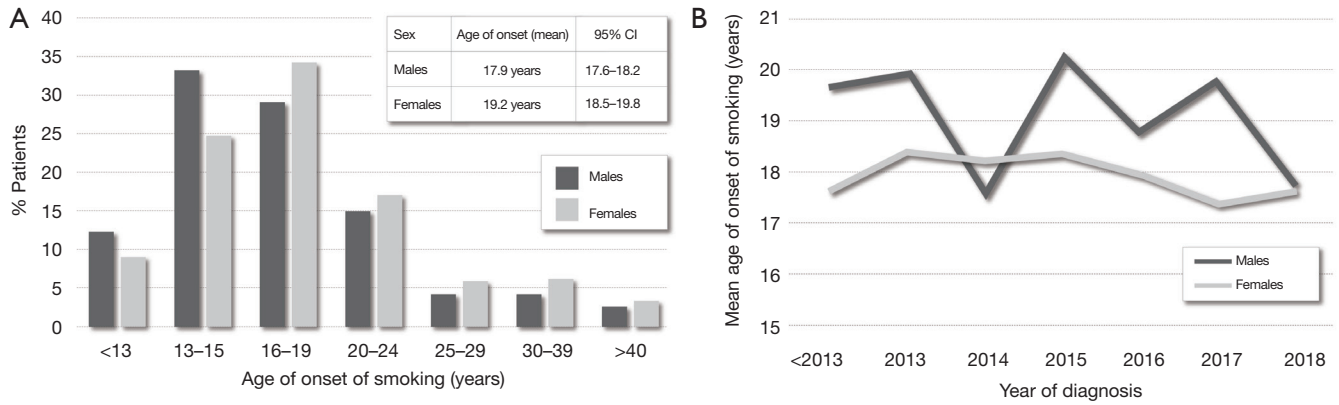

Figure 1 Age of onset of smoking. (A) The age of onset of smoking was recorded in 2,707 patients (47.9% of total current smokers and ex-smokers), with the average being 18.2 years in the total population. There were significant differences (P<0.001) between males and females, with males being earlier to start smoking (mean age 17.9 years; 95% CI: 17.6–18.2) than females (mean age 19.2 years; 95% CI: 18.5–19.8). (B) The differences in the mean age of onset of smoking between sexes remained more or less stable throughout all the years of diagnosis.

Table 4 Smoking status according to the initial stage of the disease

Variable	Total (n=6,574)		Early disease (n=2,295)		Advanced disease (n=4,279)		P value
	n	%	n	%	n	%	
Smoking status							<0.001
Never smoker	865	13.2	251	29.0	614	71.0	
Ex-smoker	3,028	46.1	1,208	39.9	1,820	60.1	
Current smoker	2,599	39.5	807	31.1	1,792	68.9	
Unknown	82	1.2	29	35.4	53	64.6	
Passive smoking							0.003
No	870	13.2	343	39.4	527	60.6	
Yes	1,039	15.8	377	36.3	662	63.7	
Unknown	4,665	71.0	1,575	33.8	3,090	66.2	

programmed death-ligand 1 (PD-L1), proto-oncogene tyrosine-protein kinase receptor Ret (RET), and tyrosine-protein kinase MET/hepatocyte growth factor receptor (MET). EGFR mutational profiling was the most frequent test, performed in about 60% of the population. Mutations in *EGFR* were detected in 18.1% of patients, including in-frame deletions in exon 19 (53.7%), point mutations in exon 21 (30.0%), and T790M mutation in exon 20 of the kinase domain (15.2%), among other mutations (15.2%). *KRAS* mutations were detected in 28.4% of patients (*Table 5*). The total percentage of biomarker characterization increased from 57.9% before 2013 to 73.7% in 2017/2018. Particularly relevant in this period was the increase in the percentage of characterization of PD-L1 (from 5.5% to 51.8%) and ALK (from 35.2% to 54.1%) (*Table 6*). In general, the mutational profile of advanced, stage IV tumors (n=3,446, 52.2%) was rather similar to that of the total set of tumors, regardless of the disease stage (*Table S5*). There were also differences in the percentage of biomarker characterization in advanced tumors (adenocarcinoma) according to the year of diagnosis. A progressive increase from before 2013 to 2017/2018 was observed in the percentage of ALK characterization (immunohistochemistry, IHC), from 30.7% to 64.8% (P<0.001) and ROS1 (fluorescence in situ hybridization, FISH), from 6.7% to 20.7% (P<0.001). In addition,

a much higher percentage of positive results for ALK rearrangements (IHC) was observed before 2013, compared to later years. The percentage of EGFR characterization, although high throughout all the years of follow-up, showed a progressive increase from 84.8% before 2013 to 92.1% in 2017/2018 (P<0.001) (*Table S6*).

