Real-world treatment patterns and survival outcomes for patients with stage III non-small cell lung cancer in Spain: a nationwide cohort study

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Background: The burden of non-small cell lung cancer (NSCLC) remains high in Spain, with lung cancer accounting for 20% of cancer-related deaths annually. Programs such as the Spanish Thoracic Tumour Registry (TTR) and the global I-O Optimise initiative have been developed to observe patients in clinical practice with the aim of improving outcomes. This analysis examined treatment patterns and survival in patients with stage III NSCLC from the TTR. These patients represent a heterogenous group with complex treatment pathways.

Methods: The TTR is an ongoing, observational, prospective, and retrospective cohort multicentre study (NCT02941458) that follows patients with thoracic cancer in Spain. Adults aged ≥18 years with stage IIIA/IIIB NSCLC enrolled in the TTR between 01 Jan 2010 and 31 Oct 2019 were included in this analysis. Initial treatment received was described by cancer stage and histology (squamous and non-squamous NSCLC). Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS) were calculated over a 5-year period.

Results: A total of 1,838 patients were included in the cohort, including 1,082 with stage IIIA (58.9%) and 756 with stage IIIB (41.1%). Median follow-up was 18.3 months. The median age of patients was 66 years, and most had non-squamous NSCLC (54.0%), were male (81.2%), and were active or former smokers (93.4%). Overall, 26.3% of patients received surgical resection (37.0% for stage IIIA and 11.1% for stage IIIB). The most frequent initial treatment received was concurrent chemoradiotherapy for stage IIIA (30.2%) and stage IIIB (37.0%) patients. Median OS was lower in patients with stage IIIB than stage IIIA

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(28 *vs.* 37 months) disease and was lower for patients with squamous than non-squamous histology (19 *vs.* 26 months). Median PFS and OS varied when patients were stratified by initial treatment.

Conclusions: This TTR analysis describes the clinical reality surrounding the initial management and survival outcomes for stage III NSCLC in Spain and presents survival outcomes comparable with other real-world evidence. It provides insights into the diverse approaches used before the availability of immunotherapies and targeted treatments in the non-metastatic NSCLC setting.

Keywords: Lung cancer; non-small cell lung cancer (NSCLC); cancer registry; I-O optimise; Spain

Introduction

The disease burden associated with lung cancer remains high. In 2020, the number of new cases of lung cancer worldwide was 2,206,771 (11.4% of all new cancer cases) and the associated mortality was 1,796,144 (18.0% of cancer deaths) (1). In Europe, lung cancer accounted for 384,176 (21.4%) cancer deaths in 2020; the death rate was similarly high in Spain (20.3%; 22,930), highlighting the need for lung cancer initiatives in this country (2,3). Non-small cell lung cancer (NSCLC) accounts for most lung cancer cases (84%); it has a poor prognosis, with a 5-year overall survival (OS) of 34–61% (non-metastatic) and 7% (metastatic) (4). The 5-year survival in patients with NSCLC stage IIIA and

IIIB is 26.2% and 17.3%, respectively (5). NSCLC is often diagnosed at a later stage due to lack of obvious symptoms (6), which can make the management of this disease challenging.

For the management of locally advanced stage III NSCLC, the European Society for Medical Oncology (ESMO)-guided treatment pathways recommend surgical resection wherever possible (7,8). The exact treatment pathway will depend on a multidisciplinary team assessment including positron emission tomography-computed tomography scans and pathological staging. For patients with resectable stage III disease, surgery with curative intent, with or without (neo)adjuvant treatments is recommended. At the time of this study, definitive concurrent chemoradiotherapy (usually with platinum-based chemotherapy with cisplatin) was the treatment of choice for patients with unresectable stage IIIA/IIIB disease, with a sequential approach as an alternative if needed (7). Programmed death ligand 1 (PD-L1) checkpoint inhibitors were being evaluated during this time as (neo)adjuvant treatment for patients with resectable disease or as consolidation therapy after chemoradiotherapy in those with unresectable disease, and they are now recommended for use in this setting (8). Durvalumab was also recently approved by the European Medicines Agency (EMA) in 2018 as maintenance therapy for unresectable stage III NSCLC tumours with PD-L1 expression ≥1% (9,10), and the ESMO guidelines were updated in 2021 to reflect this recommendation (8).

It is essential to monitor how treatment modalities are being implemented in clinical practice in relation to outcomes. To address this, the I-O Optimise initiative was developed in 2017. I-O Optimise is a multinational collaborative research framework that is providing insights into the real-world management of thoracic malignancies,

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Highlight box

Key findings
- The Thoracic Tumour Registry (TTR) is an observational study following patients with thoracic disease in Spain; this analysis of TTR data highlights the diverse approaches adopted for the treatment of stage III non-small cell lung cancer (NSCLC) resulting in variable survival outcomes over 5 years.

What is known and what is new?
- Patients with stage III NSCLC represent a heterogenous group with complex treatment pathways.
- This manuscript provides insights into the management of these patients in real-world settings in Spain using data from Jan 2010 to Oct 2019 (prior to durvalumab approval in this setting).

What is the implication, and what should change now?
- These findings highlight gaps in our current treatment pathway of stage III NSCLC, and illustrate how overall survival was impacted by treatment choice (3.9–69.4 months); it will be important to monitor how new therapies and changes to guidelines improve survival in real-world settings.

including NSCLC, with the aim of improving long-term clinical and safety outcomes (11). To date, an I-O Optimise network has been established with thoracic data sources from Europe (Denmark, France, Germany, Norway, Portugal, Sweden, and the UK) and Canada. The Spanish Lung Cancer Group (Grupo Español de Cáncer de Pulmón; GECP) has recently collaborated with the I-O Optimise network in association with the ongoing nationwide Thoracic Tumour Registry (TTR) study from Spain.

To gain a greater understanding of the management of stage III NSCLC, we performed further analysis of data from the TTR. The primary aim of this analysis was to observe treatment patterns and survival outcomes in patients with stage III NSCLC in Spain. These patients represent a heterogenous group of patients presenting with resectable and unresectable disease, and the treatment pathways are complex. A greater understanding of how these patients are being treated in real-world settings may help to tailor treatment pathways and improve outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-176/rc).

Methods

Study design and TTR overview

This is an observational study based on the TTR cohort. Patients with stage IIIA and IIIB NSCLC diagnosed between 01 Jan 2010 and 31 Oct 2019 were included. All patients were followed from their initial NSCLC diagnosis (index date) until 31 Oct 2020 (interim study end), death, or known exit from the TTR (whichever occurred first).

