Original Article

Changes in non-small cell lung cancer diagnosis, molecular testing and prognosis 2011–2016

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Background: Non-small cell lung cancer (NSCLC) is a leading cause of death all over the world. Diagnostic and therapeutic arsenals have improved in recent years, but we are unsure as to whether these advances have been transferred to clinical practice. The aim of this study was to evaluate differences in NSCLC diagnostic processes and short-term survival rates between two recent cohorts.

Methods: A prospective, observational study was conducted with patients diagnosed with NSCLC in the period of 2011–2016. Patients were divided into two cohorts (2011–2013 and 2014–2016), and monitored for up to 1 year after diagnosis.

Results: A total of 713 patients with lung cancer were selected, 500 of whom had NSCLC (222 patients in the 2011–2013 cohort, and 278 in the 2014–2016 cohort). We observed a chronological increase in the use of endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) and ultrasound-guided transthoracic puncture (US-TTP) between the cohorts. Overall short-term survival was similar between the two groups, both for locally and for advanced disease. Treatment with tyrosine kinase inhibitors (TKI) was the only therapeutic factor associated with an improved likelihood of survival.

Conclusions: Changes in diagnostic process in NSCLC have been observed towards a more precise stratification. Although short-term survival has not changed for advanced NSCLC, some of the newer therapeutic options are associated with increased survival in real-world scenarios.

Keywords: Non-small cell lung cancer (NSCLC); molecular testing; advanced disease

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Introduction

Lung cancer is a leading global cause of death, not only in developed countries, but also in developing countries (1,2). Analysis of Spanish government databases has shown that lung cancer causes more deaths in Spain that any other type of cancer, accounting for over 20,000 deaths/year and more than 25% of cancer-related deaths (3). These high figures reflect the fact that non-small cell lung cancer (NSCLC) is commonly diagnosed in advanced stages when the prognosis is already usually poor. Lung cancer survival rates are low in most countries with a similar level of access to public healthcare; 5-year survival rates are typically around 15% (4).

Over the last 20 years, changes in the diagnosis and

management of lung cancer have given rise to a new approach towards improving survival through more personalized treatment, plus earlier and more accurate diagnosis and staging. These advances have now become widely accepted and implemented by healthcare organizations. They can be classified as changes regarding more accurate diagnosis and staging (PET: positron emission tomography, EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, US-TTP: ultrasound-guided transthoracic puncture) (5), and those related to a more personalized approach (including molecular testing for selection of EGFR, epidermal growth factor receptor, and anaplastic lymphoma kinase (ALK), as well as the use of targeted therapies) (6-8). These latest must have yielded improved response and survival rates in patients with advanced NSCLC (9-13).

However, even in the light of recent progress, there is still a lack of data on how these new approaches have been translated into daily clinical practice and whether or not they have improved the prognosis for patients in advanced stages of NSCLC. Some studies have observed changes in the clinical presentation and overall course of NSCLC (14,15), but we are still unaware as to whether those changes affected patient survival.

The aim of this study was to evaluate changes in clinical presentation, diagnosis, and therapeutic schemes among two single-center cohorts with NSCLC patients, and whether these changes have led to an improvement in short-term survival rates over the last 5 years among patients with advanced stages (IIIB and IV) of NSCLC.

Methods

Study design and ethics

This prospective, 1-year follow-up, observational study recruited lung cancer patients treated at our tertiary outpatient clinic. Patients were contacted for follow-ups every 3 months for the first 5 years or until death.

Our main objectives were to compare: (I) the means of diagnosing the lung cancer and the treatment options offered to both cohorts (2011–2013 and 2014–2016); and (II) the 1-year survival rate among patients with advanced stages (IIIB and IV) of NSCLC, again between the two cohorts.

Study population

The study included adult patients diagnosed with NSLCL between 2011 and 2016, inclusive, treated at the Hospital Universitario Virgen de las Nieves de Granada. Screened patients should have a diagnosis of lung cancer (whether confirmed by histological analysis or not) and at least 35 years at the age of diagnosis. The hospital provides healthcare assistance to 327,751 people in the South-East Andalusia.

Measurements

At recruitment, data on cumulative smoking exposure, previous medical history, concomitant diseases, and previous cancer history were collated from each participant's medical records. Both the types of diagnostic test performed during the initial evaluation and their results were recorded.

