ORIGINAL ARTICLE

Real-World Treatment Pathways in Stage III Non-Small-Cell Lung Cancer Surgical Patients in Portugal

Percursos Terapêuticos em Doentes Cirúrgicos com Cancro do Pulmão de Células Não Pequenas em Estádio III na Prática Clínica em Portugal

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ABSTRACT

Introduction

Stage III non-small-cell lung cancer (NSCLC) is a complex and heterogeneous disease, with no established optimal treatment sequence. We aimed to characterize surgically treated patients with stage III NSCLC in Portugal.

Methods

PICTuRE was a multicentric, retrospective study. Adults with stage III NSCLC diagnosed in 2018 were followed until disease progression, death, loss of follow-up, or end of study. Overall survival and disease-free survival were estimated using the Kaplan-Meier method.

Results

Of 278 patients included in PICTuRE, 59 (21.2%) underwent surgery. Surgical patients had a mean age of 65±9 years and were predominantly men (57.6%) and current/former smokers (79.3%). Most presented with adenocarcinoma (71.2%) and stage IIIA disease (79.7%), with ECOG 0-1. All patients underwent at least one non-invasive staging method, while 64.4% received minimally invasive/invasive staging. Lag-times from multidisciplinary team decision to surgery ranged from approximately 1 to 11 months. Neoadjuvant treatment was administered to 22 patients. Resection margins were available for 50 patients (84% R0; 16% R1/R2). Operative mortality and morbidity rates were 3.4% and 25.5%, respectively. Adjuvant treatment was administered to 87.7% of patients, primarily chemoradiotherapy (50%). Median disease-free survival was 22 months, while overall survival was not reached.

Conclusion

Our findings highlight the complexity of stage III NSCLC and the ongoing challenges in disease management in Portugal. Staging practices remain heterogeneous. Although no single treatment strategy exists, multimodality approaches may improve survival outcomes. Future guidelines should be designed considering the implementation of efficient multidisciplinary teams targeting optimal median times for diagnosis, staging and treatment initiation.

RESUMO

Introdução

O cancro do pulmão de células não pequenas (CPCNP) em estádio III é uma doença complexa e heterogénea, sem uma sequência terapêutica ótima estabelecida. O objetivo deste estudo foi caracterizar os doentes com CPCNP em estádio III submetidos a tratamento cirúrgico em Portugal.

Métodos

O PICTuRE foi um estudo multicêntrico e retrospetivo. Adultos com CPCNP em estádio III diagnosticado em 2018 foram acompanhados até à progressão da doença, morte, perda de seguimento ou fim do estudo. A sobrevivência global e a sobrevivência livre de doença foram estimadas pelo método de Kaplan-Meier.

Resultados

Dos 278 doentes incluídos no PICTuRE, 59 (21,2%) foram submetidos a cirurgia. Os doentes cirúrgicos tinham uma idade média de 65 ± 9 anos e eram predominantemente homens (57,6%) e fumadores atuais ou ex-fumadores (79,3%). A maioria apresentava adenocarcinoma (71,2%) e doença em estádio IIIA (79,7%), com ECOG 0–1. Todos os doentes realizaram pelo menos um método de estadiamento não invasivo, enquanto 64,4% foram submetidos a estadiamento minimamente invasivo/invasivo. Os intervalos entre a decisão da equipa multidisciplinar e a cirurgia variaram aproximadamente entre 1 e 11 meses. Foi administrado tratamento neoadjuvante a 22 doentes. Informação sobre as margens de ressecção estava disponível para 50 doentes (84% R0; 16% R1/R2). As taxas de mortalidade e morbilidade operatórias foram de 3,4% e 25,5%, respetivamente. Foi administrado tratamento adjuvante a 87,7% dos doentes, sobretudo quimiorradioterapia (50%). A mediana da sobrevivência livre de doença foi de 22 meses, enquanto a mediana da sobrevivência global não foi atingida.

Conclusão

Os resultados evidenciam a complexidade do CPCNP em estádio III e os desafios atuais na gestão da doença em Portugal. As práticas de estadiamento mantêm-se heterogéneas. Embora não exista uma estratégia terapêutica única, as abordagens multimodais poderão melhorar os resultados de sobrevivência. As futuras recomendações clínicas deverão ser concebidas considerando a implementação de equipas multidisciplinares eficientes, orientadas para tempos medianos ótimos de diagnóstico, estadiamento e início do tratamento.

Keywords:
Carcinoma, Non-Small-Cell Lung/therapy; Clinical Pathways; Neoplasm Staging; Portugal

Palavras-chave:
Carcinoma Pulmonar de Não Pequenas Células/tratamento; Estadiamento de Neoplasias; Portugal; Vias Clínicas

INTRODUCTION

Lung cancer is the second-most commonly diagnosed malignancy and the leading cause of cancer-related mortality worldwide, with around 2.2 million cases and 1.8 million reported deaths every year. In Portugal, these figures exceeded 5200 new diagnoses and 4500 deaths in 2020.[1–3] Approximately 75% to 85% of all lung cancer cases are histologically classified as non-small-cell lung cancer (NSCLC), of which around one third are already locally advanced (i.e., locoregional disease) at the time of diagnosis.[4,5] Stage III NSCLC encompasses a highly heterogeneous group of clinical conditions – including patients with both potentially resectable and unresectable malignancies, and presenting wide differences in terms of tumour size, local extension, and pattern of nodal involvement. Incrementally shorter 5-year overall survival (OS) has been associated with these conditions, ranging from 36% for clinical stage IIIA disease, 26% for stage IIIB and 13% for stage IIIC,[6–8] despite the potentially curative intent of treatments.[9–11]

As a result of this heterogeneity, therapeutic options are varied and consist of definitive chemoradiation, surgery combined with neoadjuvant/adjuvant chemotherapy, and trimodality therapy.[12–16] More recently, biologically driven systemic therapies (e.g., immunotherapy, targeted therapy), have become increasingly available.[17–19] Although local therapy with surgery or chemoradiation are both well-established local control modalities, no clear large head-to-head evidence suggesting the superiority of one treatment regimen over another exists.[20–22] Thus, the management of NSCLC may vary largely, depending on available clinical recommendations, individual practitioners, and institutional preferences. Nonetheless, it should involve a multidisciplinary team (MDT) approach (e.g., thoracic surgeon, medical oncologist, radiation oncologist, pulmonologist) and a careful patient selection for surgery or radiation integrated with systemic treatment.[23–26] Moreover, pre-operative and intraoperative mediastinal staging are strongly recommended to ensure appropriate therapeutic strategy. Surgery may be indicated for N1 or single N2 station involvement, possibly after neoadjuvant chemotherapy.[15,24,27] Yet, the management of patients with ipsilateral or subcarinal mediastinal lymphatic spread (N2, tumour-node-metastasis [TNM] Union for International Cancer Control 8th edition) is still a matter of debate, especially given the lack of a universally accepted definition on NSCLC 'resectability' at advanced stages.[28–30] Although optimal treatment sequence remains a subject of discussion, adjuvant chemotherapy is proven to be effective in stage IIIA NSCLC, while neoadjuvant chemotherapy (with or without radiotherapy) remains an option when tumour reduction is required prior to surgery.[6,26]