The TTR is an ongoing, observational, prospective and retrospective, cohort, multicentre study (ClinicalTrials.gov identifier NCT02941458) that includes patients with thoracic cancers (12). As of Jul 2022, 25,018 patients with thoracic cancers from 88 centres have been included in the TTR. The TTR was initially created in 2016 by the Spanish Lung Cancer Group (GECP), a multidisciplinary oncology group that was established in 1991 to promote lung cancer research. The GECP consists of more than 400 specialists from a network of 160 hospitals in Spain.

Ethics

The TTR was approved in 2016 by the Spanish Agency for Medicines and Medical Devices (AEMPS) and the institutional review board at each study site (12). The current analysis of the TTR was performed in accordance with the principles of the Declaration of Helsinki [2013] (13), and the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (14). The study was approved by the GECP ethics committee (IRB Number PI 148.15). For prospective enrolment, informed consent was taken from all individual participants. For retrospective enrolment, individual consent for this retrospective analysis was waived.

Patient population and inclusion criteria

Men and women aged ≥18 years with a diagnosis of incident stage IIIA/IIIB NSCLC based on the 7th [2012] and 8th [2016] tumor-node-metastasis (TNM) classification (as this study was performed over a 9-year period it captured both versions depending on year of diagnosis) and clinical staging system from Jan 2010 to Jan 2019 (using ICD-10 codes C33.0, C34.0, C34.1, C34.2, C34.3, C34.8, and C34.9) who were enrolled in the TTR were included in this analysis. Stage IIIC was introduced in the 8th TNM staging edition in 2017, as such no patient records with acceptable data quality were available at the time of this study. Only data from contributing centres with large populations (n≥100) and robust linkage to mortality data were included from the TTR; patients diagnosed outside of the study period or with poor-quality data were excluded.

Design and data collection

Data on patient diagnosis were collected from 01 Jan 2010 to 31 Oct 2019 (latest data available at the time of the extraction) and follow-up data for treatments, disease progression, and death were collected until 31 Oct 2020; this timeframe was deemed sufficient to provide an overview of clinical care in Spain.

Extracted data were recorded in an electronic case report form (eCRF); these were maintained in accordance with updates from participating study sites. The following variables were recorded in the eCRF: sociodemographic and clinical characteristics including histology, Eastern Cooperative Oncology Group (ECOG) performance status, biomarker tests performed, NSCLC diagnosis (index date), initial treatments received, and death (date and cause) or last documented entry. All variables were entered in the eCRF by one reviewer and quality control was undertaken

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by a second independent reviewer.

Statistical analysis

Descriptive statistics were performed; continuous data were summarised as mean, first and third quartiles (Q1 and Q3), standard deviation (SD), median, minimum, and maximum, and categorical variables were described using percentages. No imputation methods were used to handle missing data except for date of birth; however, this was not required as all dates were complete.

Initial treatment was defined as the first date of radiotherapy administration, surgery, or first dose or prescription of systemic anticancer therapy (SACT) within 6 months of an NSCLC stage III diagnosis (index date). The proportion of patients receiving treatment and the frequency of treatment types were stratified by cancer stage (overall, IIIA, or IIIB NSCLC) and histology (squamous and non-squamous NSCLC). The initial treatments received were categorised into seven groups, which are regarded as the main therapeutic approaches in this setting: (I) neoadjuvant SACT then surgery, (II) surgery with adjuvant SACT, (III) surgery alone, (IV) sequential chemoradiotherapy, (V) concurrent chemoradiotherapy, (VI) SACT ± palliative radiotherapy, or (VII) radiotherapy alone. The rules applied to define these categories using TTR longitudinal data regarding treatment exposure are defined in Table S1. The list of SACT recorded as initial therapy is summarised in Table S2.

OS and progression-free survival (PFS) for treated patients stratified by cancer stage (overall, IIIA, or IIIB), histology, and initial treatment received were described using Kaplan-Meier methods. Kaplan-Meier estimates of PFS, OS, and treatment duration were calculated over a 5-year period. OS was defined as the time from NSCLC diagnosis (index date) to death due to any cause. PFS was defined as the time from the treatment start until the earliest date based on progression (as recorded in the database), start of next line of therapy, death, lost to follow-up (censored), or study end (censored).

The clinical characteristics associated with surgical resection and use of neoadjuvant therapy were also described. Treatment response in patients treated with chemoradiotherapy (i.e., any treatment group containing SACT) was also recorded and defined using complete response, partial response, stable disease, progressive disease, not evaluable, or not performed.

Univariate analyses were performed to identify sociodemographic and clinical covariates with a significant association with neoadjuvant treatment and surgical resection. These covariates, and any that were of clinical interest, were then entered into a multivariable selection model that used LASSO (least absolute shrinkage and selection operator) to reduce and select the final covariates. These covariates, together with sex and TN staging, were included in a multivariate regression model that examined their association with neoadjuvant therapy use (planned and actual) and surgical resection.

All statistical analyses were performed using R (version 4.1.2) and R Studio (version 2021.09.1+372) software.

Results

Patient cohort

Overall, 3,751 patients were diagnosed with stage III NSCLC and 1,838 patients met the inclusion criteria from which 1,082 (58.9%) were diagnosed at stage IIIA and 756 (41.1%) at stage IIIB NSCLC and were followed up for a median of 18.3 months (Table S3 and *Table 1*). Most patients had non-squamous (adenocarcinoma, large-cell carcinoma, specified/non-specified) NSCLC (54.0%), were male (81.2%), with a median age of 66 years at diagnosis, and were active or former smokers (93.4%). Most patients had ECOG performance status 0 (fully active; 47.1%) or 1 (strenuous physical activity restricted; 44.2%). PD-L1 status was obtained in 29.4% of patients, with slightly more testing for stage IIIB (32.4%) than stage IIIA (27.4%) NSCLC. The PD-L1 status was ≥1% in 53.8% of patients who were tested (*Table 1*).

Initial treatment patterns

The initial treatments received in patients diagnosed with stage III NSCLC are shown in *Table 2*. In total, 26.3% of patients received surgical resection (37.0% of patients with stage IIIA NSCLC and 11.1% with stage IIIB NSCLC). The most common procedure was (bi)lobectomy or pneumonectomy (18.7% overall). The breakdown of surgical intervention by initial treatment group is shown in Table S1.