Discussion

In our opinion, it is essential to have information on patients that allows the current situation of lung cancer in different European regions to be compared. Although the EUROCARE study attempts to monitor and identify the survival of cancer patients in Europe, it only covers about 1% of the population and has reported potentially important regional variations (13). At country level, several initiatives have been carried out in European countries. In England, for example, the National Lung Cancer Audit (NLCA) was established in 2004 to identify possible inequalities within the National Health Service and to highlight the potential for service improvements (14); in Denmark, the Danish Lung Cancer Registry (DLCR) was set up in 1991 to improve survival and clinical management of Danish lung cancer patients, as well as to produce a platform for lung cancer research (15); and in Sweden, the National Quality Registry for Lung Cancer was established in 2002 to provide information on diagnostic procedures, staging

Table 5 Molecular profiling of tumors at diagnosis

Biomarker	n	%
Any biomarker		
No	2,144	32.5
Yes	4,456	67.5
ALK (IHC)		
Not performed	4,209	63.8
Performed	2,391	36.2
Negative	2,289	95.7
Positive	102	4.3
ALK (FISH)		
Not performed	5,746	87.1
Performed	854	12.9
Not translocated	757	88.6
Translocated	97	11.4
ALK (RNA)		
Not performed	6,545	99.2
Performed	55	0.8
Not detected	53	96.4
Detected	2	3.6
KRAS		
Not performed	6,104	92.5
Performed	496	7.5
Not detected	355	71.6
Detected	141	28.4
BRAF		
Not performed	6,059	91.8
Performed	541	8.2
Not detected	523	96.7
Detected	18	3.3
HER2 (mutated)		
Not performed	6,569	99.5
Performed	31	0.5
Not detected	29	93.5
Detected	2	6.5
HER2 (IHC)		
Not performed	6,578	99.7
Performed	22	0.3
Negative	21	95.5
Positive	1	4.5
HER2 (FISH)		
Not performed	6,596	99.9
Performed	4	0.1
Negative	4	100.0
Positive	0	0.0
ROS1 (FISH)		
Not performed	5,836	88.4
Performed	764	11.6
Not translocated	731	95.7
Translocated	33	4.3

Table 5 (*continued*)

Table 5 (*continued*)

Biomarker	n	%
FGFR1		
Not performed	6,587	99.8
Performed	13	0.2
Not amplified	12	92.3
Amplified	1	7.7
PD-L1		
Not performed	4,837	73.3
Performed	1,763	26.7
Unknown	128	7.3
Negative	757	42.9
Positive	878	49.8
RET		
Not performed	6,556	99.3
Performed	44	0.7
Not translocated	43	97.7
Translocated	1	2.3
MET		
Not performed	6,474	98.1
Performed	126	1.9
Negative	116	92.1
Overexpressed	1	0.8
Amplified	9	7.1
EGFR		
Not performed	2,602	39.4
Performed	3,998	60.6
Unknown	12	0.3
Not mutated	3,263	81.6
Mutated	723	18.1
Exon-19	388	53.7
Exon-21	217	30.0
T790M (+)	110	15.2
T790M (–)	29	4.0
Other type	110	15.2

ALK, anaplastic lymphoma kinase; BRAF, B-RAF proto-oncogene, serine/threonine kinase oncogene; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; FGFR1, fibroblast growth factor receptor type 1; HER2, human epidermal growth factor receptor type 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, tyrosine-protein kinase MET/hepatocyte growth factor receptor; PD-L1, programmed death-ligand 1; RET, proto-oncogene tyrosine-protein kinase receptor; RNA, ribonucleic acid; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase.

methods, tumor characteristics, planned treatment, study participation and follow-up (16). In addition, registry-based studies have been published in Norway (17), France (18), Germany (19) and the Netherlands (20). In Spain, however, there has been no national hospital clinical register to date.