Little is known about recent real-world clinical management and survival outcomes among patients with stage III NSCLC in Portugal,[31,32] especially those undergoing surgery as first therapeutic approach. Yet, it is important to expand the understanding of the current management of this disease at a national level, aiming at better informing the adoption and implementation of emerging therapies into routine clinical practice, updating therapeutic guidelines, and minimizing disparities in cancer care.[29] Thus, our goal was to portray the practice patterns, treatment pathways and clinical results of a cohort of stage III NSCLC patients in Portugal (PICTuRE study), with particular focus on patients eligible for surgery.

METHODS

Study Design, Setting and Sample

PICTuRE was a real-world, retrospective, observational, multicentric study, using secondary data collected from medical records of adult patients (aged 18 or over), diagnosed between January 1st to December 31st, 2018 with lung cancer (C34, according to the International Classification of Diseases [ICD]-10 classification), NSCLC cytologically or histologically confirmed (according to the ICD for Oncology [ICD-O-3] classification) and stage III disease (according to the American Joint Committee on Cancer 8th edition), treated or untreated regardless of initial diagnosis, in 17 reference centers for lung cancer in Portugal. Patients diagnosed with earlier-stage disease that progressed during the study were included for analysis as long as the date of the first diagnosis of stage III disease was within the study period.

Patients were excluded if any of the following criteria was observed: evidence of other malignant neoplasms (except non-melanoma skin cancer or carcinoma *in situ*); not otherwise specified histology or mixed small-cell-lung cancer and NSCLC histology; active or prior documented autoimmune or inflammatory disorder; patient enrolled on a clinical trial related to the treatment of locally advanced NSCLC.

All procedures were performed according to the Declaration of Helsinki 2024. The study was approved by the Ethics Committees of all participating centers, including Centro Hospitalar e Universitário do Algarve (approval no. 102/2020), Hospital Pulido Valente – Centro Hospitalar Universitário Lisboa Norte (approval no. 480/20), Centro Hospitalar Universitário de São João (study no. P09-19), Centro Hospitalar Universitário do Porto – Hospital de Santo António (approval no. 2020.186), Centro Hospitalar de Vila Nova de Gaia (approval no. 146/2020), Instituto Português de Oncologia de Coimbra (approval no. 04/2020), CUF Porto, CUF Infante Santo, and Hospital CUF Descobertas (approval no. JMS/is – Estudo 61), Unidade Local de Saúde de Matosinhos (approval no. 68/CE/JAS), Unidade Local de Saúde do Alto Minho – Hospital de Viana do Castelo (approval no. 61/2020), Hospital Beatriz Ângelo (approval no. 3430/2020_MJHMAB/NO), Centro Clínico Académico de Braga (approval no. 02_2021), Hospital do Funchal (approval no. 14/2020), Hospital da Senhora da Oliveira (approval no. 66/2020), Centro Hospitalar de Setúbal (approval no. 035/2020F), and Hospital Garcia de Orta (approval no. 28/21). Due to the retrospective, non-interventional, and descriptive nature of this study, the requirement for informed consent was waived.

Data Collection and Measurements

The following information was collected by the researchers from patients' electronic medical records/applicable registries: demographics (age, sex, smoking status, date of diagnosis, comorbidities), disease characteristics (tumour histology, TNM staging, methods used for disease staging, Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, tumour laterality, surgical resection condition, genetic assessment, programmed cell death ligand 1 [PD-L1] assessment), treatment-related data (MDT treatment decision date, type(s) of treatment(s), both start and end treatment dates, disease progression, death from any cause or related to treatment/disease). Each patient was under observation from the index date (i.e., disease diagnosis in 2018) to the earliest end of clinical activity, death, end of study period, loss to follow-up or last documented visit. The follow-up period finished on June 30th, 2021.

All patients meeting the eligibility criteria were selected to be included in the PICTuRE study (i.e., convenience sample; no *a priori* power analyses were conducted), being classified according to treatments' intention into: radical treatments (surgery, radical radiotherapy or chemoradiation), palliative treatments (systemic therapy, palliative radiotherapy or association of systemic therapy and radiotherapy), best supportive care or no therapy. The analysis presented in this paper refers solely to the surgical population (i.e., patients undergoing surgery as first treatment approach, receiving or not neoadjuvant therapy [prior to surgery] or adjuvant therapy [after surgery]).

Data Analysis

Descriptive statistics were used to summarize the data from the surgical population, with absolute and relative frequencies to describe categorical variables, and median, interquartile range (IQR) and minimum/maximum values for continuous variables. Whenever possible, associations among dichotomous variables were measured using Pearson Chi-square or Fisher Exact tests (this last for a small number of events; sample <10; 2x2 tables). Differences among continuous variables were assessed by means of Mann-Whitney U test.

Lag times (in months) between MDT decision and treatment initiation (i.e., neoadjuvant therapy, surgery, adjuvant therapy) were calculated. The Kaplan-Meier method was used to estimate the main outcomes of OS and disease-free survival (DFS). DFS was

defined as the time between treatment initiation and the date of disease progression, death related to the disease or to the treatment, or end of follow-up, whichever occurred first. OS was defined as the time between treatment initiation and the date of death from any cause or the end of follow-up date. Survival results were reported as median and 95% confidence intervals (CI); the number of patients at risk was displayed under the survival curves. Log-rank test was used to compare event rates between defined subgroups according to patients' disease staging (IIIA versus IIIB), N2 classification (IIIA-non N2 versus IIIA-N2) and use of neoadjuvant and adjuvant therapies.

Analyses were performed in SPSS Statistics v. 24.0 (IBM Corp, Armonk, NY); *p*-values <0.05 were considered statistically significant. As this is a retrospective study, no imputation for any missing data was performed.

Role of the Funding Source

This study was funded by AstraZeneca. Employees of AstraZeneca Portugal were involved in the study design, data collection, analysis, and interpretation, critical review of the manuscript, and in the decision to submit the manuscript for publication.