Concurrent chemoradiotherapy was the most common initial treatment for patients with both stage IIIA (30.2%) and IIIB (37.0%) NSCLC. The next most used initial treatment was surgery with adjuvant SACT for patients at stage IIIA (19.5%) and SACT ± palliative radiotherapy for

Table 1 Patient demographics and clinical characteristics by stage

Patient demographics and clinical characteristics	Total	Stage IIIA NSCLC	Stage IIIB NSCLC
Patients, n (%)	1,838 (100.0)	1,082 (58.9)	756 (41.1)
Age (years) at NSCLC diagnosis, median (Q1–Q3)	66.3 (59.2–73.0)	66.5 (59.8–73.0)	65.8 (58.0–73.1)
Male, n (%)	1,493 (81.2)	889 (82.2)	604 (79.9)
Ethnicity, n (%)			
Caucasian	1,827 (99.4)	1,076 (99.4)	751 (99.3)
Latin	7 (0.4)	4 (0.4)	3 (0.4)
African	2 (0.1)	0	2 (0.3)
Other	2 (0.1)	2 (0.2)	0
Smoking status, n (%)			
Active smoker	761 (41.4)	440 (40.7)	321 (42.5)
Former smoker (not smoked within 12 months)	956 (52.0)	567 (52.4)	389 (51.5)
Never smoker (≤100 cigarettes ever smoked)	112 (6.1)	69 (6.4)	43 (5.7)
Missing	9 (0.5)	6 (0.6)	3 (0.4)
T stage			
T0	1 (0.1)	0	1 (0.1)
T1	179 (9.7)	122 (11.3)	57 (7.5)
T2	387 (21.1)	304 (28.1)	83 (11.0)
T3	448 (24.4)	281 (26.0)	167 (22.1)
T4	736 (40.0)	330 (30.5)	406 (53.7)
Tx	78 (4.2)	42 (3.9)	36 (4.8)
Missing	9 (0.5)	3 (0.3)	6 (0.8)
N stage, n (%)			
N0	239 (13.0)	239 (22.1)	0
N1	193 (10.5)	192 (17.7)	1 (0.1)
N2	1,064 (57.9)	621 (57.4)	443 (58.6)
N3	288 (15.7)	0	288 (38.1)
Nx	46 (2.5)	27 (2.5)	19 (2.5)
Missing	8 (0.4)	3 (0.3)	5 (0.7)
M stage, n (%)			
M0	1,746 (95.0)	1,038 (95.9)	708 (93.7)
M1	3 (0.2)	1 (0.1)	2 (0.3)
Mx	81 (4.4)	40 (3.7)	41 (5.4)
Missing	8 (0.4)	3 (0.3)	5 (0.7)

Table 1 (*continued*)

Table 1 (*continued*)

Patient demographics and clinical characteristics	Total	Stage IIIA NSCLC	Stage IIIB NSCLC
ECOG performance status, n (%)			
0	865 (47.1)	550 (50.8)	315 (41.7)
1	812 (44.2)	442 (40.9)	370 (48.9)
2	131 (7.1)	74 (6.8)	57 (7.5)
3	27 (1.5)	14 (1.3)	13 (1.7)
4	2 (0.1)	1 (0.1)	1 (0.1)
Missing	1 (0.1)	1 (0.1)	0
Histology, n (%)			
Non-squamous cell and others[†]	993 (54.0)	588 (54.3)	405 (53.6)
Squamous-cell	845 (46.0)	494 (45.7)	351 (46.4)
PD-L1 test performed[‡], n (%)			
Yes	541 (29.4)	296 (27.4)	245 (32.4)
No	1,297 (70.6)	786 (72.6)	511 (67.6)
PD-L1 status (in those tested)			
Positive	291 (53.8)	159 (53.7)	132 (53.9)
Negative	220 (40.7)	123 (41.6)	97 (39.6)
Unknown	1 (0.2)	1 (0.3)	0
Missing	29 (5.4)	13 (4.4)	16 (6.5)
Time (days) from diagnosis to initial treatment, median (Q1–Q3)	37.0 (22.0–62.0)	36.0 (20.0–62.0)	37.0 (23.0–61.0)
Time (months) from diagnosis to end of follow-up, median (Q1–Q3)	18.3 (9.2–34.3)	20.3 (10.7–36.8)	15.7 (7.5–28.5)

[†], includes adenocarcinoma, large cell carcinoma, other NSCLC (specified or non-specified); [‡], biomarker test results recorded closest to initial treatment, if unavailable, tests performed at diagnosis were used. NSCLC, non-small cell lung cancer; Q, quartile; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand 1.

those at stage IIIB (27.1%). When SACT was used in the adjuvant setting (13.8%), treatment was started within a median of 43.5 days post surgery. When SACT was used in the neoadjuvant setting (7.2%), surgery was performed within a median of 96.5 days from start of preoperative/ neoadjuvant SACT (98.5 days for stage IIIA and 83.0 days for stage IIIB). Of the patients who were intended to receive neoadjuvant therapy followed by surgery, 52% (n=113/216) with stage IIIA and 38% (n=25/65) with stage IIIB NSCLC went on to receive surgery. Among patients receiving neoadjuvant SACT, R0 resection was achieved (62.0% for stage IIIA and 54.2% for stage IIIB).

OS and PFS

Median (Q1 to Q3) OS was lower in patients with stage IIIB than stage IIIA NSCLC and was also lower in patients with squamous than non-squamous NSCLC [27.6 (12.6 to 57.6) *vs.* 37.4 (16.3 to 79.7) months for stage IIIA and 19.4 (8.7 to 42.4) *vs.* 25.7 (12.0 to 55.6) months for stage IIIB, respectively] (*Figure 1*).

Median OS also varied when patients were stratified by initial treatment use, and ranged from 3.9 months (stage IIIB, non-squamous, radiotherapy alone) to 69.4 months (stage IIIA, non-squamous, neoadjuvant SACT then surgery) (*Figure 2*). Median OS for patients receiving