The TTR study reflects the current epidemiology and treatment of lung cancer in Spain, based on a very large sample size. Among the main findings, we observed that, at the time of diagnosis, the median age was 64 years and 52% of patients presented with advanced stage IV disease. Despite the fact that the majority of cases corresponded to males (about 73%), females already account for around 1 in 4 cases of lung cancer (27%), following the upward global trend observed in recent years (21). Data published in 2017 showed that, among all countries with an increasing incidence among women, Spain had the second highest average annual percentage change (8.2, 95% CI: 6.6–9.9; P<0.001) in the last 10 years (22).

Tobacco use was a risk factor that was present in 86% of our patients, with 46% being active smokers (42% among males and 34% among females) at the time of diagnosis, confirming that tobacco smoke is the main cause of this type of tumor (4,21). Comparing tobacco use by sex, striking differences were observed, with a higher percentage of male ex-smokers (nearly twice that of females) and a very much higher percentage (more than 8-fold) of female never-smokers. The percentage of active female smokers, although slightly less, was dangerously close to that of males. These data are somewhat worrying, since, although not without controversy, several studies have argued that women are more vulnerable to tobacco carcinogens (23,24) and are more predisposed than men to molecular aberrations resulting from the carcinogenic effects of tobacco smoke (25). Furthermore, female smokers are more likely than male smokers to develop adenocarcinoma of the lung, and those women who have never smoked are more likely to develop lung cancer than men (26). Considering the entire study population, the average age of onset of smoking was 18.2 years, with males starting to smoke significantly earlier; however, among women, a much higher percentage of later onset of smoking—from 16 to 19 years old—was observed, supporting the concern about the dangerous growing tendency of women to start smoking. Additionally, we must take into account that passive smoking causes many of the same diseases as direct smoking, and is a risk factor for lung cancer as well as other types of cancer (27). In this study, and in line with this evidence, a lower percentage of patients with early-stage disease at diagnosis were non-

Table 6 Molecular profiling of tumours according to year of diagnosis

Biomarker	All years (n=5,755)		≤2012 (n=916)		2013–2014 (n=1,066)		2015–2016 (n=1,679)		2017–2018 (n=2,094)		P value
	n	%	n	%	n	%	n	%	n	%	
Any biomarker											<0.001
Yes	4,456	77.4	530	57.9	720	67.5	1,138	67.8	1,544	73.7	
ALK (IHC)											<0.001
Performed	2,164	37.6	217	23.7	351	32.9	688	41.0	908	43.4	
Positive	93	4.3	15	6.9	18	5.1	25	3.6	35	3.9	
ALK (FISH)											0.002
Performed	683	11.9	103	11.2	142	13.3	230	13.7	208	9.9	
Translocated	95	13.9	13	12.6	26	18.3	33	14.3	23	11.1	
ALK (RNA)											0.150
Performed	49	0.9	3	0.3	9	0.8	20	1.2	17	0.8	
Detected	2	4.1	1	33.3	1	11.1	0	0.0	0	0.0	
KRAS											<0.001
Performed	462	8.0	52	5.7	97	9.1	148	8.8	165	7.9	
Detected	135	29.2	10	19.2	33	34.0	45	30.4	47	28.5	
BRAF											<0.001
Performed	502	8.7	83	9.1	103	9.7	134	8.0	182	8.7	
Detected	17	3.4	3	3.6	2	1.9	6	4.5	6	3.3	
HER2 (Mutated)											<0.001
Performed	31	0.5	7	0.8	17	1.6	7	0.4	0	0.0	
Detected	2	6.5	0	0.0	2	11.8	0	0.0	–	–	
HER2 (IHC)											–
Performed	22	0.4	4	0.4	10	0.9	6	0.4	2	0.1	
Positive	1	4.5	0	0.0	0	0.0	0	0.0	1	50.0	
HER2 (FISH)											–
Performed	3	0.1	1	0.1	0	0.0	2	0.1	0	0.0	
Positive	0	0.0	0	0.0	–	–	0	0.0	–	–	
ROS1 (FISH)											<0.001
Performed	691	12.0	84	9.2	97	9.1	212	12.6	298	14.2	
Translocated	31	4.5	5	6.0	9	9.3	8	3.8	9	3.0	
FGFR1											–
Performed	12	0.2	2	0.2	4	0.4	4	0.2	2	0.1	
Amplified	1	8.3	0	0.0	1	25.0	0	0.0	0	0.0	