RESULTS

Overall, 278 patients with stage III NSCLC were included in PICTuRE study of whom 21.2% (n=59) underwent surgery as the first therapeutic approach. Of these, 22 patients (37.3%) received neoadjuvant therapy before surgery, mostly chemotherapy (n=21; 95.5%) consisting of platinum-based combinations; one patient (4.5%) received preoperative concurrent chemoradiation. Adjuvant therapy was provided for most patients after surgery (n=50/57, 87.7%; no data available for two patients) as follows: chemoradiotherapy (n=25, 50.0%), chemotherapy (n=19, 38.0%) and radiotherapy (n=6, 12%). See the flowchart of the treatment pattern in Fig. 1.

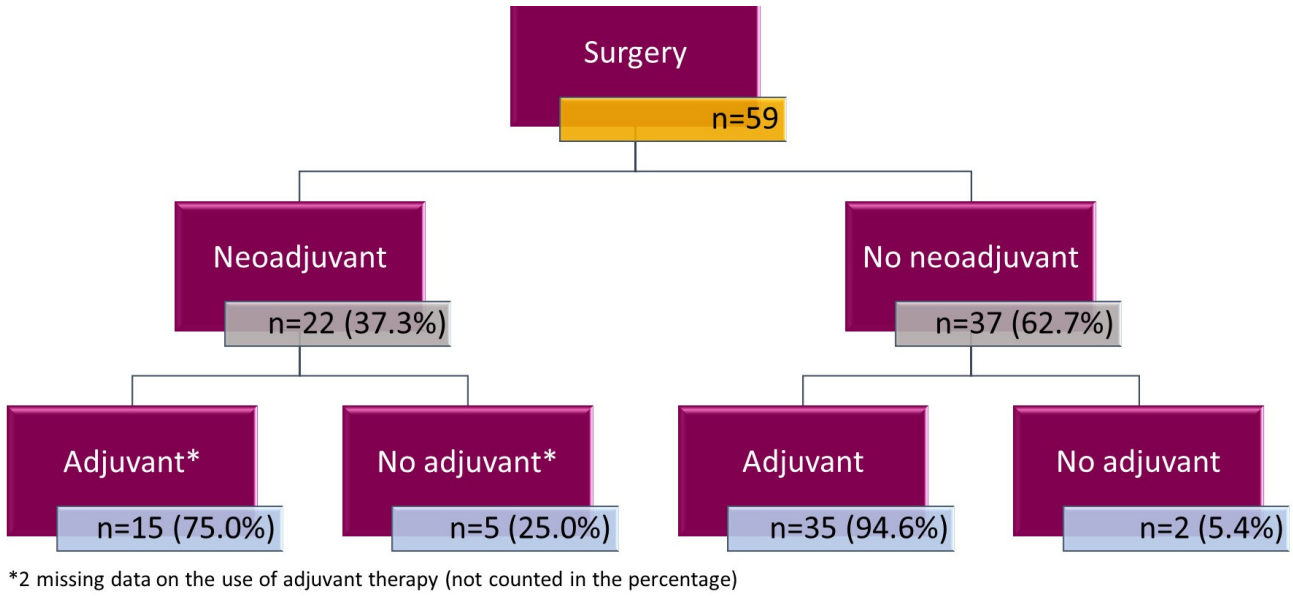


Figure 1 Flowchart of the surgical population's treatment pattern

Table 1 depicts the main characteristics of the total surgical population and by subgroups according to the use of neoadjuvant therapy before surgery.

Table 1 Baseline demographic and tumour characteristics of surgically treated stage III NSCLC patients, overall and by neoadjuvant therapy use

Variable	Overall (n=59)	Neoadjuvant therapy (n=22)	No neoadjuvant therapy (n=37)	*p*-value[a]
Patient demographics				
Age, median [IQR]	65.0 [60.5-75.0]	64.0 [60.5-75.0]	66.0 [60.5-75.0]	0.255
Sex				
Female	34 (57.6%)	14 (41.2%)	20 (58.8%)	0.589
Male	25 (42.4%)	8 (32.0%)	17 (68.0%)	
Smoking status				
Current smoker	23 (39.65%)	9 (31.9%)	14 (60.9%)	0.558
Former smoker	23 (39.65%)	10 (43.5%)	13 (56.5%)	
Never	12 (20.7%)	3 (25.0%)	9 (75.0%)	
Unknown	1	0	1	
Main comorbidities				
COPD	13 (22.0%)	4 (30.8%)	9 (69.2%)	0.749
Diabetes (without end-organ damage)	8 (13.6%)	2 (25.0%)	6 (75.0%)	0.697
Hypertension	28 (47.5%)	8 (28.6%)	20 (71.4%)	0.281
Dyslipidemia	18 (30.5%)	6 (33.3%)	12 (66.7%)	0.565
ECOG performance status				
0	31 (55.4%)	15 (48.4%)	16 (51.6%)	0.048
1	25 (44.6%)	5 (20.0%)	20 (80.0%)	
Unknown	3	2	1	
Tumour characteristics				
Tumour histology				
Squamous cell carcinoma	15 (25.4%)	6 (40.0%)	9 (60.0%)	0.742
Large cell carcinoma	1 (1.7%)	0	1 (100.0%)	
Adenocarcinoma	42 (71.2%)	16 (38.1%)	26 (61.9%)	
Other NSCLC	1 (1.7%)	0	1 (100.0%)	
Clinical stage (AJCC 8th edition)				
IIIa	47 (79.7%)	16 (34.0%)	31 (66.0%)	0.334
IIIb	12 (20.3%)	6 (50.0%)	6 (50.0%)	
Staging methods[b]				
Computerized tomography	59 (100%)	22 (100%)	37 (100%)	--
Positron emission tomography	56 (94.9%)	22 (39.3%)	34 (60.7%)	0.286
Magnetic resonance imaging	13 (22.0%)	6 (46.2%)	7 (53.8%)	0.524
Bone Scintigraphy	1 (1.7%)	0	1 (100.0%)	1.00
Bronchoscopy	28 (47.5%)	10 (35.7%)	18 (64.3%)	0.812
EBUS	17 (28.8%)	9 (52.9%)	8 (47.1%)	0.143
EUS	3 (5.1%)	3 (100.0%)	0	0.047
Mediastinoscopy	4 (6.8%)	2 (50.0%)	2 (50.0%)	0.624
TTNA biopsy	1 (1.7%)	0	1 (100.0%)	1.00
Clinical T classification				
x	0	--	--	0.521
is	0	--	--	
1	1 (1.7%)	0	1 (100.0%)	
1a	1 (1.7%)	0	1 (100.0%)	
1b	3 (5.1%)	1 (33.3%)	2 (66.7%)	
1c	6 (10.2%)	3 (50.0%)	3 (50.0%)	
2	3 (5.1%)	1 (33.3%)	2 (66.7%)	
2a	12 (20.3%)	2 (16.7%)	10 (83.3%)	
2b	3 (5.1%)	1 (33.3%)	2 (66.7%)	
3	17 (28.8%)	6 (35.3%)	11 (64.7%)	
4	13 (22.0%)	8 (61.5%)	5 (38.5%)	