We also made a record of each patient's definitive NSCLC diagnosis (16), the type of NSCLC, and stage according to current guidelines (17). For cohorts' comparison, patients were classified in localized NSCLC (stages I to IIIA) and advanced NSCLC (IIIB to IV)

Patients were classified according to the type of mutation observed in their histological samples as revealed by molecular testing at diagnosis (6,7,18). Information regarding treatment strategies, surgical interventions, or target-specific therapeutic agents was also collected.

Survival status was assessed every 3 months through either scheduled visits to the hospital or over the telephone. Exact dates of death were collected from the Andalusian Regional Health System's electronic health records.

Ethical aspects

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study. The study was approved by institutional ethics committee of Granada (No. 17/023).

Statistical analysis

Results are presented as sample size (n), range, median (interquartile range), or mean ± standard deviation, as appropriate. Categorical variables were compared using the χ^2 test, whereas continuous variables were compared with ANOVA, *t*-test or Mann-Whitney U tests, as required. Statistical significance was defined as $P<0.01$ in order to

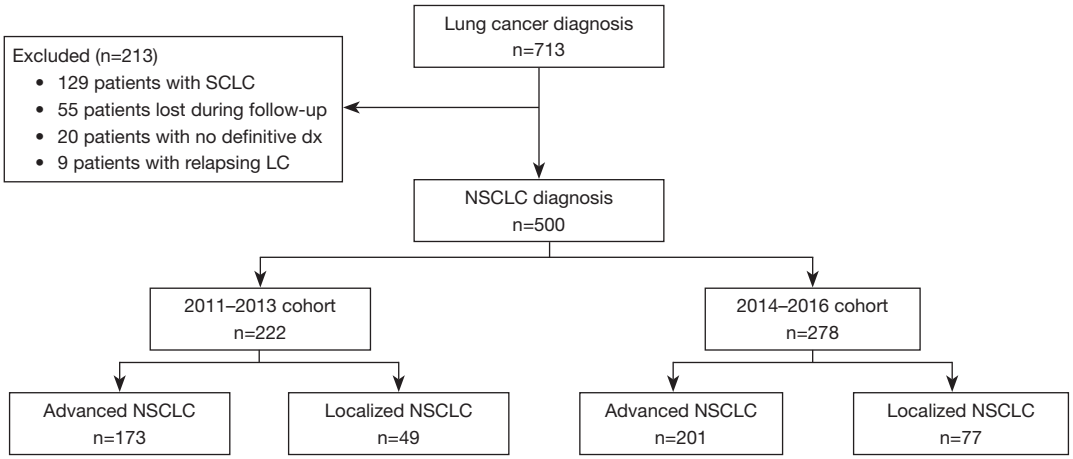

Figure 1 STROBE diagram for the study participants, and their classification in the 2011–2013 and 2014–2016 cohorts. SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; LC, lung cancer.

account for multiple comparisons. We used Cox regression analysis to compare time to death in each group after adjusting for age, gender, smoking status, chemotherapy agent, and initial staging. Analyses were performed using the statistical software package SPSS version 20.0 (IBM Corporation, NY, USA).

Results

Between 2011 and 2016, inclusive, we received 713 patients who were diagnosed with lung cancer; 500 (70.1%) had NSCLC, while 129 cases presented SCLC (18.0%). *Figure 1* shows the STROBE diagram for the study population.

Mean baseline characteristics for NSCLC patients according to study cohort are presented in *Table 1*. Briefly, most patients were men in their 60s with a heavy smoking history (a cumulative tobacco consumption history of more than 40 pack/years). Adenocarcinoma was the most frequent histological type of NSCLC followed by squamous cell carcinoma, while changes in cough pattern were the most common symptom observed during the initial evaluation. Most patients were at an advanced stage of the disease at diagnosis (74.6% of the NSCLC sample).

There were statistically significant differences between the two study cohorts in terms of a higher proportion of women in the 2014–2016 cohort, as well as an increase in the proportion of never smokers and patients with a previous history of cancer. However, no significant differences were observed between the two cohorts with regards to baseline staging, the histological type of NSCLC, or the proportion of patients with advanced stages of the disease at the time of diagnosis.