Table 6 (*continued*)

Table 6 (*continued*)

Biomarker	All years (n=5,755)		≤2012 (n=916)		2013–2014 (n=1,066)		2015–2016 (n=1,679)		2017–2018 (n=2,094)		P value
	n	%	n	%	n	%	n	%	n	%	
PD-L1											<0.001
Performed	1,514	26.3	50	5.5	118	11.1	262	15.6	1,084	51.8	
Positive	768	50.7	21	47.7	54	45.8	103	39.3	590	54.4	
RET											<0.001
Performed	44	0.8	36	3.9	2	0.2	3	0.2	3	0.1	
Translocated	1	2.3	1	2.8	0	0.0	0	0.0	0	0.0	
MET											<0.001
Performed	124	2.2	2	0.2	15	1.4	89	5.3	18	0.9	
Overexpressed/ amplified	10	8.1	0	0.0	4	26.7	6	6.7	0	0.0	
EGFR											0.003
Performed	3,521	61.2	511	55.8	671	62.9	1,050	62.5	1,289	61.6	
Mutated	642	18.2	109	21.3	126	18.8	190	18.1	217	16.8	

ALK, anaplastic lymphoma kinase; BRAF, B-RAF proto-oncogene, serine/threonine kinase oncogene; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; FGFR1, fibroblast growth factor receptor type 1; HER2, human epidermal growth factor receptor type 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, tyrosine-protein kinase MET/ hepatocyte growth factor receptor; PD-L1, programmed death-ligand 1; RET, proto-oncogene tyrosine-protein kinase receptor Ret; RNA, ribonucleic acid; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase.

passive smokers. It should be noted that a higher than expected percentage of passive smokers was found among females. In our opinion, and in view of these results, the social and political pressure to reduce tobacco consumption among the population should be reinforced, particularly among youth.

Our data highlight the change of histological subtype presentation already suggested in EUROCARE studies (13). Although these studies have limitations derived from the high number of patients with non-specific histological subtypes and lack of diagnostic uniformity between different countries, it seems clear that there is an increasing frequency of adenocarcinoma (26,28,29), which was also the subtype most frequently observed in the TTR study. Since the 1970s in the US, adenocarcinoma as a percentage of all lung carcinomas has nearly doubled in men and increased from ~25% to ~33% in women, among whom adenocarcinoma has long been the most commonly diagnosed histological type (30). Although it has not been fully demonstrated, the decrease in tars and increase in nitrosamines in filtered cigarettes has been suggested as the cause of the recent change of dominant cell type from squamous cell to adenocarcinoma (31).

Regarding the presentation of the disease at diagnosis, our data were comparable to those from registries from the US, Canada and Australia, as well as European countries, such as the UK, Denmark, Norway and Sweden. However, it is worth noting the earlier diagnosis in our country, at mean age 64 *vs.* ~70 years in most of these countries, which is probably due to more complete, globalized healthcare coverage (32-35).

The molecular characterization of lung cancer has considerably changed the classification and treatment of these tumors, becoming an essential component of pathologic diagnosis and oncologic therapy decisions (36). In this study, just over two thirds of patients (67.5%) underwent molecular testing, reaching the significant percentage of 81.4% in patients with stage IV disease. It is worth highlighting not only the high percentage of *EGFR* mutation testing, but also the progressive and rapid increase in some biomarker profiling, as was the case of PD-L1 expression and determination of *ALK* rearrangements.

Mutations in *EGFR* were detected in almost one fifth of patients (18%), a percentage that is comparable with that previously reported for Caucasian patients with lung adenocarcinoma (37,38). *EGFR* is the most important driver gene in NSCLC (37), and tumors bearing *EGFR* mutations can be treated with first-line targeted therapies, such as the tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, afatinib, and osimertinib, leading to higher response rates (55–78%) than with standard chemotherapy (39). In about 15% of our patients, the so-called gatekeeper T790M mutation in exon 20 was detected, which is considered the most common resistance mechanism to TKIs (40).