Variable	Overall (n=59)	Neoadjuvant therapy (n=22)	No neoadjuvant therapy (n=37)	*p*-value[a]
Clinical N classification				
0	8 (13.6%)	5 (62.5%)	3 (37.5%)	0.215
1	13 (22.0%)	4 (30.8%)	9 (69.2%)	
2	37 (62.7%)	12 (32.4%)	25 (67.6%)	
3	1 (1.7%)	1 (100.0%)	0	
x	0	--	--	
Tumour laterality				
Right	25 (42.4%)	9 (36.0%)	16 (54.0%)	0.861
Left	34 (57.6%)	13 (38.2%)	21 (61.8%)	

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; AJCC, American Joint Committee on Cancer; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; TTNA, Transthoracic needle aspiration.
[a] Comparison among patients receiving neoadjuvant therapy versus not receiving neoadjuvant therapy.
[b] More than one staging method could have been performed per patient

Few statistical differences among subgroups (neoadjuvant versus no neoadjuvant) were found. Yet, we highlight that most patients receiving radiotherapy as an adjuvant modality after surgery were previously treated with a neoadjuvant approach (83.3% *vs* 16.7%), whereas chemoradiation was mostly used by non-neoadjuvant patients (92.0% *vs* 8.0%) ($p<0.001$).

Surgical patients' median age was 65.0 [IQR 60.5-75.0], mostly were men (n=34; 57.6%), current/former smokers (n=46; 79.3%), with adenocarcinoma (n=42; 71.2%), stage IIIA (n=47; 79.7%) and IIIB (n=12; 20.3%), left side tumour (n=34; 57.6%) and all patients with ECOG between 0-1 (most patients not receiving neoadjuvant therapy before surgery presented an ECOG of 1; $p=0.048$). Patients' main reported comorbidities included diabetes, hypertension, dyslipidemia, and chronic obstructive pulmonary disease; yet nine (15.3%) patients had no recorded comorbidities. According to the clinical TNM classification, T3 and T4 accounted for 30 cases (50.8%), while N2 summed 37 (62.7%) patients (these referred to 12 on neoadjuvant therapy and the remaining 25 not using neoadjuvant therapy). Yet, some changes in patients' staging were observed when considering the pathological TNM classification for surgery: 11 downgraded cases (being nine from the neoadjuvant subgroup) and four upgraded cases (being one on the neoadjuvant subgroup).

All patients were submitted to at least one non-invasive method for disease staging (mostly computerized tomography and positron emission tomography), while in only 64.4% of patients (n=38/59) a minimally invasive or invasive method (i.e., bronchoscopy, endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS), mediastinoscopy) was performed. Overall, 40.5% (n=15/37) of N2 patients did not undergo invasive staging as recommended.

PD-L1 assessment was performed in 49 (89.1%) patients, of which most were positive (n=26; 53.1%), with only seven cases (14.3%) presenting scores >50% (Table 2). Pathological assessment of neoadjuvant treatment was performed in n=18/22 (81.8%) patients; pathological complete response (pCR) or residual viable tumour cells ≤10% (major pathological response [MPR]) were found for one patient each.

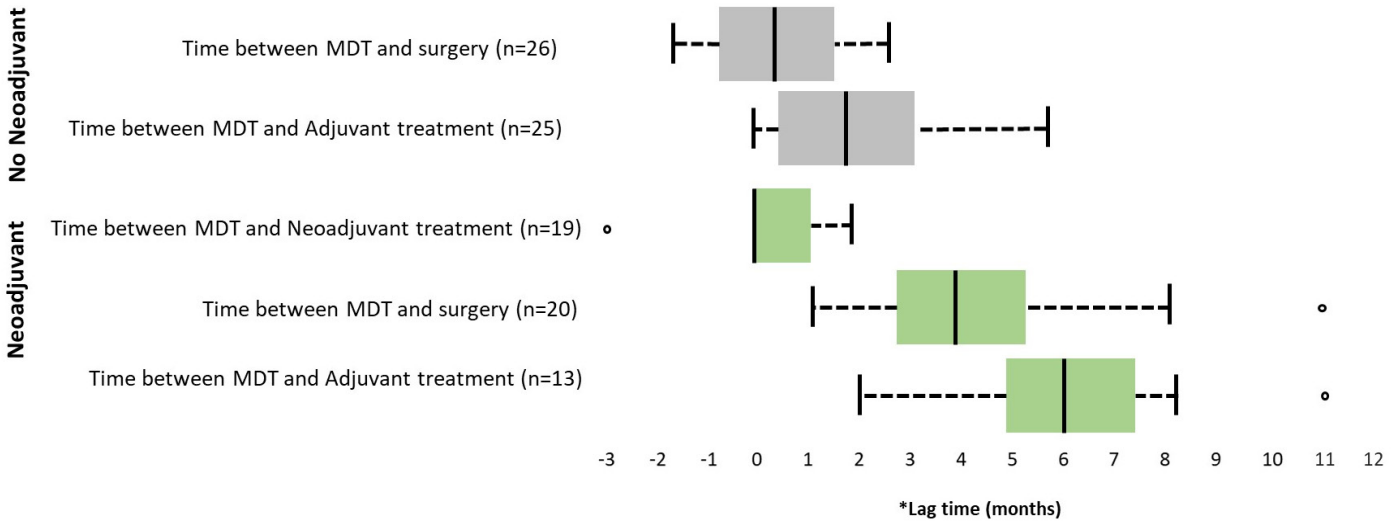
The most common surgery modality was lobectomy (n=45; 76.3%). Resection margins were reported for 50 patients (84.0% with microscopically margin-negative resection [R0] and 16.0% with microscopic or macroscopic residual tumour [R1/R2]) being the results similar for both subgroup of patients (neoadjuvant versus no neoadjuvant) [data unknown for 9 cases]. Postoperative mortality and morbidity related to surgery were of 3.4% and 25.5%, respectively.