Table 2 Treatment patterns in patients with stage III NSCLC

Treatment pattern	Total stage III NSCLC (N=1,838)	Stage IIIA NSCLC (n=1,082)	Stage IIIB NSCLC (n=756)
Surgery, n (%)	484 (26.3)	400 (37.0)	84 (11.1)
(Bi)lobectomy or pneumonectomy	344 (18.7)	295 (27.3)	49 (6.5)
Other and unspecified procedures	88 (4.8)	62 (5.7)	26 (3.4)
Other and unspecified resection	19 (1.0)	14 (1.3)	5 (0.7)
Other lung or tracheobronchial resection	19 (1.0)	16 (1.5)	3 (0.4)
Thoraco-mediastinal resection	0	0	0
Missing	14 (0.8)	13 (1.2)	1 (0.1)
Any radiotherapy, n (%)	1,095 (59.6)	609 (56.3)	486 (64.3)
Planned neoadjuvant treatment, n (%)	281 (15.3)	216 (20.0)	65 (8.6)
Planned neoadjuvant treatment and went on to receive surgery, n (%)	138 (7.5)	113 (10.4)	25 (3.3)
Initial treatment received, n (%)			
Neoadjuvant SACT then surgery	133 (7.2)	105 (9.7)	28 (3.7)
Surgery with adjuvant SACT	254 (13.8)	211 (19.5)	43 (5.7)
Surgery alone	92 (5.0)	80 (7.4)	12 (1.6)
Sequential chemoradiotherapy	193 (10.5)	91 (8.4)	102 (13.5)
Concurrent chemoradiotherapy	607 (33.0)	327 (30.2)	280 (37.0)
SACT ± palliative radiotherapy	373 (20.3)	168 (15.5)	205 (27.1)
Radiotherapy alone	80 (4.4)	45 (4.2)	35 (4.6)
No treatment	92 (5.0)	45 (4.2)	47 (6.2)
Other treatments[†]	14 (0.8)	10 (0.9)	4 (0.5)
Time (days) from start of neoadjuvant SACT to surgery			
n (%)	124 (6.7)	100 (9.2)	24 (3.2)
Median (Q1–Q3)	96.5 (82.0–118.0)	98.5 (85.0–121.0)	83.0 (68.0–111.0)
Completeness of resection, n (%)			
R0	75 (60.5)	62 (62.0)	13 (54.2)
R1	7 (5.6)	5 (5.0)	2 (8.3)
R2	7 (5.6)	5 (5.0)	2 (8.3)
Missing	35 (28.2)	28 (28.0)	7 (29.2)
Time (days) from start of surgery to adjuvant SACT			
n (%)	254 (13.8)	211 (19.5)	43 (5.7)
Median (Q1–Q3)	43.5 (35.0–54.0)	43.0 (35.0–54.0)	46.0 (35.0–55.0)

[†], includes surgery with (neo)adjuvant radiotherapy, curative SACT with radiotherapy, concurrent chemoradiotherapy with immunotherapies, and other SACT with radiotherapy. NSCLC, non-small cell lung cancer; SACT, systemic anticancer therapy; Q, quartile.
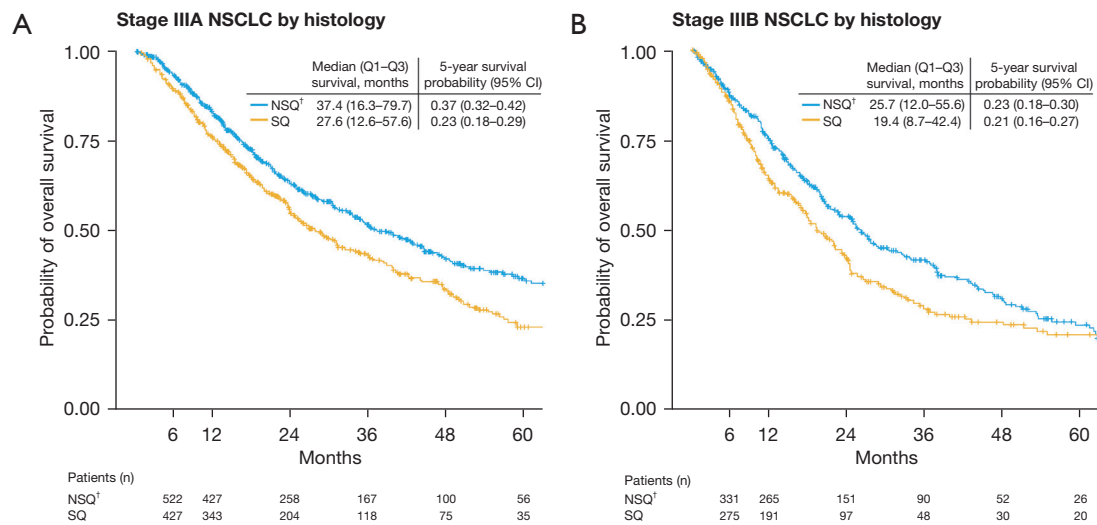
Figure 1 Kaplan-Meier estimates of overall survival in patients with stage (A) IIIA or (B) IIIB NSCLC by histology. [†], includes adenocarcinoma, large cell carcinoma, other NSCLC (specified or non-specified). NSCLC, non-small cell lung cancer; Q, quartile; NSQ, non-squamous; SQ, squamous; CI, confidence interval.

neoadjuvant SACT then surgery was 69.4 (non-squamous) and 56.3 months (squamous) for stage IIIA and 48.2 months (non-squamous) for stage IIIB NSCLC (OS was not reached in patients with stage IIIB squamous histology). Median OS for patients receiving surgery with adjuvant SACT was 48.7 (non-squamous) and 59.0 months (squamous) for stage IIIA and 30.3 (non-squamous) and 56.9 months (squamous) for stage IIIB NSCLC. Median OS for patients receiving chemoradiotherapy ranged from 28.9 [stage IIIB (squamous)] to 38.9 months [stage IIIA (squamous)] (concurrent) and from 23.5 [stage IIIA (squamous)] to 27.7 months [stage IIIB (non-squamous)] (sequential) (*Figure 2*).

Median PFS was approximately 10 months in stage IIIA NSCLC and 8 months in stage IIIB NSCLC and was similar in patients with non-squamous and squamous histologies (*Figure 3*). Median PFS varied widely when patients were stratified by initial treatment used, and ranged from 3.9 (stage IIIB, non-squamous, radiotherapy alone) to 21.0 months (stage IIIA, squamous, surgery then adjuvant SACT) (*Figure 4*).

Chemoradiotherapy treatment response

Treatment response for stage III NSCLC patients who received chemoradiotherapy is shown in *Table 3*. Of the patients with evaluable chemoradiotherapy data, 7.0% had complete response and 37.9% had partial response. Complete

response rate was slightly higher among patients with stage IIIA NSCLC (9.1%) than stage IIIB NSCLC (4.1%).

Factors associated with surgical resection and neoadjuvant therapy

Multivariate regression analyses revealed that patients were more likely to receive surgical resection if they were younger, had lower TN staging, had lower ECOG performance status, or had squamous histology (Figure S1). Patients were more likely to receive (or have planned receipt of) neoadjuvant treatment in stage IIIA NSCLC if they had higher TN staging and squamous histology (Figure S2) compared with all other patients receiving surgery as their initial treatment. There were no factors significantly associated with neoadjuvant treatment choice in stage IIIB NSCLC.