Mutations in *KRAS* were detected in 28% of patients, a population that, according to published data, has a poor prognosis. The percentage of *KRAS* mutations in our population is also comparable with that reported for Caucasian patients with lung adenocarcinoma, estimated at around 30% (41). The KRAS pathway links the EGFR pathway to cell proliferation and survival, and *KRAS* mutations, which are associated with former or current smokers (41), have been shown to mediate resistance to TKIs, being a negative predictive factor in advanced NSCLC (42). ALK translocations were detected in 11% of patients included in the study. This percentage is somewhat higher than that previously published for NSCLC, ranging from 3% to 7.0% (43,44). The ALK fusion defines a distinct subpopulation of patients with lung adenocarcinoma who are highly responsive (57–74%) to ALK inhibitors such as crizotinib (45). It has been shown that EGFR, KRAS, and ALK molecular alterations are mutually exclusive events; nevertheless, they have been described in up to 2.7% of lung adenocarcinoma cases with concurrent molecular alterations (36). PD-L1 expression, which has been identified—although not without controversy—as a potential predictor of response to anti-PD-1 (e.g., pembrolizumab) and anti-PD-L1 (e.g., durvalumab) monoclonal antibody therapy and also as a prognostic biomarker, was detected in nearly 50% of patients in our cohort. A real-world study showed that, among patients with metastatic or recurrent NSCLC diagnosis eligible for the study, only 48% had one or more tests for PD-L1 determination, with 18% tested in 2015 and 71% in 2017 (46). These findings are important, since there are effective first-line therapies to treat patients with NSCLC who overexpress PD-L1 (47). In the clinical setting, correctly identifying these patients is imperative.

Other biomarkers analyzed showed percentages of positivity roughly similar to those previously published in adenocarcinoma, although some variability was expected due to the low number of patients evaluated: *ROS1* rearrangements (observed *vs.* literature), 4.3% *vs.* 1–2%; MET amplification, 7.1% *vs.* 4–5%; RET fusions, 2.3% *vs.* 1–2%; BRAF mutations, 3.3% *vs.* 1–3%; HER2 mutations, 6.5% *vs.* 1.6–4%; and FGFR1 amplification, 7.7% *vs.* 3% (36,48).

Interestingly, the frequency of all these molecular alterations was similar when analyzed in the subgroup of patients with advanced stage IV disease. In this regard, a previous study by Pi *et al.* reported that early-stage and advanced-stage lung adenocarcinoma exhibited the same EGFR mutation frequencies and types (49).

A possible limitation of the study could be the potential bias due to the data sources, perhaps with greater representation of patients recruited in large hospitals. However, the study has many advantages, such as the large number of patients included to date and the considerable number of sites involved, of all sizes and from virtually the entire national territory; also important is the fact that Spain has a National Health System with universal coverage and, thus, all patients follow the same diagnostic work-up and have the same treatment opportunities, regardless of where they live or their income. A further advantage is that all patients have been recruited in a short-time period, allowing the comparison of treatments.

Conclusions

We believe that the TTR study accurately describes the clinical reality of lung cancer in Spain, including useful information with respect to demographic, clinical and molecular aspects that can be used to drive improvements in health care. In this sense, this type of studies should be extended to other European countries (50). Tobacco smoking, along with other environmental pollutants, remains the most important risk factor for lung cancer; social and political pressure to reduce tobacco consumption among the population should be reinforced, particularly among youth.

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Footnote

Conflicts of Interest: Dr. M Provencio has received personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme (MSD), Roche, Novartis, and Takeda and research grants from Roche and Bristol-Myers Squibb. Dr. R López-Castro has received personal fees from Roche, Boehringer Ingelheim, AstraZeneca, Bristol Myers Squibb and Merck Serono and non-financial support from Roche and Bristol Myers Squibb. Dr. J Bosch-Barrera has received personal fees from Bristol-Myers Squibb, Boheringer Ingelheim, MSD, and Roche and research grants from Pfizer, Boheringer-Ingelheim, and Roche. Dr. M Domine has received personal fees from Abbvie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, MSD, Pfizer, and Roche. The other authors no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the provisions of the Declaration of Helsinki. Protocol approval was obtained from the institutional review board at each study site. The registry was approved in 2016 by the Spanish Agency for Medicines and Medical Devices (AEMPS) and is registered on the ClinicalTrials.gov database (NCT02941458). Protocol approval was obtained from the institutional review board of Hospital Universitario Puerta de Hierro Majadahonda (No. PI 148/15).