Table 2 Pathological, treatment, and surgical characteristics of surgical patients with stage III NSCLC, overall and by adjuvant therapy use

Variable	Overall (n=59)	Neoadjuvant therapy (n=22)	No neoadjuvant therapy (n=37)	*p*-value[a]
Pathological and molecular assessment				
PD-L1 assessment[a]				
Yes	49 (89.1%)	18 (36.7%)	31 (63.3%)	0.100
No	6 (10.9%)	4 (66.7%)	2 (33.3%)	
PD-L1 score[b]				
Positive (PD-L1 ≥1%)	26 (53.1%)	12 (66.7%)	14 (45.2%)	0.235
Negative	23 (46.9%)	6 (33.3%)	17 (54.8%)	
PD-L1 score categories[c]				
1%	2 (8.0%)	1 (50.0%)	1 (50.0%)	0.838
2-49%	16 (64.0%)	7 (43.8%)	9 (56.2%)	
>50%	7 (28.0%)	4 (57.1%)	3 (42.9%)	
Unknown	1	0	1	
Genetic assessment[a]				
Yes	34 (61.8%)	15 (44.1%)	19 (55.9%)	0.202
No	21 (38.2%)	7 (33.3%)	14 (66.7%)	
Adjuvant treatment				
Adjuvant therapy				
Yes	50 (87.7%)	15 (30.0%)	35 (70.0%)	0.084
No	7 (12.3%)	5 (71.4%)	2 (28.6%)	
Unknown	2	2	0	
Adjuvant therapy modality[d]				
Chemotherapy	19 (38.0%)	8 (42.1%)	11 (57.9%)	<0.001
Radiotherapy	6 (12.0%)	5 (83.3%)	1 (16.7%)	
Chemoradiation	25 (50.0%)	2 (8.0%)	23 (92.0%)	
Surgical characteristics				
Surgery modality				
Lobectomy	45 (76.3%)	15 (33.3%)	30 (66.7%)	0.284
Pneumectomy	6 (10.2%)	4 (66.7%)	2 (33.3%)	
Other	8 (13.5%)	3 (37.5%)	5 (62.5%)	
Resection margin				
R0	42 (84.0%)	15 (35.7%)	27 (64.3%)	0.465
R1	6 (12.0%)	1 (16.7%)	5 (83.3%)	
R2	2 (4.0%)	1 (50.0%)	1 (50.0%)	
Unknown	9	5	4	
Postoperative outcomes				
Surgery-related mortality				
Yes	2 (3.4%)	1 (50.0%)	1 (50.0%)	0.391
No	56 (96.6%)	20 (35.7%)	36 (64.3%)	
Unknown	1	1	0	
Surgery-related morbidity				
Yes	12 (25.5%)	6 (50.0%)	6 (50.0%)	0.593
No	35 (74.5%)	12 (34.3%)	23 (65.7%)	
Unknown	12	4	8	

PD-L1, programmed cell death ligand 1; R0, microscopically margin-negative resection; R1, microscopic residual tumour; R2, macroscopic residual tumour.
[a]Comparison among patients receiving neoadjuvant therapy versus not receiving neoadjuvant therapy.
[a]n=55 patients who underwent PD-L1 assessment
[b]n=49 patients with available PD-L1 results
[c]n=26 patients with positive PD-L1 results
[d]n=50 patients who received adjuvant therapy after surgery

Median lag times between MDT and treatment initiation are represented in Fig. 2.



Negative lag times may exist (i.e., treatment started before MDT decision)

Outliers
Time between MDT and surgery (neoadjuvant): one patient with lag times of 11 months
Time between MDT and Neoadjuvant treatment (neoadjuvant): one patient with lag time of -3 months
Time between MDT and Adjuvant treatment (neoadjuvant): one patient with lag time of 11 months

Figure 2 **Median lag time between MDT and treatment initiation. The sample for each subgroup includes only patients with available lag-time data.** MDT, multidisciplinary.

Although the median time from treatment decision to neoadjuvant initiation was less than one month (varying from -3 months [i.e., treatment started even before MDT decision] to a maximum of 2 months), patients on the neoadjuvant subgroup waited longer to surgery (median: 4 months [range: 1 – 11]) and to adjuvant treatment (median: 6 months [range: 2 – 11]) compared to those that did not receive neoadjuvant approach (median lag times of 0.5 [range: -2 – 3] and 2 [range: 0 – 6], respectively).

Fig. 3 and Fig. 4 depict the results for the survival analyses. The median DFS of all 59 surgical patients was 22 months (95% CI, 10.2 – 33.8) (Fig. 3A), while the OS was not reached during the study's follow-up, neither in the overall nor subgroup analyses (Fig. 4). Although no statistical differences between treatment subgroups were found in the DFS analyses, survival curves may provide some insights into the results. Similar DFS medians comparing stage IIIA N2 (24 months [95% CI, 7.3 – 40.7]) and no-N2 (19 months [95% CI, 11.7 – 26.3]) patients (p=0.841) were observed. Conversely, patients receiving neoadjuvant therapy (n=22) presented a higher median DFS (37 months [95% CI, 8.7 – 52.3] compared to the 17 months (95% CI, 10.2 – 33.8) of patients not receiving this therapy (n=37) (log rank p=0.115). Patients on adjuvant therapy may also present higher survival rates (n=50, median 22 months [95% CI, 8.3 – 35.7]) compared to those without further therapy (n=7, median 2 months [95% CI, 1 – 2.9]; p=0.479). The use of both neoadjuvant and adjuvant therapies (n=15 cases) led to a median DFS of 37 months [95% CI, 15.8 – 58.3].

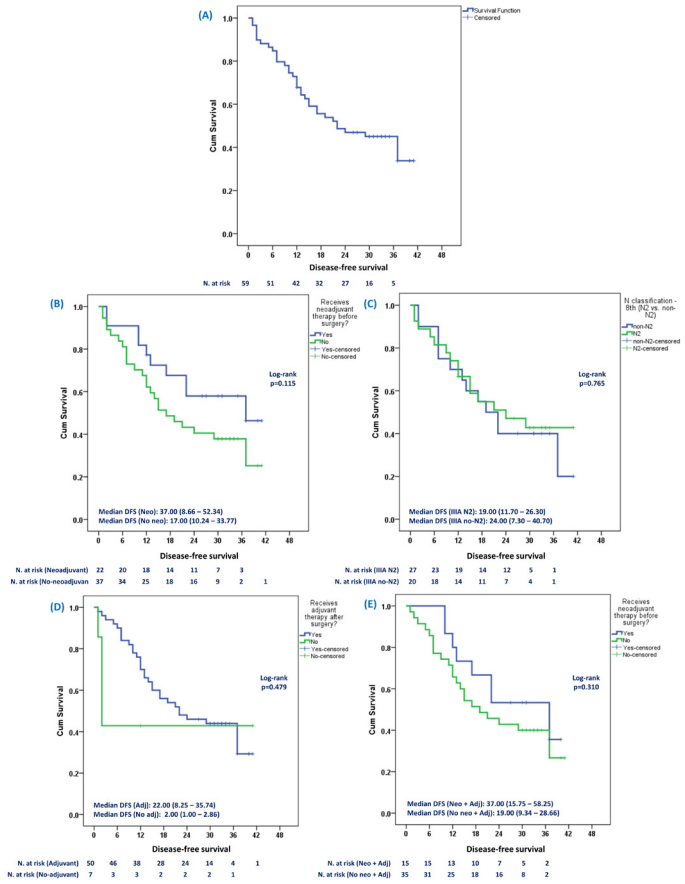


Figure 3 **Median DFS according to treatment subgroups:** (**A**) overall DFS, (**B**) Neoadjuvant versus no neoadjuvant therapy, (**C**) stage IIIA N2 versus non-N2, (**D**) adjuvant versus no adjuvant therapy, (**E**) patients using both neoadjuvant and adjuvant therapy versus none.
DFS, disease-free survival.