Discussion

This analysis of the TTR study provides insight into the diverse approaches adopted for the treatment of stage III NSCLC in Spain from 2010 to 2019 and their impact on survival outcomes. Consistent with previous studies and recently reported incidence figures (12,15), the majority of patients in the TTR were male (81.2%). Concurrent chemoradiotherapy was found to be the most common

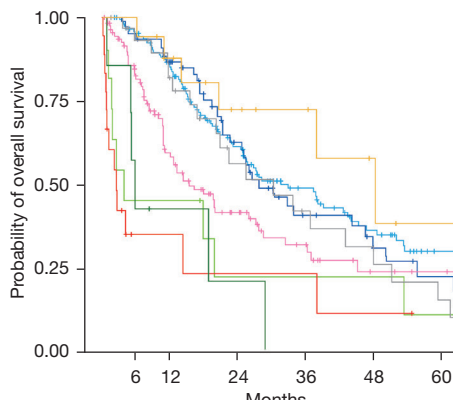**A** NSQ† stage IIIA NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	5-year survival probability (95% CI)
cCRT	36.2 (16.7–116.7)	0.36 (0.27–0.47)
naSACT then surgery	69.4 (33.6–82.5)	0.55 (0.39–0.77)
RT alone	21.8 (13.8–75.4)	0.26 (0.12–0.56)
SACT ± palliative RT	18.6 (8.9–36.6)	0.18 (0.08–0.41)
sCRT	26.4 (13.2–101.0)	0.40 (0.25–0.62)
Surgery alone	54.9 (18.8–NR)	0.45 (0.29–0.70)
Surgery with aSACT	48.7 (26.0–76.9)	0.42 (0.32–0.55)
Untreated	8.3 (4.4–13.9)	0 (NR)
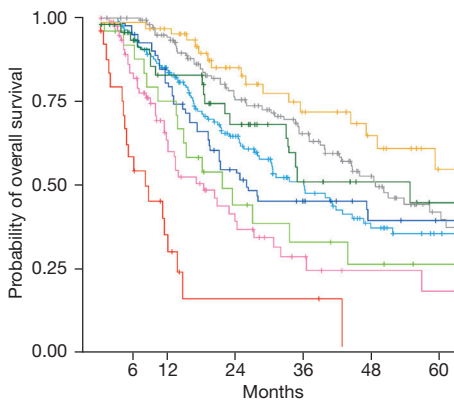
Patients (n)					
cCRT	147	124	71	43	26	17
naSACT then surgery	60	56	36	24	17	7
RT alone	22	18	9	6	4	2
SACT ± palliative RT	58	35	17	8	4	3
sCRT	38	30	18	12	7	4
Surgery alone	38	31	22	12	8	5
Surgery with aSACT	141	124	83	60	34	18
Untreated	14	7	2	2	0	0

B NSQ† stage IIIB NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	5-year survival probability (95% CI)
cCRT	32.9 (15.7–92.7)	0.30 (0.22–0.42)
naSACT then surgery	48.2 (20.6–69.3)	0.39 (0.15–1.00)
RT alone	3.9 (1.8–19.8)	0.11 (0.02–0.70)
SACT ± palliative RT	15.4 (7.9–45.1)	0.24 (0.15–0.39)
sCRT	27.7 (19.4–55.6)	0.23 (0.12–0.43)
Surgery alone	5.9 (5.1–18.8)	0 (NR)
Surgery with aSACT	30.3 (15.5–51.1)	0.16 (0.06–0.44)
Untreated	2.6 (0.9–14.3)	0.12 (0.02–0.67)

Patients (n)					
cCRT	136	119	70	42	27	12
naSACT then surgery	17	13	8	6	3	1
RT alone	5	5	2	2	2	1
SACT ± palliative RT	82	51	27	15	6	4
sCRT	58	50	28	14	8	5
Surgery alone	3	2	1	0	0	0
Surgery with aSACT	26	21	12	8	5	3
Untreated	3	3	2	2	1	0

C SQ stage IIIA NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	5-year survival probability (95% CI)
cCRT	38.9 (18.2–64.5)	0.26 (0.19–0.37)
naSACT then surgery	56.3 (26.0–NR)	0.44 (0.29–0.68)
RT alone	23.8 (9.0–34.3)	0.14 (0.02–0.77)
SACT ± palliative RT	11.0 (4.7–29.0)	0.11 (0.04–0.27)
sCRT	23.5 (14.4–36.2)	0.04 (0.01–0.29)
Surgery alone	17.5 (9.4–36.8)	0.12 (0.04–0.40)
Surgery with aSACT	59.0 (23.4–NR)	0.45 (0.29–0.68)
Untreated	6.5 (2.1–17.7)	0.06 (0.01–0.39)
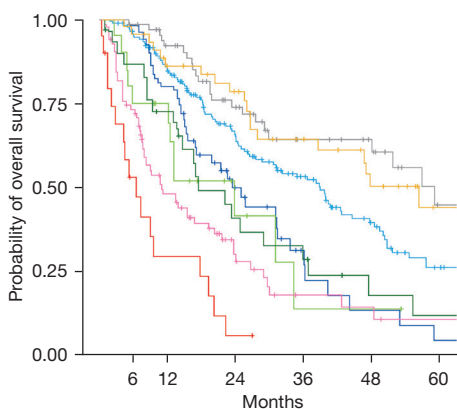
Patients (n)					
cCRT	158	136	88	55	32	17
naSACT then surgery	42	35	29	21	14	6
RT alone	15	13	4	1	1	0
SACT ± palliative RT	58	35	14	5	4	2
sCRT	50	40	18	7	3	1
Surgery alone	25	20	10	7	3	2
Surgery with aSACT	64	55	37	21	17	7
Untreated	9	5	1	0	0	0

D SQ stage IIIB NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	5-year survival probability (95% CI)
cCRT	28.9 (13.5–63.7)	0.27 (0.18–0.40)
naSACT then surgery	NR	0.51 (0.26–1.00)
RT alone	19.3 (7.3–NR)	0.26 (0.12–0.54)
SACT ± palliative RT	9.8 (6.9–16.9)	0.07 (0.03–0.16)
sCRT	24.0 (14.6–32.2)	0.17 (0.07–0.45)
Surgery alone	9.3 (4.7–15.7)	0 (NR)
Surgery with aSACT	56.9 (19.6–NR)	0.50 (0.24–1.00)
Untreated	4.2 (2.2–21.7)	0 (NR)
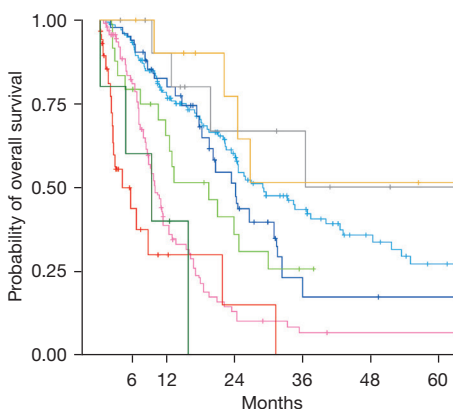
Patients (n)					
cCRT	121	94	54	32	18	11
naSACT then surgery	11	9	6	4	4	3
RT alone	18	14	7	1	0	0
SACT ± palliative RT	65	28	9	4	3	3
sCRT	38	31	14	3	3	2
Surgery alone	3	2	0	0	0	0
Surgery with aSACT	11	9	5	4	2	1
Untreated	7	3	1	0	0	0

Figure 2 Kaplan-Meier estimates of overall survival in patients with (A) NSQ† stage IIIA, (B) NSQ† stage IIIB, (C) SQ stage IIIA, and (D) SQ stage IIIB NSCLC from diagnosis. †, includes adenocarcinoma, large cell carcinoma, other NSCLC (specified or non-specified). NSQ, non-squamous; NSCLC, non-small cell lung cancer; Q, quartile; CI, confidence interval; cCRT, concurrent chemoradiotherapy; naSACT, neoadjuvant systemic anticancer therapy; RT, radiotherapy; SACT, systemic anticancer therapy; sCRT, sequential chemoradiotherapy; NR, not reached; aSACT, adjuvant systemic anticancer therapy; SQ, squamous.
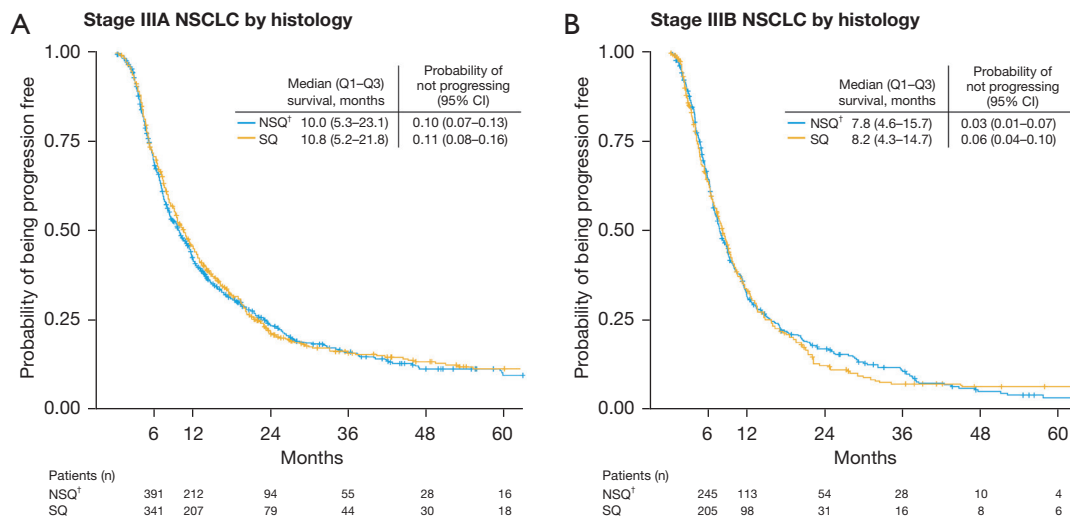
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Figure 3 Kaplan-Meier estimates of progression-free survival in patients with stage (A) IIIA or (B) IIIB NSCLC by histology. [†], includes adenocarcinoma, large cell carcinoma, other NSCLC (specified or non-specified). NSCLC, non-small cell lung cancer; Q, quartile; NSQ, non-squamous; SQ, squamous; CI, confidence interval.

initial treatment used for patients with stages IIIA and IIIB NSCLC in Spain during this period irrespective of stage or histology. (Neo)adjuvant therapy was more common in patients with stage IIIA NSCLC, and SACT ± palliative radiotherapy was more commonly used in patients with stage IIIB.

Survival outcomes were affected by several factors, including initial treatment choice. Concurrent chemoradiotherapy was associated with survival of 29–39 months. The OS in patients receiving surgery with (neo)adjuvant SACT was high: up to 69 months. Similar findings were observed with PFS, although the effects were less pronounced. Furthermore, patients receiving palliative radiotherapy ± SACT had lower survival in our study; this is not the recommended treatment for stage III and its use may reflect those patients with poorer prognosis whereas patients receiving surgical resection would be those with a better prognosis, i.e., patients who were younger, had smaller tumours, and had less metastatic spread.

These findings are consistent with published data. One study showed that only 20–25% of patients with stage III NSCLC treated with concurrent chemoradiotherapy will survive more than 5 years (16). Survival has been shown to be higher in patients with resectable NSCLC receiving surgery with neoadjuvant therapy. Neoadjuvant chemotherapy was associated with a 13% reduction in the risk of death, resulting in a 5-year survival improvement of

5% (from 40% to 45%) in a meta-analysis of 15 randomised controlled trials (2,385 resectable patients with stage IB to IIIA NSCLC) (17). A more recent study in a real-world setting found that 5-year survival was 47.9% in resectable patients with stage III NSCLC (18). Studies from Spain (NADIM and NADIM II) also showed that the addition of neoadjuvant nivolumab to platinum-based therapy in patients with resectable stage IIIA NSCLC resulted in improved PFS and OS; both studies also included nivolumab as adjuvant monotherapy, which may have impacted PFS and OS (19,20). The OS at 24 months was 84.7% with nivolumab plus chemotherapy *vs.* 63.4% with chemotherapy [hazard ratio =0.40; 95% confidence interval (CI): 0.17–0.93; P=0.034] in NADIM II (20). Based on these findings, the authors hoped that the perception of locally advanced lung cancer could change from one that is potentially lethal to one that is curable (19).

The surgery rates and median OS observed in our study were generally consistent with those observed in other real-world settings, such as the KINDLE study—a retrospective study of 3,151 patients with stage III NSCLC from 19 countries (in Africa, Asia, Latin America, and the Middle East) in which the curative resection rate was 21.4%, median PFS was 12.5 months, and median OS was 34.9 months; concurrent chemoradiotherapy was also the most common treatment (29.4%) (21). These investigators found significant associations with sex, stage, histology, and