The vast majority of patients presented some symptoms at the time of diagnosis, but there were no differences between the cohorts. The proportion of asymptomatic patients in both groups was near to statistical significance (13.9% in the 2011–2013 cohort *vs.* 16.9% in the 2014–2016 cohort, P=0.054). However, fewer patients manifested constitutional symptoms at the time of diagnosis (42.9% *vs.* 32.7% respectively, P=0.005), and a lower proportion of patients debuting with hemoptysis at the time of diagnosis (23.5% *vs.* 16.3% respectively, P=0.016).

Table 2 summarizes the diagnostic tests performed during the initial evaluation, and the molecular mutations screened at baseline. CT-guided biopsies were standard of care at the time the study was started and were not included in the analysis. There was an increase in the rates of EBUS or US-TTP performed between both cohorts, and a non-significant decrease in the rate of mediastinoscopies needed to confirm the diagnosis. There were no differences in terms of diagnostic rates between both cohorts neither for EBUS-TBNA nor for US-TTP. There were no significant differences between the molecular tests performed in both cohorts or the prevalence of the most important mutations identified in histological samples.

Regarding survival rates, the overall rate of 1-year survival assessed for both cohorts was similar after adjusting for confounding variables (*Figure 2*). *Table 3* summarizes the survival rates between groups and the mean and median time to death for patients with localized and advanced

Table 1 Baseline characteristics of participants in the 2011–2013 (n=222) and 2014–2016 (n=278) cohorts

Variable	2011–2013	2014–2016	P
Age, years	66.3±10.5	66.8±11.7	0.753
Sex (male/female), %	83.9/16.1	76.6/23.4	0.032
Smoking history			
Never smokers, n (%)	23 (10.3)	52 (18.7)	0.007
Pack-years	44.8±25.6	44.6±34.2	0.941
Symptoms at diagnosis, n (%)			
Asymptomatic	31 (13.9)	47 (16.9)	0.054
Chest pain	123 (39.7)	134 (33.7)	0.099
Hemoptysis	73 (23.5)	65 (16.3)	0.016
Cough	126 (40.6)	184 (46.2)	0.137
Constitutional symptoms	133 (42.9)	130 (32.7)	0.005
Dyspnea	108 (34.8)	162 (40.7)	0.111
Oncologic history			
Previous LC, n (%)	4 (1.8)	12 (4.3)	0.182
Previous cancer, n (%)	41 (18.4)	105 (37.7)	<0.001
Histological type of NSCLC, n (%)			
Adenocarcinoma	114 (51.3)	139 (50.0)	0.493
Squamous cell	103 (46.4)	130 (48.8)	0.232
Other	5 (2.3)	9 (3.2)	0.147
Baseline staging, n (%)			0.373
Stage I	11 (4.9)	15 (8.1)	
Stage II	20 (9.0)	22 (7.9)	
Stage III	68 (30.6)	96 (34.5)	
Stage IV	127 (57.2)	148 (53.2)	
Localized *vs.* advanced, n (%)			0.150
Localized stage	49 (22.1)	77 (27.7)	
Advanced stage	173 (77.9)	201 (72.3)	

LC, lung cancer; NSCLC, non-small cell lung cancer.

disease. The two cohorts did not present any differences in terms of mean or median survival, or the overall survival in both localized or advanced disease.

Table 4 shows the results of the Cox proportional hazards regression model for survival across the whole sample. Factors associated with improved survival during the study were surgical resection [odds ratio (OR) 2.045, 95% CI: 1.338–3.126], age (1.016, 95% CI: 1.006–1.027) and tyrosine kinase inhibitor therapy (TKI) (OR 2.303, 95% CI: 1.123–4.723). Factors associated with a decreased probability of survival were advanced disease and the standardized uptake value (SUV) as determined by PET-CT. In summary, there was no increased chance of survival observed between cohorts 2011–2013 and 2014–2016.