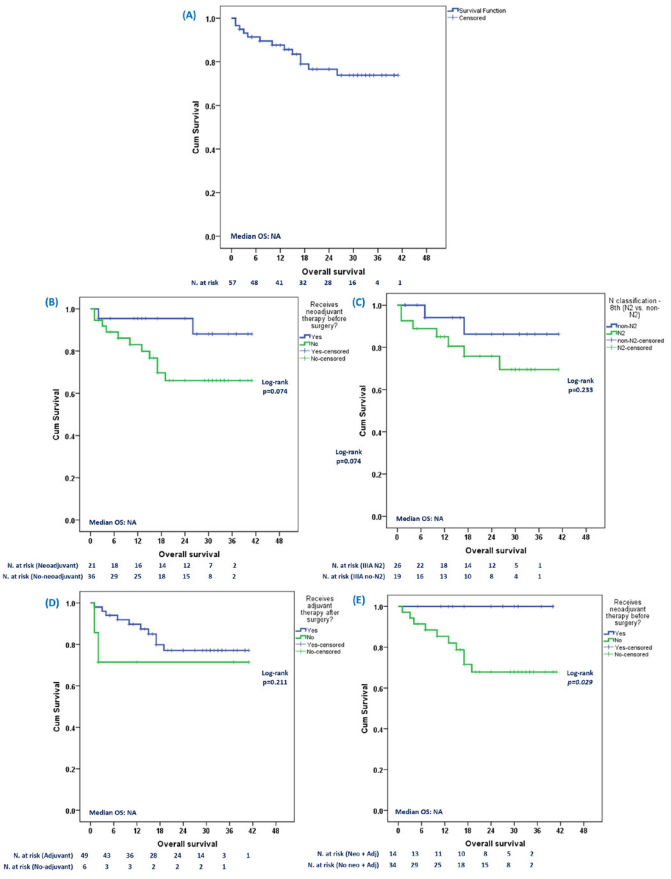


Figure 4 **Median OS according to treatment subgroups:** (**A**) overall OS, (**B**) neoadjuvant versus no neoadjuvant therapy, (**C**) stage IIIA N2 versus non-N2, (**D**) adjuvant versus no adjuvant therapy, (**E**) patients using both neoadjuvant and adjuvant therapy versus none.
OS, overall survival.

DISCUSSION

This retrospective, observational, multicentric study of patients with stage III NSCLC followed in Portugal between 2018-2021 provides a detailed description of the recent treatment patterns and clinical management of the disease in real-world settings in the country. The demographic and disease characteristics of this cohort are consistent with previous retrospective analyses performed in Portugal and other countries, both in short and long-term studies, showing a high prevalence of older patients (>60-65 years), males, current/former smokers with adenocarcinoma at stage IIIA, N2 and ECOG between 0-1.[33–36] This population presents an overall poor prognosis, which highlights the ongoing challenges that healthcare professionals face daily in managing this highly complex and heterogeneous condition.[8]

According to international clinical practice guidelines, stage III NSCLC patients can be classified as 'potentially resectable' or 'definitely unresectable,'[15,21,23,37] although no single definition of 'resectability' at advanced stages of NSCLC is universally accepted, being usually determined on a case-by-case basis by an experienced thoracic surgeon in a MDT environment.[28] Unresectable tumours usually represent a greater proportion of cases as they include stage IIIB disease and some of the stage IIIA patients presenting unresectable bulky nodal disease.[38] We found that around 21% of all patients from the PICTuRE study were classified as 'resectable' and underwent surgery as first therapeutic approach, which was preceded by neoadjuvant treatment in about 37% of cases; around 85% of patients received adjuvant therapy. This percentage of

patients receiving surgery is slightly higher than the one reported in literature in other countries (Canada, the United States, Italy, the United Kingdom), usually ranging from 10.3% to 17.5% in stage III according to the recent meta-analysis from Waser *et al* 2022.[39] It has been reported that around 37% to 44% of patients receive neoadjuvant chemotherapy/chemoradiation; rates of adjuvant therapy are 30%-40%.[9,39] Some of these discrepancies may be due to the intrinsic differences among populations, updated clinical practices over the past years regarding disease diagnosis, staging and available therapies (i.e., temporal trends) and health systems organizations between countries and regions.

In fact, the selection between treatments such as surgery or chemoradiotherapy-based regimens for stage III NSCLC is not always straightforward, especially considering that no clear evidence demonstrating a significant survival benefit for either approach exists, particularly for stage IIIA N2 patients.[40] This reinforces the role of a MDT setting and shared decision-making with the patient, together with a precise disease diagnosis and complete staging (including nodal classification), which provides accurate information on the extent of the malignancy, guides the choice of the treatment (including adjuvant therapy), and determines patients' prognosis.[11,41,42] Computed tomography of the thorax (employed in all patients in our study), positron emission tomography (used in around 95% of the sample), and cerebral magnetic resonance imaging (used in 22% of cases) are the most recommended noninvasive methods for this matter.[24,27,28,43] However, the sensitivity and specificity of these methods are relatively low when compared to invasive staging (overall accuracy agreement between clinical and pathologic staging of only 50% to 60%), with previous studies additionally reporting up to 20% of cases of understaging of the mediastinal lymph nodes.[44–46] Thus, the combined use of minimally invasive or invasive staging methods and imaging is currently highly advocated. EBUS, for instance, presents sensitivity and specificity rates of 89% and 100%, respectively, and can be completed in an outpatient setting with fewer reported complications than mediastinoscopy (sensitivity and specificity rates of around 78% and 100%, respectively). Moreover, the combination of EUS/EBUS is associated with significant improvements in staging accuracy; sensitivity ranging from 91%-100%.[47,48] Nonetheless, literature suggests an important underutilization of invasive mediastinal staging.[49] In our study, for about one-third of patients, no minimally invasive or invasive methods for staging were employed (among N2 patients, this rate was even higher; 40.5%). Although no current standardized guidelines for mediastinal lymph node staging in NSCLC are available, suggested algorithms have been published to help guide this process and should be further consulted by MDTs to advance diagnosis and disease management.[24,41]