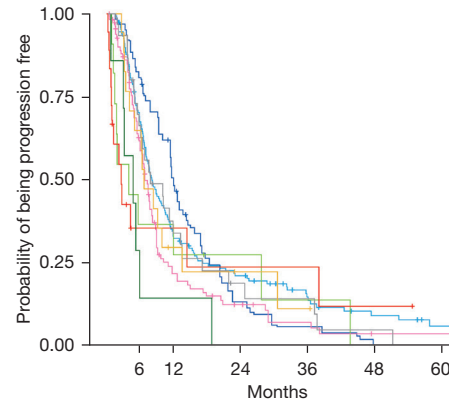**A** NSQ† stage IIIA NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	Probability of not progressing (95% CI)
cCRT	7.3 (4.1–17.6)	0.10 (0.06–0.18)
naSACT then surgery	8.6 (5.7–35.4)	0 (NR)
RT alone	10.1 (7.1–20.4)	0 (NR)
SACT ± palliative RT	6.9 (4.5–9.8)	0.03 (0.01–0.20)
sCRT	13.2 (7.8–22.9)	0.06 (0.02–0.22)
Surgery alone	7.4 (3.9–18.6)	0.05 (0.01–0.30)
Surgery with aSACT	17.2 (8.6–42.0)	0.17 (0.11–0.28)
Untreated	8.3 (4.4–13.9)	0 (NR)

B NSQ† stage IIIB NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	Probability of not progressing (95% CI)
cCRT	8.1 (5.0–17.2)	0.06 (0.02–0.14)
naSACT then surgery	6.8 (4.1–13.4)	0.11 (0.02–0.58)
RT alone	3.9 (1.5–27.7)	0(NR)
SACT ± palliative RT	7.0 (4.5–10.0)	0.04 (0.01–0.13)
sCRT	12.0 (7.0–18.4)	0 (NR)
Surgery alone	4.7 (3.0–5.9)	0 (NR)
Surgery with aSACT	7.8 (5.0–17.1)	0 (NR)
Untreated	2.6 (0.9–14.3)	0.12 (0.02–0.67)

Patients (n) — Panel A

cCRT	93	49	18	14	7	5
naSACT then surgery	41	23	11	6	3	0
RT alone	19	11	3	2	0	0
SACT ± palliative RT	40	8	4	2	1	1
sCRT	36	22	7	2	2	2
Surgery alone	24	11	2	1	0	0
Surgery with aSACT	122	80	47	26	15	8
Untreated	14	7	2	2	0	0

Patients (n) — Panel B

cCRT	96	45	28	14	7	3
naSACT then surgery	11	4	2	1	0	0
RT alone	4	3	2	1	0	0
SACT ± palliative RT	61	19	9	4	1	1
sCRT	50	29	7	3	0	0
Surgery alone	1	1	0	0	0	0
Surgery with aSACT	19	9	4	3	1	0
Untreated	3	3	2	2	1	0

C SQ stage IIIA NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	Probability of not progressing (95% CI)
cCRT	9.9 (5.2–20.1)	0.11 (0.06–0.18)
naSACT then surgery	19.1 (5.7–26.4)	0.20 (0.11–0.38)
RT alone	9.5 (5.3–15.9)	0.17 (0.06–0.50)
SACT ± palliative RT	7.5 (4.1–13.7)	0.02 (0.00–0.16)
sCRT	11.2 (6.5–19.5)	0.05 (0.01–0.26)
Surgery alone	11.6 (7.0–28.9)	0.12 (0.04–0.38)
Surgery with aSACT	21.0 (8.3–NR)	0.26 (0.15–0.45)
Untreated	6.5 (2.1–17.7)	0.06 (0.01–0.39)

D SQ stage IIIB NSCLC from initial diagnosis

	Median (Q1–Q3) survival, months	Probability of not progressing (95% CI)
cCRT	8.2 (4.4–18.8)	0.08 (0.04–0.16)
naSACT then surgery	13.4 (6.3–14.7)	0 (NR)
RT alone	9.4 (4.9–22.2)	0.05 (0.01–0.31)
SACT ± palliative RT	6.6 (3.5–10.2)	0.03 (0.01–0.11)
sCRT	12.8 (8.5–19.0)	0.05 (0.01–0.32)
Surgery alone	4.7 (4.3–8.2)	0 (NR)
Surgery with aSACT	9.4 (8.6–NR)	0.27 (0.09–0.81)
Untreated	4.2 (2.2–21.7)	0 (NR)
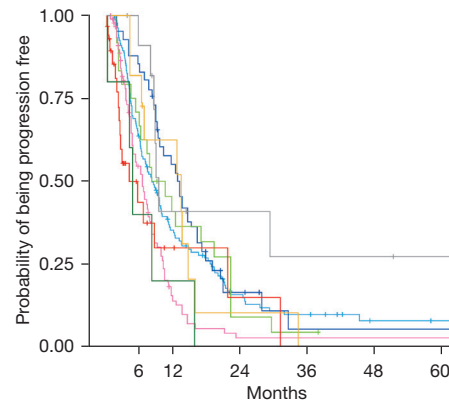
Patients (n) — Panel C

cCRT	114	67	24	14	10	8
naSACT then surgery	32	25	12	7	4	1
RT alone	13	8	1	1	1	0
SACT ± palliative RT	48	23	4	3	2	1
sCRT	40	25	7	2	2	1
Surgery alone	22	13	7	5	3	2
Surgery with aSACT	57	38	22	12	8	5
Untreated	9	5	1	0	0	0

Patients (n) — Panel D

cCRT	83	43	16	10	3	2
naSACT then surgery	9	6	1	0	0	0
RT alone	16	9	2	1	0	0
SACT ± palliative RT	43	10	2	2	2	2
sCRT	34	21	5	1	1	1
Surgery alone	2	1	0	0	0	0
Surgery with aSACT	10	4	3	2	2	1
Untreated	7	3	1	0	0	0

Figure 4 Kaplan-Meier estimates of progression-free survival in patients with (A) NSQ† stage IIIA, (B) NSQ† stage IIIB, (C) SQ stage IIIA, and (D) SQ stage IIIB NSCLC from diagnosis. †, includes adenocarcinoma, large cell carcinoma, other NSCLC (specified or non-specified). NSQ, non-squamous; NSCLC, non-small cell lung cancer; Q, quartile; CI, confidence interval; cCRT, concurrent chemoradiotherapy; naSACT, neoadjuvant systemic anticancer therapy; NR, not reached; RT, radiotherapy; SACT, systemic anticancer therapy; sCRT, sequential chemoradiotherapy; aSACT, adjuvant systemic anticancer therapy; SQ, squamous.

Table 3 Treatment response in patients with stage III NSCLC treated with chemotherapy

Treatment response	Total stage III NSCLC with chemotherapy (N=1,757)	Stage IIIA NSCLC (n=1,024)	Stage IIIB NSCLC (n=733)
Patients treated with chemotherapy, n (%)	1,757 (100.0)	1,024 (100.0)	733 (100.0)
Complete response	123 (7.0)	93 (9.1)	30 (4.1)
Partial response	666 (37.9)	394 (38.5)	272 (37.1)
Stable disease	225 (12.8)	109 (10.6)	116 (15.8)
Progressive disease	194 (11.0)	98 (9.6)	96 (13.1)
Not listed[†]	549 (31.2)	330 (32.2)	219 (29.9)

[†], includes not evaluable, not performed, and missing data. NSCLC, non-small cell lung cancer.

ECOG performance status, similar to the findings from the factor analysis models conducted in our study, which emphasises the importance of taking these associations into account when devising treatment plans; this is in line with guideline recommendations (22). We also note the high rate of tobacco use, which is consistent with the smoking prevalence in Spain. This is a key area where lifestyle interventions are warranted.

With respect to PD-L1 expression, a predictor of response to some anti-PD-1/L1 monoclonal antibodies, we found that nearly 30% of patients were tested, and a positive PD-L1 status ($\geq$1%) was observed in >50% of these patients. This large proportion of positive results suggests that it is being used prognostically and that a significant number of patients could benefit from treatment directed at overexpression of PD-L1. The increasing use of PD-1/L1 testing in patients with NSCLC is a key area for further research in the TTR study cohort.

It should be noted, however, that the findings reflect staging and treatment recommendations at the time this study was undertaken [2010–2019], and staging procedures had significantly changed during these years. During this time, concurrent chemoradiotherapy was treatment of choice in unresectable locally advanced stage IIIA or IIIB NSCLC and was usually based on platinum-doublet chemotherapy (7). The initial SACT used in this study was primarily platinum-doublet chemotherapy for stage IIIA [832 (99.4%)] and stage IIIB [587 (97.4%)] NSCLC, which is consistent with the recommendations available during the study period. Surgical resection remains treatment of choice for resectable locally advanced stage III NSCLC (7). For patients with stage IIIA NSCLC, we found lower than expected use of surgery (37.0%). It is possible that the resectable patients in this

study only received chemoradiotherapy as thoracic surgery teams/departments are not available at all sites in Spain. This may partly explain the range of treatments observed in this study, and we can see the impact that this had on PFS and OS, which varied widely.

The NADIM study, which evaluated induction therapy in stage III NSCLC has reported promising results, with the addition of checkpoint inhibitors to platinum-based chemotherapy resulting in an unprecedented major pathological response rate of 50–83% and pathological complete response of 21–59% (16). However, newer treatments such as immunotherapies and tyrosine kinase inhibitors were not widely used as initial therapy at the time of the analysis [2010–2019]. Durvalumab has been available in Spain since January 2020 for patients with stage IIIA/IIIB NSCLC who receive and complete concurrent chemoradiotherapy, but its use is restricted to PD-L1-positive tumours (usually >1% PD-L1 expression). Durvalumab is already included in the Sociedad Española de Oncología Médica (SEOM) and ESMO clinical guidelines based on the findings from the PACIFIC trial (8,23-25). In this trial of 713 patients with unresectable stage III NSCLC, durvalumab demonstrated durable median PFS (16.8 *vs.* 5.6 months), median OS/time to distant metastasis (23.2 *vs.* 14.6 months) benefits, and estimated 5-year survival probability (95% CI) of 0.43 (0.38–0.47) *vs.* 0.33 (0.28–0.38) after chemoradiotherapy versus placebo (26). The 5-year OS rates seen in the PACIFIC trial are comparable with results presented here for patients receiving neoadjuvant SACT plus surgery, which range from 0.39 (95% CI: 0.15–1.00) in stage IIIB patients with non-squamous histology to 0.55 (95% CI: 0.39–0.77) in stage IIIA patients with squamous histology.

Since the release of the ESMO and SEOM guidelines, several new trials have reported data for treatment in stage III NSCLC. Osimertinib (EGFR targeted therapy) was associated with significantly longer disease-free survival in a study of 682 patients with *EGFR*-positive stage IB–IIIA NSCLC (27). At 3 years, 84% of patients (stage II–IIIA) were disease free compared with 34% who received placebo; OS data were immature at the time of publication (28). The phase II KEYNOTE-799 trial has also been published and found that immunotherapy (pembrolizumab) plus concurrent chemoradiotherapy in 112 patients with stage III NSCLC had promising antitumour activity based on objective response rate (>70%) (29). Furthermore, the US Food and Drug Administration (FDA) recently approved nivolumab with platinum-doublet chemotherapy for adults with resectable NSCLC in the neoadjuvant setting based on the findings of the CheckMate 816 trial in patients with resectable, histologically confirmed stage IB, II, or IIIA NSCLC (30). Atezolizumab was also recently approved by the FDA for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II–IIIA NSCLC whose tumours have PD-L1 expression ≥1% (31) and by the EMA in patients with stage II–IIIA NSCLC whose tumours have PD-L1 expression ≥50% (32). However, some of these findings have not yet resulted in updates to official European guidelines for the treatment of stage III NSCLC.

Strengths and limitations

Our data were taken from a large registry in Spain that has undergone rigorous protocol assessment by an independent GECP committee. This registry represents a nationwide cohort and Spain has a National Health System with universal coverage ensuring that all patients undergo the same diagnostic work-up (12). Another strength of this study was that data collected from the GECP would cover a sizeable population receiving secondary care in multiple hospital centres in Spain. There were minimal missing data for the variables assessed within this population. The study design was longitudinal, which allowed tracking of all patients over time. However, selection bias may have reduced the generalisability of the results, and a change in treatment guidelines over the period of this study may mean that the prognosis for patients differed depending on when the patients were treated. All contributing centres with <100 patients were excluded from the study due to poor data quality on vital status and they did not frequently review data in the TTR. In addition, hospitals in the GECP network have a special focus on research and inclusion in the registry is voluntary; therefore, it is likely that the largest medical centres with access to a wider range of treatment options were over-represented and that care received in these hospitals may not be representative of care received across the entire Spanish population. This study was descriptive by design and statistical testing was hampered by confounding, small patient numbers among certain sub-cohorts, and limited 5-year follow-up for outcome evaluation.

Conclusions

This analysis of the TTR study describes the clinical reality surrounding the initial management and survival outcomes for stage III NSCLC in Spain over a 9-year period. It provides insights into the diverse approaches adopted for the treatment of stage III NSCLC prior to the availability of immunotherapies and targeted treatments in this setting. Survival outcomes are comparable with other real-world evidence, but improvement is still warranted. This is also a pivotal time in the management of NSCLC as (neo)adjuvant immunotherapies increasingly become the standard of care—and further research exploring the impact of these novel treatment strategies, including various immunotherapy regimens, may provide hope for improved patient outcomes. It may be necessary to monitor how these new clinical trial data are being incorporated into clinical practice and how they could improve the lung cancer patient's outcomes.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-176/rc

Data Sharing Statement: Available at https://tlcr.amegroups.

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