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Supplementary

Table S1 Patient symptoms according to the initial stage of the disease

Symptoms	Total (n=6,574)		Early disease (n=2,295)		Advanced disease (n=4,279)		P value
	n	%	n	%	n	%	
Unknown	1,174	17.9	435	37.1	739	62.9	<0.001
No	913	13.9	574	62.9	339	37.1	
Yes	4,487	68.3	1,286	28.7	3,201	71.3	
Cough	1,964	43.8	584	29.7	1,380	70.3	<0.001
Pain	1,606	35.8	353	22.0	1,253	78.0	<0.001
Dyspnoea	1,488	33.2	387	26.0	1,101	74.0	<0.001
Hemoptysis	671	15.0	265	39.5	406	60.5	0.009
Weight loss	1,184	26.4	241	20.4	943	79.6	<0.001
Anorexia	290	6.5	57	19.7	233	80.3	<0.001
Asthenia	396	8.8	97	24.5	299	75.5	<0.001
Others	1,448	32.3	367	25.3	1,081	74.7	<0.001

Table S2 Relationship between exposure to potential carcinogens and the initial stage of the disease

Probable carcinogen	Total (n=6,574)		Early disease (n=2,295)		Advanced disease (n=4,279)		P value
	n	%	n	%	n	%	
Not listed/unknown	5,770	87.8	1,992	34.5	3,778	65.5	0.020
Related to asbestos	141	2.1	67	47.5	74	52.5	
Related to arsenic	16	0.2	2	12.5	14	87.5	
Radon/silica	38	0.6	18	47.4	20	52.6	
Dyes	39	0.6	12	30.8	27	69.2	
Paintings	105	1.6	40	38.1	65	61.9	
Acrylonitrile	8	0.1	2	25.0	6	75.0	
Diesel engine smoke	144	2.2	55	38.2	89	61.8	
Others	313	4.8	107	34.2	206	65.8	

Table S3 Relationship between personal and family history of cancer and the initial stage of the disease

History of cancer	Total (n=6,574)		Early disease (n=2,295)		Advanced disease (n=4,279)		P value
	n	%	n	%	n	%	
Personal history of cancer							<0.001
Unknown	807	12.3	249	30.9	558	69.1	
No	4,799	73.0	1,585	33.0	3,214	67.0	
Yes	968	14.7	461	47.6	507	52.4	
Family history of cancer							0.902
Unknown	2,031	30.9	704	34.7	1,327	65.3	
No	2,215	33.7	770	34.8	1,445	65.2	
Yes	2,328	35.4	821	35.3	1,507	64.7	

Table S4 Passive-smoking according to sex

Passive smoking	Total (n=6,600)		Male sex (n=4,847)		Female sex (n=1,753)		P value
	n	%	n	%	n	%	
Unknown	4,686	71.0	3,511	74.9	1,175	25.1	<0.001
No	873	13.2	675	77.3	198	22.7	
Yes	1,041	15.8	661	63.5	380	36.5	

Table S5 Molecular profiling of stage IV tumors at diagnosis

Biomarker	n	%
Any biomarker		
No	642	18.6
Yes	2,804	81.4
ALK (IHC)		
Not performed	1,924	55.8
Performed	1,522	44.2
Negative	1,448	95.1
Positive	74	4.9
ALK (FISH)		
Not performed	2,913	84.5
Performed	533	15.5
Not translocated	466	87.4
Translocated	67	12.6
ALK (RNA)		
Not performed	3,407	98.9
Performed	39	1.1
Not detected	37	94.9
Detected	2	5.1
KRAS		
Not performed	3,131	90.9
Performed	315	9.1
Not detected	203	64.4
Detected	85	27.0
BRAF		
Not performed	3,111	90.3
Performed	335	9.7
Not detected	321	95.8
Detected	14	4.2
HER2 (mutated)		
Not performed	3,428	99.5
Performed	18	0.5
Not detected	17	94.4
Detected	1	5.6
HER2 (IHC)		
Not performed	3,431	99.6
Performed	15	0.4
Negative	14	93.3
Positive	1	6.7
HER2 (FISH)		
Not performed	3,444	99.9
Performed	2	0.1
Negative	2	100.0
Positive	0	0.0
Positive	0	0.0
ROS1 (FISH)		
Not performed	2,979	86.4
Performed	467	13.6
Not translocated	443	94.9
Translocated	24	5.1
FGFR1		
Not performed	3,439	99.8
Performed	7	0.2
Not amplified	7	100.0
Amplified	0	0.0
PD-L1		
Not performed	2,379	69.0
Performed	1,067	31.0
Unknown	447	41.9
Negative	535	50.1
Positive	85	8.0
RET		
Not performed	3,437	99.7
Performed	9	0.3
Not translocated	9	100.0
Translocated	0	0.0
MET		
Not performed	3,366	97.7
Performed	80	2.3
Negative	73	91.3
Overexpressed	1	1.3
Amplified	6	7.5
EGFR		
Not performed	872	25.3
Performed	2,574	74.7
Unknown	8	0.3
Not mutated	2,043	79.4
Mutated	523	20.3
Exon-19	285	54.5
Exon-21	161	30.8
T790M (+)	84	16.1
T790M (–)	23	4.4
Other type	72	13.8