The goal of rapid diagnosis and treatment of lung cancer is to maximize cure rates for patients with early-stage disease, increase the number of patients with resectable tumours, and avoid tumour growth and upstaging (i.e., improve survival rates).[50,51] However, previous scoping reviews demonstrated that the intervals from lung cancer diagnosis to treatment in real-world practice remain longer than the recommended in several countries (a mean of 27 days; ranging from 6-45 days).[52–54] In Portugal, in a survey performed in 2020, physicians reported delays of around 20 days from patients' primary care admission until specialty consultation, with an additional 23 days for disease diagnosis and more than 30 days from MDT decision until surgery (cumulative lag time to treatment ranging from 42-61 days).[55] Slightly shorter delays between MDT and treatment initiation in the subgroup of stage III NSCLC patients undergoing surgery without neoadjuvant therapy were found in our study (median of 15 days), but with a wide range, reaching a maximum of 90 days. Nonetheless, some patients were operated even before the final MDT decision (negative lag times) and also had slightly earlier access to adjuvant therapy (still within 60 days after MDT). Conversely, patients on neoadjuvant therapy, although receiving this approach within one month after MDT decision, waited longer to surgery (over 120 days) and, consequently, to receive adjuvant treatment. A recent analysis on the impact of the interval between neoadjuvant immunochemotherapy and surgery on 171 NSCLC patients in China reported a shorter median time-to-surgery interval (around 46 days), with most patients (around 61%) receiving the treatment after 43 days; yet, less than 10% of the population was treated within 28 days.[56] Nonetheless, authors discussed that these lag times had no significant effect on the feasibility and safety of the surgery. The percentages of patients who achieved pathologic responses (assessments of pCR and MPR) were of around 30% and 50%, respectively, in the early-surgery subgroup and of around 40% and 58%, respectively, in the delayed-surgery subgroup. Although a tendency for delayed surgery to be associated with a pathological response in NSCLC was highlighted, this association was not statistically significant (p=0.140 for pCR and p=0.380 for MPR).[56] Another analysis performed in the United States (2010-2015), including 5946 stage IIIA NSCLC patients undergoing surgical intervention, reported that the delays in resection (ranging from less than 60 days to over 114 days) were not associated with increased early mortality (up to 1-year), however, they may have led to worse 3-year postresection survival.[57] These data reinforce the need of further optimal treatment strategy and timing standardization of procedures (including diagnosis, staging

and treatment initiation) for this population.

Currently, while it is clear that multimodality therapy is beneficial for NSCLC (i.e., meaningful improvements in clinical outcomes), especially for patients with stage IIIA-N2 disease, the optimal composition of the treatment regimen remains a work in progress.[58] Nonetheless, it is agreed that decision-making should take into consideration patients' age, disease stage, chemotherapy regimens, and timing after surgery.[59] In a previous phase III trial (RTOG 89-01), patients undergoing surgery after induction chemotherapy presented an OS of 19.4 months; another randomized controlled study found rates of 16.4 months in patients given induction chemotherapy followed by surgery.[60,61] In our study, OS were not achieved during the study's follow-up; yet this should be interpreted with caution due to the small sample size. DFS for all stage III NSCLC patients was 22 months (95% CI, 10.2 – 33.8). Longer median survival was observed for patients receiving neoadjuvant therapy and adjuvant therapy, although no statistical differences among subgroups were obtained probably given the small sample size and data heterogeneity (i.e, wide CI).

Neoadjuvant treatment has theoretical advantages, including *in vivo* assessment of response to chemotherapy, downstaging with improved resectability, early treatment of micrometastatic disease, and enables the identification of surrogate clinical and biological markers that may correlate with response to therapy and long-term outcomes. Previous meta-analyses of trials showed that neoadjuvant chemotherapy improved 5-year OS with an absolute benefit of 5%-6%, which is similar to the results obtained from adjuvant chemotherapy (LACE meta-analysis of 4584 patients reported a 5.4% absolute 5-year OS benefit).[62,63] In patients with stage IIIA NSCLC, the neoadjuvant therapy outside the clinical trial led to a median OS of 22 months and a 3-year survival rate of 34%.[64] On the other hand, neoadjuvant therapy may delay in local therapy (i.e., surgery) due to toxicity and pre-operative complications and risk of disease progression in chemoresistant patients.[59,62]

Although optimal treatment sequencing remains controversial, a recent network meta-analysis on available treatments for stage IIIA-N2 NSCLC (18 trials including 13 treatments) provided some insights that can be transposed to daily clinical practice – especially due the absence of direct comparisons between adjuvant and neoadjuvant treatments. Authors found neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or radiotherapy ranking superior to other approaches in terms of survival (HR 1.14 [95% credible interval [CrI], 0.21-5.93]). Neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy was significantly more effective in prolonging clinical outcomes than surgery alone (HR 0.38 [95% CrI, 0.18-0.81]), surgery plus adjuvant radiotherapy (HR 0.51 [95% CrI, 0.29-0.92]) and potentially surgery plus adjuvant chemotherapy (HR 0.49 [95% CrI, 0.23-1.05]).[65]

More recently – grounded on the promising results obtained in advanced and stage III non-resectable NSCLC patients, several ongoing phase II and phase III trials are evaluating the effects of neoadjuvant immunotherapy in resectable NSCLC (e.g., AEGEAN trial [NCT03800134], CheckMate-77T [NCT04025879], Impower030 [NCT03456063], KEYNOTE-671 [NCT03425643]) and the impact of adding immune anti-PD1/PD-L1 checkpoint inhibitors to adjuvant chemotherapy after complete tumour resection.[66,67] The overall aim of these studies is to improve survival rates and quality of life for patients with lung cancer, which is still considered low. The NADIM study (phase II, single-arm, open-label), for instance, by assessing the use of combined neoadjuvant chemotherapy (paclitaxel plus carboplatin) and immunotherapy (nivolumab) in stage IIIA NSCLC followed by adjuvant treatment with nivolumab found a progression-free survival at 24 months of 77.1% (95% CI, 59.9-87.7); MPR 83%, pCR 63%, and 1-year OS rate of 97.8%.[19,68] Thus, given this rapidly and dramatically changing of treatment landscape for NSCLC worldwide, there is a need for continuous up-to-date evidence regarding patients' characteristics, utility of several parameters (e.g., PD-L1, tumour mutational burden, circulating tumour DNA) as predictive biomarkers for therapy personalization – especially due the heterogeneity of stage III NSCLC, and treatment patterns with both short- and long-term outcomes in the real-world, especially now during the immunotherapy era.

Our study has some limitations. Although patients attending different hospitals across Portugal participated in the study, the results may not be immediately transposed to the clinical environment and practices of all medical centers in the country. We also acknowledge the relatively small sample size of stage III NSCLC and missing information for some variables (i.e., retrospective data) – especially for some subgroup analyses; however, data reflect the available population in the country, similar to what was reported in previous studies. Patients' diagnosis and therapeutic decisions were at each physician's discretion, which may increase the heterogeneity in clinical practice and according to available methods at the time of diagnosis (2018). Although this study lasted over 3 years, OS was not achieved, requiring longer follow-ups for further conclusions to be drawn. Nevertheless, the information collected here may be used towards the improvement and standardization of stage III NSCLC management in Portugal.

CONCLUSION

The real-world analysis of the surgical population in the Portuguese PICTuRE study highlights the complexity and heterogeneity of stage III NSCLC, as well as the ongoing challenges in disease management. Although some recommendations and algorithms for tumour staging exist, practices are not yet consensual, particularly for N2 patients, with few undergoing minimally invasive or invasive methods. No single optimal treatment strategy exists due to variability in tumour extension and nodal involvement; nonetheless, multimodality treatment, including neoadjuvant therapy followed by surgery and adjuvant therapy, may potentially improve survival outcomes. Optimal therapeutic strategy requires careful balancing of patient characteristics, treatment effectiveness and safety within an MDT in a timely process (i.e., reduced delays between diagnosis, staging and treatment initiation). This approach may ensure the delivery of tailored approaches and optimize outcomes for this population. Further studies should evaluate the impact of novel therapies, such as immunotherapy, on treatment patterns and patient outcomes in real-world settings.

Learning Points/Take Home Messages

- Stage III NSCLC remains a complex and heterogeneous disease with poor prognosis.
- Surgically treated patients represented 21.1% of stage III NSCLC cases. Of these, over three quarters underwent lobectomy, 37.3% received neoadjuvant therapy, and 87.7% received adjuvant treatment, most commonly chemoradiotherapy.
- Multimodality treatment, including neoadjuvant therapy followed by surgery and adjuvant therapy, may potentially improve survival outcomes, though results are not conclusive.
- Invasive mediastinal staging is underutilized, particularly in N2 patients, highlighting gaps in guideline adherence.
- MDT-based, individualized decision-making with timely diagnosis, staging, and treatment is crucial.
- Ongoing evaluation of novel therapies, including immunotherapy, is needed to optimize real-world outcomes.

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Prizes and Previous Presentations

This study was presented at the ESMO Congress 2021 as an ePoster and at the 1st Iberic Thoracic Meeting 2022 as a poster.

Data Sharing Statement

Deidentified individual participant data underlying the results reported in this article, along with the study protocol and statistical analysis plan, are available for researchers who provide a methodological sound proposal. Data will be available from the time of publication until 5 years thereafter and may be used for any analysis, including individual participant data meta-analyses. Requests should be directed to the corresponding author (Filipa Bernardo, filipa.bernardo@astrazeneca.com), and a data access agreement must be signed before data are shared.

Ethical Disclosures:

Conflicts of Interest: FE was a speaker and participated as an advisory board member for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen-Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, and Takeda. FB and SF are AstraZeneca employees; CA was employed by AstraZeneca at the time of this work but is currently an ICON PLC employee. The remaining authors declare no conflicts of interest.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

The study was approved by the Ethics Committees of all participating centers, including Centro Hospitalar e Universitário do Algarve (approval no. 102/2020), Hospital Pulido Valente – Centro Hospitalar Universitário Lisboa Norte (approval no. 480/20), Centro Hospitalar Universitário de São João (study no. P09-19), Centro Hospitalar Universitário do Porto – Hospital de Santo António (approval no. 2020.186), Centro Hospitalar de Vila Nova de Gaia (approval no. 146/2020), Instituto Português de Oncologia de Coimbra (approval no. 04/2020), CUF Porto, CUF Infante Santo, and Hospital CUF Descobertas (approval no. JMS/is – Estudo 61), Unidade Local de Saúde de Matosinhos (approval no. 68/CE/JAS), Unidade Local de Saúde do Alto Minho – Hospital de Viana do Castelo (approval no. 61/2020), Hospital Beatriz Ângelo (approval no. 3430/2020_MJHMAB/NO), Centro Clínico Académico de Braga (approval no. 02_2021), Hospital do Funchal (approval no. 14/2020), Hospital da Senhora da Oliveira (approval no. 66/2020), Centro Hospitalar de Setúbal (approval no. 035/2020F), and Hospital Garcia de Orta (approval no. 28/21). Due to the retrospective, non-interventional, and descriptive nature of this study, the requirement for informed consent was waived.

Provenance and Peer Review: Not commissioned; externally peer-reviewed

Responsabilidades Éticas:

Conflitos de Interesse: *FE foi orador e participou como membro do conselho consultivo da AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen-Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi e Takeda. FB e SF são funcionários da AstraZeneca; CA era funcionário da AstraZeneca na altura da realização deste trabalho, mas é atualmente funcionário da ICON PLC. Os restantes autores declaram não ter conflitos de interesses.*

Fontes de Financiamento: *Não existiram fontes externas de financiamento para a realização deste artigo.*

Confidencialidade dos Dados: *Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.*

Proteção de Pessoas e Animais: *Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.*

O estudo foi aprovado pelas Comissões de Ética de todos os centros participantes, incluindo o Centro Hospitalar e Universitário do Algarve (aprovação n.º 102/2020), o Hospital Pulido Valente – Centro Hospitalar Universitário Lisboa Norte (aprovação n.º 480/20), o Centro Hospitalar Universitário de São João (estudo n.º P09-19), Centro Hospitalar Universitário do Porto – Hospital de Santo António (aprovação n.º 2020.186), Centro Hospitalar de Vila Nova de Gaia (aprovação n.º 146/2020), Instituto Português de Oncologia de Coimbra (aprovação n.º 04/2020), CUF Porto, CUF Infante Santo e Hospital CUF Descobertas (aprovação n.º JMS/is – Estudo 61), Unidade Local de Saúde de Matosinhos (aprovação n.º 68/CE/JAS), Unidade Local de Saúde do Alto Minho – Hospital de Viana do Castelo (aprovação n.º 61/2020), Hospital Beatriz Ângelo (aprovação n.º 3430/2020_MJHMAB/NO), Centro Clínico Académico de Braga (aprovação n.º 02_2021), Hospital do Funchal (aprovação n.º 14/2020), Hospital da Senhora da Oliveira (aprovação n.º 66/2020), Centro Hospitalar de Setúbal (aprovação n.º 035/2020F) e Hospital Garcia de Orta (aprovação n.º 28/21). Devido à natureza retrospetiva, não intervencionista e descritiva deste estudo, dispensou-se a exigência de consentimento informado.

Proveniência e Revisão por Pares: *Não comissionado; revisão externa por pares.*

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