Table 2 Staging procedures and molecular testing performed during initial evaluation according to study group

Variable	2011–2013 (n=222)	2014–2016 (n=278)	P
Staging procedures, n (%)			
PET-CT	159 (72.2)	215 (77.5)	0.220
EBUS-TBNA	30 (13.6)	50 (17.9)	0.001
US-TTP	1 (0.4)	22 (8.0)	0.004
Mediastinoscopy	6 (2.5)	2 (0.6)	0.94
Molecular testing, n (%)			
No tests	136 (61.2)	184 (66.1)	0.453
One or more tests	86 (38.8)	94 (33.9)	0.634
EFGR + mutations	9 (4.5)	12 (4.3)	0.609
ALK + mutations	0 (0.0)	3 (1.0)	0.262
K-ras + mutations	0 (0.0)	2 (0.6)	0.358
BRAF + mutations	0 (0.0)	0 (0.0)	0.368

PET-CT, positron emission tomography-computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; US-TTP, ultrasound-guided transthoracic puncture; EFGR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; K-ras, Kirsten rat sarcoma viral oncogene homolog; BRAF, B-Raf proto-oncogene.

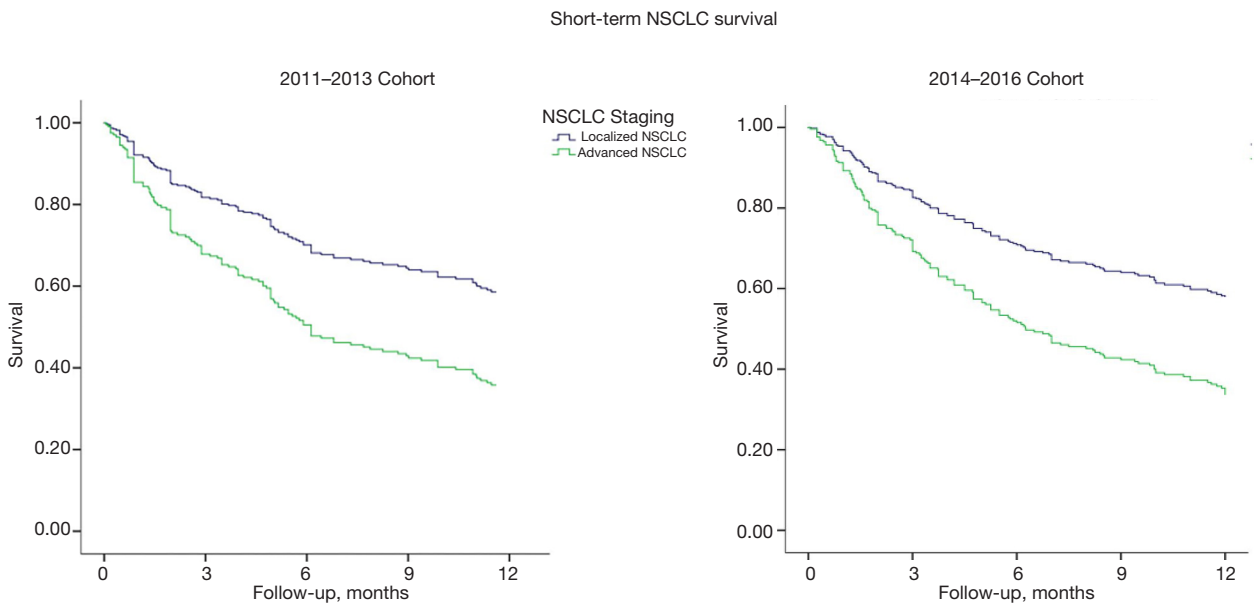

Figure 2 Kaplan-Meier survival curves for localized and advanced NSCLC for both the 2011–2013 and 2014–2016 cohorts. Log-rank test P>0.5 for comparison of 1-year survival between both cohorts. Log-rang test P<0.5 for comparison between localized and advanced NSCLC in both cohorts. NSCLC, non-small cell lung cancer.

Table 3 One-year survival rates for patients with advanced NSCLC in the 2011–2013 (n=222) and 2014–2016 (n=278) cohorts

Outcome	2011–2013	2014–2016	P*
Deaths	176	197	
Localized disease	30	41	
Advanced disease	146	156	
Overall 1-year survival, %	20.7	29.1	0.140
Localized disease	38.7	46.7	
Advanced disease	15.6	22.4	
Median survival (months), OR (95% CI)	17.7 (14.4–20.9)	17.9 (15.1–22.9)	0.824
Localized disease	28.6 (21.4–37.3)	29.4 (21.0–39.1)	
Advanced disease	12.3 (9.6–15.1)	12.4 (9.7–15.0)	
Mean survival (months), OR (95% CI)	7.7 (5.1–10.3)	8.4 (5.7–11.0)	0.232
Localized disease	20.0 (8.9–33.0)	18.0 (4.6–31.3)	
Advanced disease	5.6 (4.7–6.4)	5.0 (3.7–6.2)	

*, log-rank test.

Table 4 Cox proportional hazard regression model (factors associated with overall survival between 2011 and 2016)

Variable	OR	95% CI	P
Age (per year)	1.016	1.006–1.027	0.002
Sex (male)	0.787	0.588–1.052	0.105
SUV_{max}	0.978	0.963–0.993	0.003
Advanced disease	0.494	0.360–0.678	0.000
Cohort 2011–2013 vs. 2014–2016	1.145	0.934–1.403	0.193
TKI therapy	2.303	1.123–4.723	0.023
Platinum-based chemotherapy	1.202	0.884–1.634	0.240
Anti-PD-1 inhibitor	2.173	0.524–9.020	0.285
Surgical resection	2.045	1.338–3.126	0.001

SUV, standardized uptake value at PET-CT; TKI, tyrosine kinase inhibitor (erlotinib, gefitinib, afatinib); anti-PD-1 inhibitor, anti-programmed death ligand inhibitor (pembrolizumab).

Discussion

The main results of study show that, although the tools and molecular tests used to diagnose patients with NSCLC have improved over the last 5 years, this has not fully translated into an improvement in the real-life situation; neither in terms of the proportion of patients treated with new therapeutic agents, nor in the short-term survival for those with advanced NSCLC. Our results highlight the need to strive for an earlier diagnosis of NSCLC through screening programs and wider access to new chemotherapeutic agents.

We have observed that the evaluation of NSCLC is more accurate, at least at the time of diagnosis, with more techniques, such as EBUS-TBNA and US-TTP, available for the clinician to confirm the extension of the disease. This changes in diagnostic procedures management in NSCLC probably are not expected to impact directly on overall survival but could do so indirectly by shortening the time to initiation of targeted therapies and sparing

inappropriate surgical resections. There is a plateau in the use of PET-CT during initial staging, with more than three quarters of patients diagnosed at our region via a PET-CT scan. The results also show some changes in the symptoms presented at diagnosis, with a reduction in the proportion of patients with hemoptysis or constitutional symptoms. This could reflect a slight increase in the general population's awareness of lung cancer. However, only a small proportion of patients manifested localized NSCLC at the time of diagnosis. This finding is in line with previous Spanish studies that reported changes in the symptoms present at initial NSCLC diagnosis (14) in this decade, and also with other results reported in other countries (15,19).

Survival analysis carried out in both the 2011–2013 and 2014–2016 cohorts did not reveal any improvements in short-term survival for patients with advanced stages of NSCLC in terms of both overall and median survival, although Cox proportional hazards regression modelling showed that patients treated with TKI had an increased OR for survival. This concurs with results from randomized controlled trials examining survival benefit in patients with EGFR mutations (10,20). The authors did not observe any effect from other new agents (i.e., ALK inhibitors), but this could be explained by the lower tumor mutation rates in our series and also by the fact that some of the treatments (e.g., anti-PD1 inhibitors) were not widely used at that time. Another issue that has been observed is the low molecular testing workup in both cohorts, this could have been explained by small sampling or that many patients were referred for palliative care.

We are obliged to point out the weaknesses in our study, the most important being that we only recorded first-line treatments, and some effects of second-line options may have gone undetected. Another defect is that we only recorded overall survival, not time to disease progression, as this parameter is recorded by oncologists and the information was not available at the time of the follow-up visits. Another limitation is the absence of registration of comorbidities, which could have biased our results (21). Moreover, our study population is relatively small so it could be possible that smaller survival rates could not be detected. It is possible that a longer follow up could have detected treatment effect on survival rates too.

Conclusions

In summary, NSCLC diagnosis and treatment has changed over the last years, not only due to improved techniques which can better characterize the initial disease extension, but also because of greater access to new therapeutic options; some of these factors improve the likelihood of survival during the follow-up period.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics committee of Granada (No. 17/023) and the informed consent was obtained from all individual participants included in the study.

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