ALK, anaplastic lymphoma kinase; BRAF, B RAF proto-oncogene, serine/threonine kinase oncogene; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; FGFR1, fibroblast growth factor receptor type 1; HER2, human epidermal growth factor receptor type 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, tyrosine-protein kinase MET/hepatocyte growth factor receptor; PD-L1, programmed death-ligand 1; RET, proto-oncogene tyrosine-protein kinase receptor Ret; RNA, ribonucleic acid; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase.

Table S6 Molecular profiling of stage IV tumors (adenocarcinoma only) according to year of diagnosis

Biomarker	All years (n=2,570)		Unknown (n=323)		≤2012 (n=283)		2013–2014 (n=418)		2015–2016 (n=714)		2017–2018 (n=832)		P value
	n	%	n	%	n	%	n	%	n	%	n	%	
ALK (IHC)													
Not performed	1,219	47.4	214	66.3	196	69.3	230	55.0	286	40.1	293	35.2	–
Performed	1,351	52.6	109	33.7	87	30.7	188	45.0	428	59.9	539	64.8	<0.001
Negative	1,278	94.6	102	93.6	76	87.4	175	93.1	413	96.5	512	95.0	–
Positive	73	5.4	7	6.4	11	12.6	13	6.9	15	3.5	27	5.0	0.004
ALK (FISH)													
Not performed	2,092	81.4	221	68.4	257	90.8	342	81.8	561	78.6	711	85.5	–
Performed	478	18.6	102	31.6	26	9.2	76	18.2	153	21.4	121	14.5	<0.001
Not translocated	413	86.4	101	99.0	20	76.9	59	77.6	128	83.7	105	86.8	–
Translocated	65	13.6	1	1.0	6	23.1	17	22.4	25	16.3	16	13.2	0.321
ALK (RNA)													
Not performed	2,535	98.6	321	99.4	281	99.3	412	98.6	700	98.0	821	98.7	–
Performed	35	1.4	2	0.6	2	0.7	6	1.4	14	2.0	11	1.3	0.483
Not detected	33	94.3	2	100.0	1	50.0	5	83.3	14	100.0	11	100.0	–
Detected	2	5.7	0	0.0	1	50.0	1	16.7	0	0.0	0	0.0	–
ROS1 (FISH)													
Not performed	2,153	83.8	282	87.3	264	93.3	362	86.6	585	81.9	660	79.3	–
Performed	417	16.2	41	12.7	19	6.7	56	13.4	129	18.1	172	20.7	<0.001
Not translocated	393	94.2	40	97.6	15	78.9	49	87.5	124	96.1	165	95.9	–
Translocated	24	5.8	1	2.4	4	21.1	7	12.5	5	3.9	7	4.1	–
EGFR													
Not performed	286	11.1	69	21.4	43	15.2	54	12.9	54	7.6	66	7.9	–
Performed	2,284	88.9	254	78.6	240	84.8	364	87.1	660	92.4	766	92.1	<0.001
Unknown	7	0.3	0	0.0	0	0.0	0	0.0	1	0.2	6	0.8	–
Not mutated	1,774	77.7	203	79.9	183	76.3	275	75.5	519	78.6	594	77.5	–
Mutated	503	22.0	51	20.1	57	23.8	89	24.5	140	21.2	166	21.7	0.621

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; RNA, ribonucleic acid; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase.