ORIGINAL ARTICLE

Health Services Access Inequalities in Brazil Result in Poorer Outcomes for Stage III NSCLC—RELANCE/LACOG 0118

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Received 31 July 2023; revised 29 January 2024; accepted 31 January 2024
Available online - 3 February 2024

ABSTRACT

Introduction: Stage III NSCLC is a heterogeneous disease, representing approximately one-third of newly diagnosed lung cancers. Brazil lacks detailed information regarding stage distribution, treatment patterns, survival, and prognostic variables in locally advanced NSCLC.

Methods: RELANCE/LACOG 0118 is an observational, retrospective cohort study assessing sociodemographic and clinical data of patients diagnosed with having stage III NSCLC from January 2015 to June 2019, regardless of treatment received. The study was conducted across 13 cancer centers in Brazil. Disease status and survival data were collected up to June 2021. Descriptive statistics, survival analyses, and a multivariable Cox regression model were performed. *p* values less than 0.05 were considered significant.

Results: We recruited 403 patients with stage III NSCLC. Most were male (64.0%), White (31.5%), and smokers or former smokers (86.1%). Most patients had public health

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Cite this article as: de Lima VCC, Gelatti A, Moura JFP, et al. Health services access inequalities in Brazil result in poorer outcomes for stage III NSCLC—RELANCE/LACOG 0118. *JTO Clin Res Rep*. 2024;5:100646.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100646

insurance (67.5%), had stage IIIA disease (63.2%), and were treated with concurrent chemoradiation (53.1%). The median follow-up time was 33.83 months (95% confidence interval [CI]: 30.43–37.50). Median overall survival (OS) was 27.97 months (95% CI: 21.57–31.73), and median progression-free survival was 11.23 months (95% CI: 10.70–12.77). The type of treatment was independently associated with OS and progression-free survival, whereas the types of health insurance and histology were independent predictors of OS only.

Conclusions: Brazilian patients with stage III NSCLC with public health insurance are diagnosed later and have poorer OS. Nevertheless, patients with access to adequate treatment have outcomes similar to those reported in the pivotal trials. Health policy should be improved to make lung cancer diagnosis faster and guarantee prompt access to adequate treatment in Brazil.

Keywords: NSCLC; Epidemiology; Stage III; Health insurance; Survival

Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Despite a suboptimal registry, it is estimated that lung cancer will account for 32,560 new cases in Brazil in 2023.[2] Nonetheless, there are no official data regarding stage distribution, patterns of treatment, and outcomes by stage for NSCLC in Brazil.

Stage III NSCLC represents 20% to 35% of newly diagnosed NSCLC cases.[3–6] Locally advanced NSCLC includes tumors that have grown into adjacent mediastinum structures or spread to other lobes and beyond the ipsilateral hilar lymph nodes. Owing to its heterogeneous nature, patients with stage III NSCLC are amenable to many therapeutic strategies ranging from upfront surgery to palliative care. Ideally, the management of stage III NSCLC should always be discussed in a multidisciplinary environment. When unresectable, the discussion usually includes concurrent radiotherapy and chemotherapy, which have become the standard treatment for a long time.[7,8]

The management of this group of patients had evolved very little in the past decade until recently when the PACIFIC trial revealed improved progression-free survival (PFS) and overall survival (OS) with the addition of durvalumab as consolidation treatment after concurrent chemoradiation (CCRT).[9] After the publication of the PACIFIC trial, consolidation durvalumab had become the standard of care after CCRT for locally advanced NSCLC.

So far, few studies have explicitly looked at stage III NSCLC in Brazil.[10–12] The PARSIMONY study collected data from patients diagnosed with having unresectable stage III NSCLC in five Brazilian cancer centers and described the survival outcomes of patients receiving CCRT followed or not by consolidation chemotherapy (N = 165). The median OS in the entire population was 19 months. The only independent factor associated with better OS was a total delivered dose of irradiation of 61 Gy or greater. Nevertheless, many patients were excluded for various reasons, such as neoadjuvant chemotherapy, surgery, lack of information in the medical records regarding treatment delivered, and palliative treatment only.[12] Thus, we still lack an accurate epidemiologic characterization of locally advanced NSCLC. This critical gap in knowledge hampers planning strategies to improve health care and drug access in these populations.

RELANCE (Retrospective Epidemiological Study of Locally Advanced Non-Small Cell Lung Cancer) is a large multi-institutional study that aimed to retrospectively collect information about the diagnosis, treatment, and outcome of patients with locally advanced NSCLC in Brazil. We hypothesize that there is significant heterogeneity in treatment patterns owing to inequities in access to adequate staging methods, optimal treatment, and multidisciplinary teams in Brazil.

Materials and Methods

Study Design and Population

RELANCE is an observational, retrospective cohort study that collected sociodemographic and clinical data from patients diagnosed with having stage III NSCLC from January 2015 to June 2019 in Brazilian cancer treatment institutions.

We collected sociodemographic characteristics, clinicopathologic features, treatment patterns, and outcomes from medical charts. We collected disease status and survival data up to June 2021.

We included patients 18 years old or older with a histologic or cytologic diagnosis of NSCLC and locally advanced disease defined as clinical stage IIIA and IIIB, according to the seventh edition TNM staging system or clinical stages IIIA, IIIB, and IIIC eighth edition TNM staging system. Patients were included regardless of the treatment they received. We excluded patients with SCLC diagnosis, noninvasive NSCLC, synchronous NSCLC, or a second primary tumor within five years of NSCLC diagnosis (except nonmelanoma skin cancer). Patients

were excluded if they lacked adequate information in their medical charts.

The study was approved by the local Human Investigations Committee, and it is registered on ClinicalTrials.gov under the number NCT03836469. Informed consent was obtained from each participant, and all procedures involving human participants followed the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Variables and Outcomes Definitions

We collected the following information from the medical charts: demographics, clinical and pathologic characteristics, date of NSCLC diagnosis, medical and oncological history, staging, cancer treatment patterns, date of first and last treatments, disease status, the best response to treatment, date of disease progression, date of death, cause of death, date last known to be alive, and vital status at last follow-up.

We defined OS as the time from diagnosis to death of any cause and cancer-specific survival as the time from diagnosis to cancer-related death. PFS was defined as the time from initiating any line of treatment to disease progression or death of any cause.

Sample Size and Power Calculation

The expected target sample size was 400 patients with locally advanced NSCLC. We estimated a total number of 400 patients to generate a minimum of 240 events (death) at the date of the last follow-up date and produce a two-sided 95% confidence interval (95% CI) with a width equal to 3.723 for survival analysis when the expected median OS is 14.6 months (95% CI: 12.916–16.639).

The study required the enrollment of 30 to 40 patients from each participating institution, from January 2015 to June 2019, with a minimum follow-up period from the last patient of 24 months.

Statistical Analysis

The primary goal of this study was to establish a Brazilian patient registry that would facilitate a better understanding of treatment patterns for locally advanced NSCLC and their associations with survival. As such, the study was not specifically designed around a particular set of hypotheses. Nonetheless, the success of the registry relies on patient enrollment that is sufficient both to robustly estimate survival and treatment variations and to identify gaps in treatment care related to demographic and socioeconomic factors.

The primary objective of this study was to describe the OS from all enrolled populations.

Measures of center and spread (e.g., mean, median, SD, and centile range) were reported for continuous variables, and tabulated summaries were reported for categorical variables. Continuous variables were compared using Student's t test, and categorical variables were compared using chi-square or Fisher's exact tests, whenever appropriate.

Analyses of OS and PFS were performed using the Kaplan-Meier method for describing time-to-event data overall and separately by potential variables such as health insurance coverage (public and private).

We used multivariable analysis to identify prognostic factors for survival using Cox regression. Confounder selection varied by model, depending on the treatments being compared, and included age, staging, histology, treatment type, and health insurance. Hazard ratios comparing clinical-pathologic and demographic characteristics were estimated from confounder-adjusted Cox regression models. To reduce the number of groups compared, we included cases diagnosed at the time as bronchioloalveolar carcinoma and large cell non-squamous carcinoma in the adenocarcinoma group.

Results

Demographics, Clinicopathologic Characteristics, and Treatment Patterns

We collected data from 403 patients with stage III NSCLC from 13 Brazilian cancer treatment institutions (three private, six public, and four mixed) (Fig. 1).

The median age was 66 (range 27–90) years. Patients were predominantly male (64.0%); White (31.5%), although race was not reported for 40.5% of patients; and smokers (30.5%) or former smokers (55.6%). Most patients (67.5%) had public health insurance coverage. Approximately 70% of patients in the cohort had comorbidities; nevertheless, most patients had good performance status with 26.6% having Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and 48.9% having ECOG PS of 1 (Table 1).

A familial history of cancer was reported for 189 patients (46.9%), and lung cancer was the second most frequently reported (20.1%), preceded by a familial history of breast cancer (29.1%), especially among first-degree relatives (Table 1).

Patients' initial evaluation was performed by their primary physician (18.1%), by a respirologist (16.9%), or at the emergency department (13.4%). A computed tomography (CT) scan was performed in 75.4% of patients, and 6.9% had a positron emission tomography (PET)-CT as their first image. From 71 patients who were not submitted to a CT scan or a PET scan as their first image,

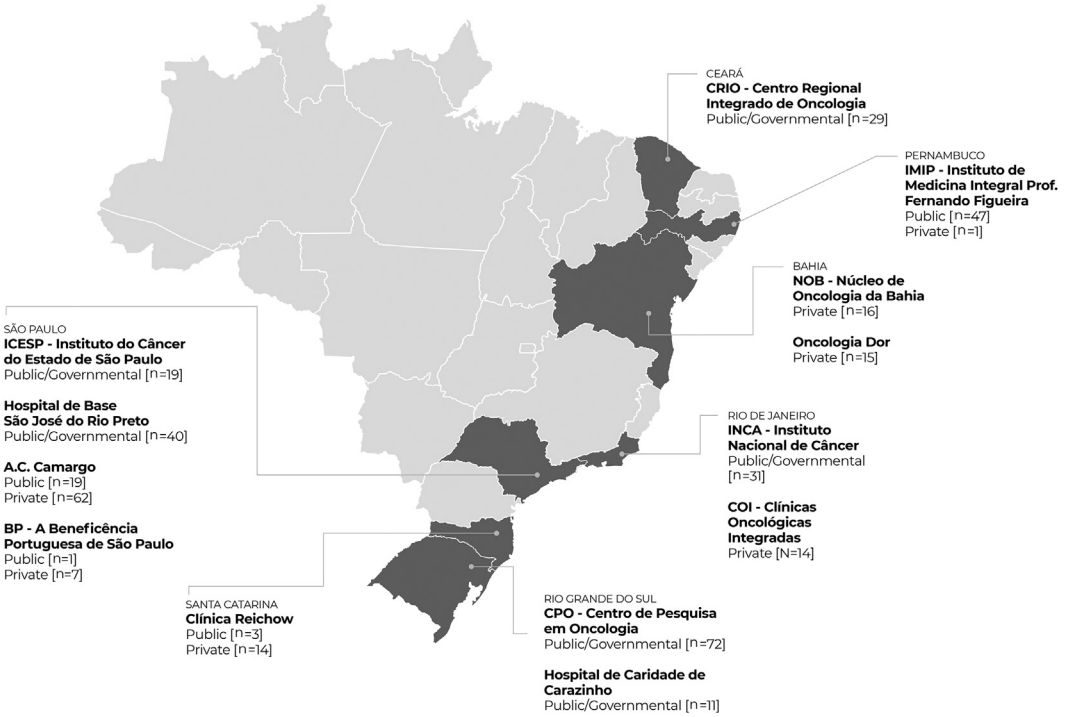


Figure 1. Diagram depicting the geographic location of the participating institutions and the number of patients included from each that had private or public health insurance.

69 (17.12%) were submitted to a CT scan or PET scan posteriorly as part of their staging workup. Two (0.50%) had no information recorded in the form (unknown).

Only 16.1% of patients were submitted to invasive mediastinal staging (endobronchial ultrasound or mediastinoscopy) at any time. Most patients had T3 (30.3%) or T4 (33.5%) tumors and had N2 lymph node disease (58.8%), according to the seventh American Joint Committee on Cancer (AJCC) edition (Supplementary Table 1). Thus, 62.3% were staged as IIIA. Owing to the retrospective nature of the study, we were unable to reclassify the staging according to the eighth AJCC in 30.3% of the patients; however, among those with available information (n = 281), 43.1% were stage IIIA, 48.4% were stage IIIB, and 8.5% were stage IIIC. The most frequent histologic subtype was adenocarcinoma, present in 203 cases (50.4%). Of this total, molecular tests were performed for EGFR in 25.6% of the cases, for ALK in 17.1%, and of ROS-1 in 2.7%. Only 13.7% of patients had programmed death-ligand 1 tested (Table 1).

Approximately 59% of the patients with available information (n = 301) were discussed in a multidisciplinary tumor board (MTB). The CCRT was performed in 53.1% of patients. Patients treated with CCRT mostly received three-dimensional–conformal radiotherapy (59.4%), and 91.1% completed their treatment (Table 2). Only nine patients received consolidation with durvalumab. Surgery, preceded or not by (neo)adjuvant chemotherapy, was performed in 19.1% of the cases, being the second most common treatment strategy. Among patients submitted to surgery (n = 77), lobectomy was the most common procedure (70.1%), with 66.3% obtaining R0 resections. Adjuvant radiotherapy was performed in 36.4% of patients operated on, and systemic treatment was offered to 81.2%, mainly cytotoxic chemotherapy (95.5%) (Table 2).

Disease Recurrence and Patterns of Recurrence

Disease recurrence or progression was observed in 57.3% (n = 231) of patients. Locoregional recurrence was observed in 58.9% of patients who relapsed or progressed. New sites of distant metastasis, associated or not with locoregional recurrence, were observed in 41.1% of patients. The bones (35.8%) and the central nervous system (25.3%) were the most frequent sites of distant relapse (Supplementary Table 2).

OS, Cancer-Specific Survival, and PFS

Eight patients did not have information on the vital status nor the date of last visit or death and were not included in the OS analysis. Two patients had only the date for disease progression collected. These two patients were included in the OS analysis and were censored at the date of disease progression, which was also considered the date of the last visit.

Table 1. Demographics and Clinical Characteristics of Patients Included in the RELANCE/LACOG 0118 Cohort (N = 403)

Characteristics	Total (N = 403)
Median age, y (min-max)	66 (27-90)
Sex	
Male	258 (64.02)
Female	145 (35.98)
Race	
White	127 (31.51)
Black	17 (4.22)
Brown	77 (19.11)
Hispanic	19 (4.71)
Unknown	163 (40.45)
Smoking status	
Never smoker	51 (12.66)
Former smoker	224 (55.58)
Current smoker	123 (30.52)
Unknown	5 (1.24)
Highest level of education	
No education	22 (5.46)
Incomplete first-degree	57 (14.14)
Completed first-degree	34 (8.44)
Incomplete second-degree	18 (4.47)
Completed second-degree	47 (11.66)
Incomplete third-degree	5 (1.24)
Completed third-degree	36 (8.93)
Unknown	184 (45.66)
Health insurance	
Private	131 (32.51)
Public (governmental)	272 (67.49)
ECOG performance status	
0	107 (26.55)
1	197 (48.88)
2	55 (13.65)
3	25 (6.20)
4	3 (0.74)
Unknown	16 (3.97)
Comorbidity	
Yes	283 (70.22)
No	120 (29.78)
Familial history of cancer	
No	141 (34.99)
Yes	189 (46.90)
Unknown	73 (18.11)
Type of cancer among relatives (n = 189)[a]	
Breast cancer	55 (29.10)
Lung cancer	38 (20.11)
Prostate cancer	17 (8.99)
Stomach cancer	16 (8.47)
Esophagus cancer	11 (5.82)
Colon cancer	37 (19.58)
Kidney cancer	3 (1.59)
Pancreas cancer	6 (3.17)
Other cancer	112 (59.26)
Stage (AJCC stage - seventh edition)	
Stage IIIA	251 (62.28)
Stage IIIB	152 (37.72)
Histology	
Squamous cell carcinoma	182 (45.16)
Adenocarcinoma	203 (50.37)
Bronchioloalveolar carcinoma	1 (0.25)
Large cell carcinoma	1 (0.25)
Mixed	3 (0.74)
Other	13 (3.23)
Molecular testing	
EGFR	103 (25.56)
ALK	69 (17.12)
ROS1	11 (2.73)
RET	4 (0.99)
BRAF	26 (6.45)
Other	15 (3.72)
PD-L1 testing	
Yes	55 (13.65)
No	346 (85.86)
Unknown	2 (0.50)
PD-L1 expression (TPS %) (n = 55)[b]	
<1%	18 (32.73)
1%-49%	16 (29.09)
≥50%	16 (29.09)
Unknown	5 (9.09)
Tumor site[c]	
Right lung	243 (59.11)
Left lung	145 (35.22)
Lymph nodes only	24 (5.67)

[a]The total number of responses is conditioned to the total number of patients who had family history of cancer, and then the sum is higher than 100% because some patients had more than one relative diagnosed with cancer.
[b]The total number of responses is conditioned to the total number of patients who performed PD-L1 testing.
[c]The sum is higher than 100% because some patients had more than one tumor site.
AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

At the last study update (June 9, 2022), 89 (22.1%) were alive, and the leading cause of death was cancer itself or cancer treatment (77.6%). Nevertheless, 24.8% (n = 100) were lost to follow-up (Supplementary Table 3).

The median follow-up time for the entire cohort was 33.83 months (95% CI: 30.43–37.50). The median OS was 27.97 months (95% CI: 21.57–31.73) (Fig. 2*A*), whereas cancer-specific survival was slightly longer, at 35.77 months (95% CI: 30.17–46.07) (Fig. 2*B*). The median PFS was 11.23 months (95% CI: 10.70–12.77) (Fig. 2*C*).

Kaplan-Meier Analyses and Multivariable Logistic Regression Analyzing Factors Affecting Outcomes

We found that patients with private insurance had longer OS (44.13 versus 18.4 mo; $p < 0.0001$) (Fig. 3*A*) and longer PFS (14.27 versus 10.30 mo; $p = 0.0133$)

Table 2. Pathologic Characteristics and Treatment Patterns of Patients Included in the RELANCE/LACOG 0118 Cohort (N = 403)

Characteristics	Total (N = 403)
To whom did the patient first present with signs or symptoms of index event	
Primary care physician	73 (18.11)
ER department	54 (13.40)
Pulmonary physician	68 (16.87)
Clinical oncologist	23 (5.71)
Thoracic surgeon	54 (13.40)
Screening program	2 (0.50)
Other	26 (6.45)
Unknown	103 (25.56)
First examination for diagnosis of lung cancer	
Chest radiograph	66 (16.38)
CT scan	304 (75.43)
MRI scan	2 (0.50)
PET scan (incl. PET-CT)	28 (6.95)
Unknown	3 (0.74)
Invasive diagnosis procedure[a]	
Flexible fiberoptic bronchoscopy	120 (29.78)
Rigid bronchoscopy	85 (21.09)
EBUS	17 (4.22)
Mediastinoscopy	48 (11.91)
Thoracoscopy	9 (2.23)
Other	138 (34.24)
Was the patient's case discussed at a multidisciplinary team meeting?	
No	123 (30.52)
Yes	178 (44.17)
Unknown	102 (25.31)
Type of treatment	
Surgery with or without (neo)adjuvant treatment	77 (19.10)
Chemotherapy only	56 (13.90)
Radiotherapy only	28 (6.95)
Concomitant chemoradiation	214 (53.10)
Best supportive care	28 (6.95)
Surgery type (n = 77)	
Wedge resection	1 (1.30)
Segmentectomy	1 (1.30)
Lobectomy	54 (70.13)
Pneumonectomy	12 (15.58)
Bilobectomy	5 (6.49)
Other	4 (5.19)
Systemic therapy—Chemotherapy only (n = 56)[b]	
Immunotherapy	3 (4.92)
Cytotoxic chemotherapy	57 (93.44)
Targeted therapy	1 (1.64)
Radiotherapy type—Radiotherapy only (n = 28)	
SBRT	3 (10.71)
EBRT	3 (10.71)
IMRT	3 (10.71)
3D-CRT	17 (60.71)
VMAT	2 (7.14)
Radiotherapy type—Concomitant chemoradiation (n = 214)	
SBRT	6 (2.80)
EBRT	39 (18.22)
IMRT	25 (11.68)
3D-CRT	127 (59.35)
VMAT	12 (5.61)
Unknown	5 (2.34)
Systemic therapy—Concomitant chemoradiation (n = 214)[c]	
Immunotherapy	12 (4.94)
Cytotoxic chemotherapy	227 (93.42)
Targeted therapy	2 (0.82)
Other	2 (0.82)

[a]Because the same patient may have been submitted to more than one invasive procedure, percentage sum might be greater than 100%.
[b]Therapy class has more than 56 answers because five patients performed two classes of therapy, so the total number of answers in the therapy class variable is 61, and it was used as a denominator.
[c]Therapy class has more than 214 answers because one patient performed four classes of therapy; three patients performed three classes of therapy; 20 patients performed two classes of therapy; 184 patients performed one class of therapy. The total number of answers in the therapy class variable is 243, and it was used as a denominator.
EBRT, external beam RT otherwise undefined; 3D-CRT, three-dimensional-conformal RT; CT, computed tomography; EBUS, endobronchial ultrasound; ER, emergency room; IMRT, intensity-modulated RT; MRI, magnetic resonance imaging; PET, positron emission tomography; SBRT, stereotactic body radiotherapy; VMAT, volumetric-modulated arc therapy.

compared with patients with public health coverage (Fig. 3*B*).

The diagnosis of adenocarcinoma was also associated with better OS (39.50 versus 16.70; $p < 0.001$) (Fig. 4*A*) and PFS (13.2 versus 10.4 mo; $p = 0.0151$) (Fig. 4*B*).

With regard to treatment, patients submitted to surgery had better OS (median OS: 64.63 mo, 95% CI: 34.43–77.87) (Fig. 5*A*) and PFS (median PFS: 22.40 mo, 95% CI: 15.97–30.20) compared with patients not receiving surgery (Fig. 5*B*). Median OS for patients treated with CCRT was 27.97 months (95% CI: 20.57–34.13) (Fig. 5*A*).

Next, we performed a multivariable model adjusting for age, staging, histology, treatment type, and health insurance, looking for OS and PFS outcomes. ECOG PS was also associated with OS and PFS (Supplementary Fig. 1), but we excluded it from the model because it was associated with health insurance (Table 4).

All kinds of treatment were associated with poorer OS and PFS compared with surgery, except for radiotherapy alone. Public health insurance and squamous histology were also independent predictors of inferior OS (Table 3).

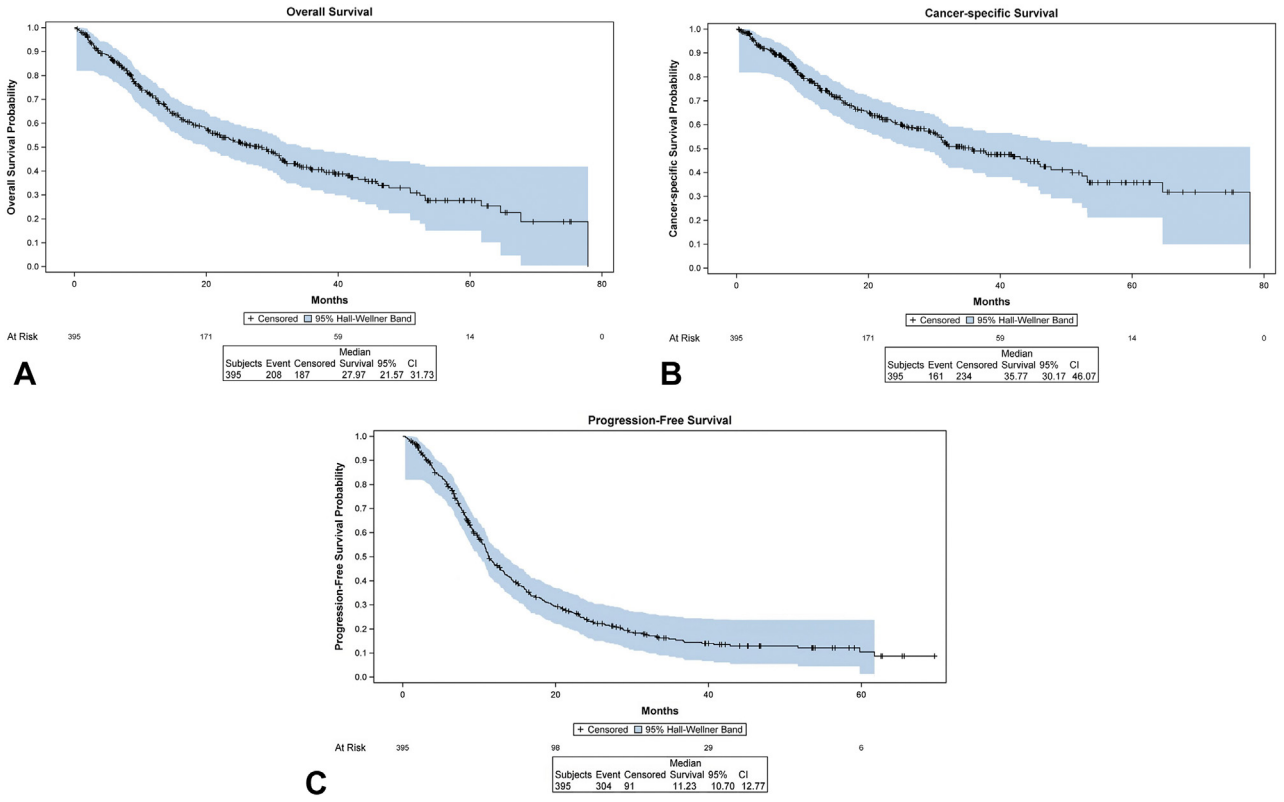


Figure 2. Kaplan-Meier curves reveal (*A*) overall survival, (*B*) cancer-specific survival, and (*C*) progression-free survival for the entire cohort (N = 403). CI, confidence interval.

Differences Between Patients Treated in the Private and Public Health Systems

Compared with patients treated in the private health system, patients from the public health system were predominantly male and active smokers. Patients treated in the public health system were more likely to perform a chest radiograph for staging. In addition, patients from the public health system were diagnosed with larger tumors, more frequently with squamous histology, had poorer performance status, and were less regularly submitted to surgery (Table 4).

Discussion

RELANCE/LACOG 0118 is the most extensive contemporaneous study that collected detailed information regarding demographics, clinical-pathologic, and treatment patterns from patients diagnosed with having stage III NSCLC in Brazil.

Demographics were as expected for NSCLC, with most patients diagnosed being male and smokers or former smokers. Roughly 30% of patients were treated in the private health system, which mirrors the proportion of patients with access to private health insurance in Brazil.[13] We found that patients treated in the public health system were diagnosed in later stages (had larger tumors), had a higher prevalence of squamous cell carcinoma, had less access to optimal staging (PET-CT and brain magnetic resonance imaging), and did not undergo surgery.

A recent study that collected data from 5016 stage III and IV patients treated in private hospitals in Brazil between 2011 and 2016 reported a median OS of 11.5 months for stage III NSCLC. Nonetheless, the study did not gather detailed treatment and clinic-pathologic information.[14] In contrast, the median OS (27.97 mo) in our cohort was equivalent to that observed in the control arm of the PACIFIC study (29.1 mo).[9] Similarly, the median PFS (11.23 mo) was also close to that reported in the PARSIMONY study.[12] These results are consistent with most patients having been treated with CCRT (53.1%).

Stage III NSCLC is a very heterogeneous disease, and it has been largely revealed that discussion by an MTB is associated with better outcomes.[15,16] Almost 60% of the cases were discussed in an MTB. Most participating institutions are dedicated cancer centers where the patient is more likely to be assisted by a thoracic multidisciplinary team.

Ronden et al.[16] (2021) reported the outcomes of 3363 Brazilian patients with stage IIIA NSCLC followed for 19 years. They retrieved data regarding sex, age at

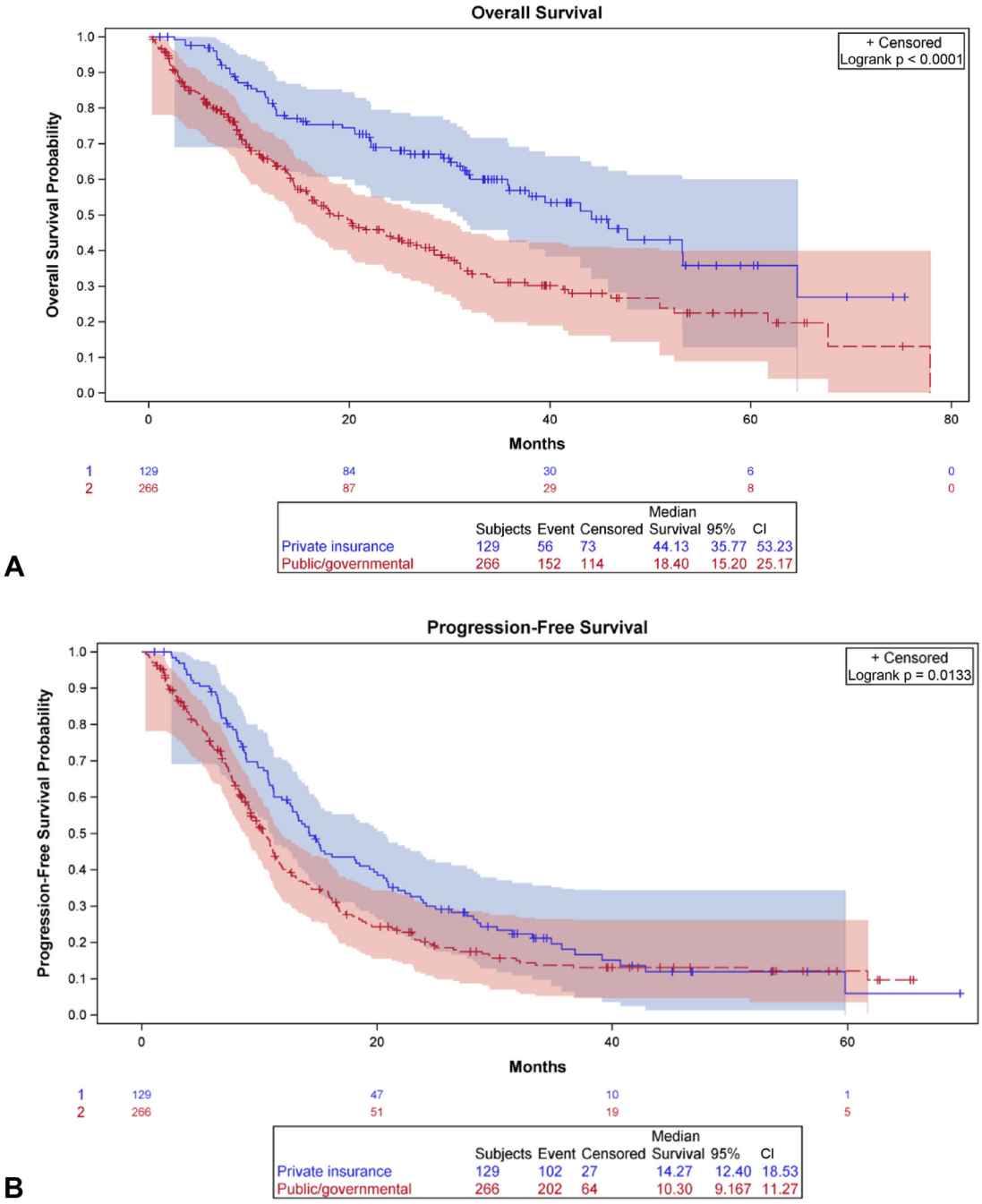


Figure 3. Impact of type of health insurance on (*A*) overall survival and (*B*) progression-free survival. Survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. CI, confidence interval.

diagnosis, clinical stage, patients' region of origin, tumor histology, and type of treatment from electronic registries from 72 hospitals. The patients' characteristics were very similar to what we found (median age 66 y, predominantly male), except for histology insofar as they reported more squamous cell carcinomas (41.2%). They also observed better OS for patients treated with surgery plus chemotherapy (31.5 mo) or chemotherapy plus radiotherapy plus surgery (33.8 mo), followed by those treated with CCRT (18.4 mo).[16] These results are on par with ours, although we observed longer median OS for these subgroups in our cohort (64.60 and 27.97 mo for patients who underwent surgery and CCRT, respectively). This difference may stem from better staging, improved technologies, and the incorporation of newer treatments and supportive strategies because ours included only patients diagnosed more recently (2015–2019). Moreover, as highlighted previously, many

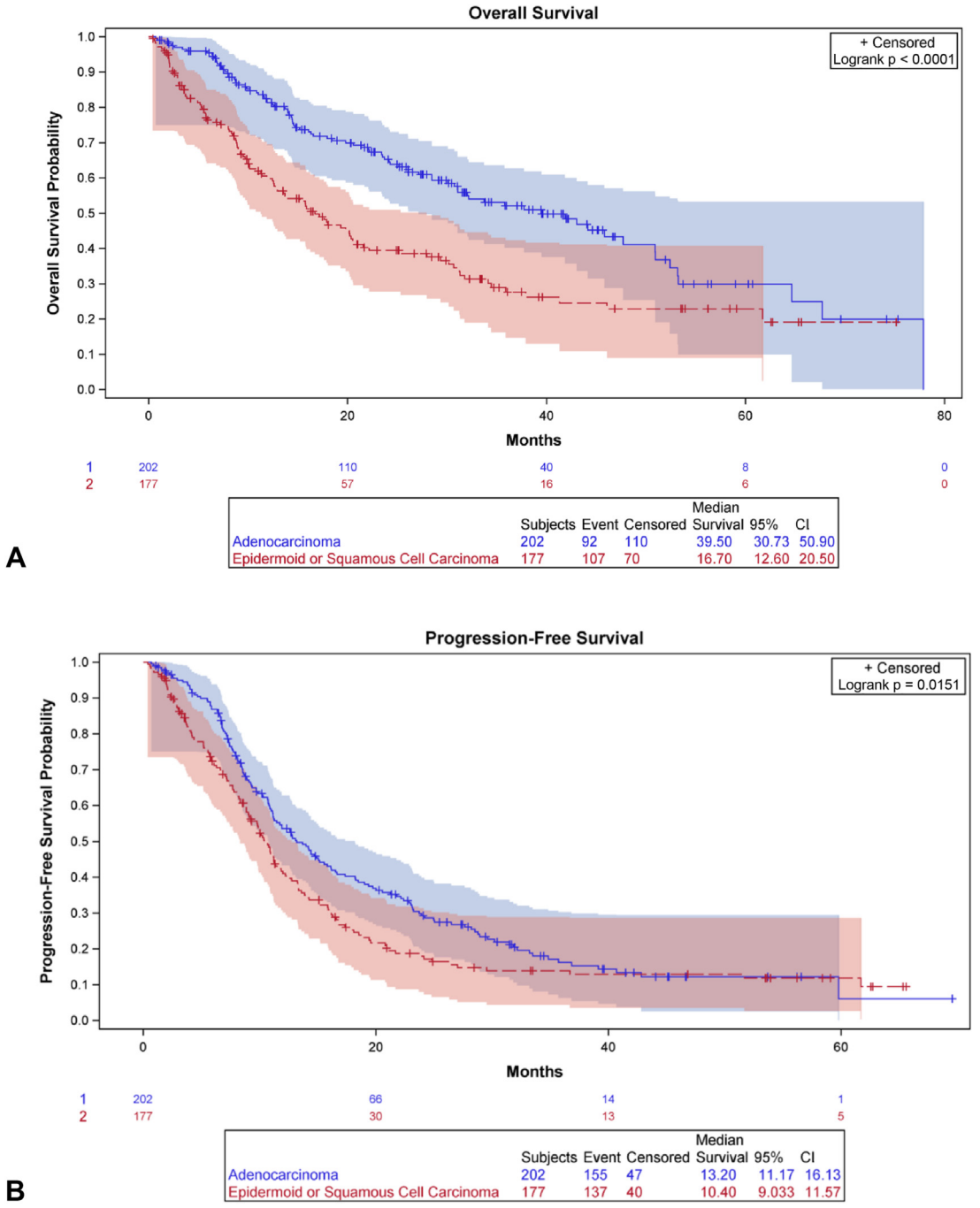
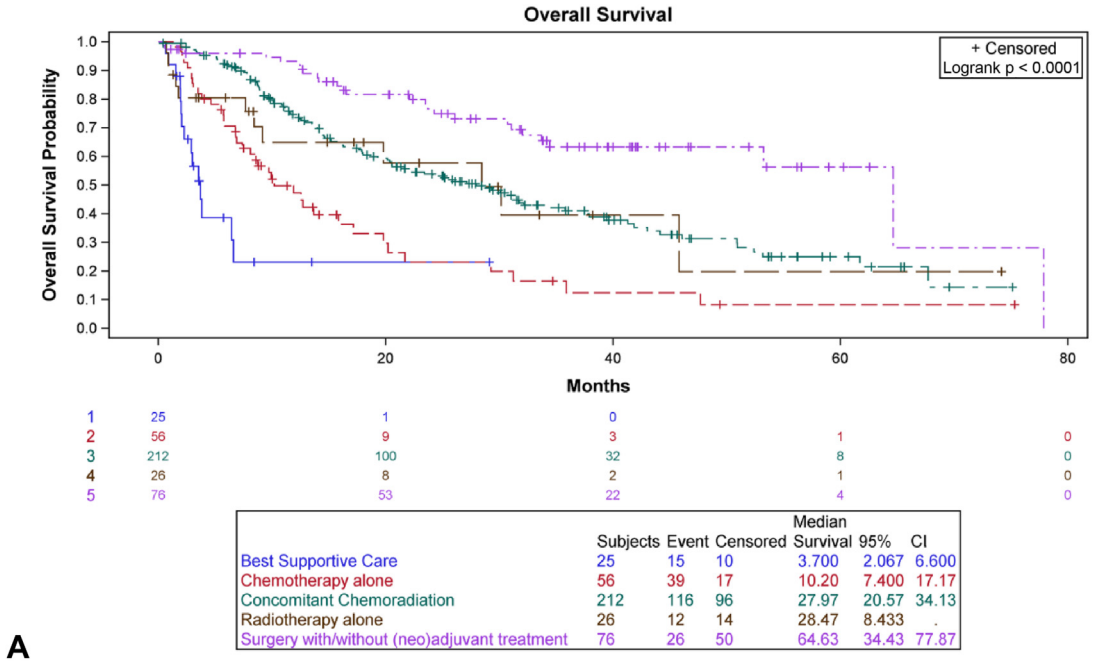


Figure 4. Impact of histology on (*A*) overall survival and (*B*) progression-free survival. Survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. Adenocarcinomas, bronchioloalveolar carcinomas, and large cell carcinomas were grouped in the adenocarcinoma group for this comparison. CI, confidence interval.

participating institutions in our cohort have dedicated thoracic oncology teams, which may result in improved outcomes, although our analysis was not restricted to stage IIIA only.

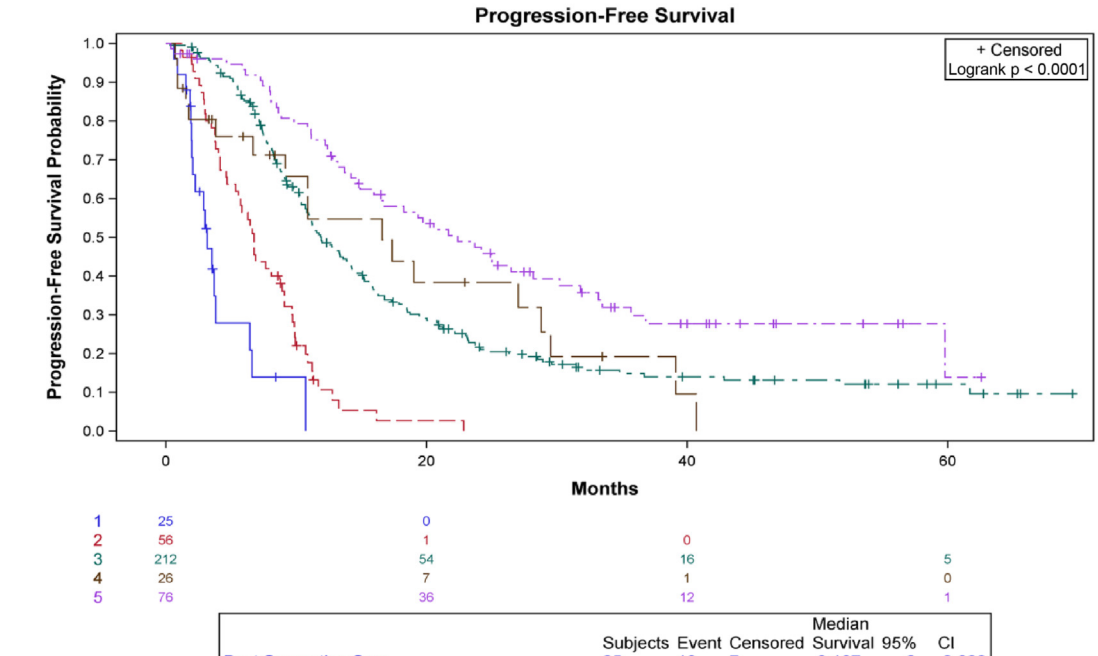
In a multivariable regression analysis, sex (male) and age (older than 70 y) were independently associated with death by all causes in the cohort reported by Ronden et al.[16] In our cohort, best supportive care only, squamous histology, and public health insurance were independent predictors of shorter OS.

In a study reported by Rice et al.,[17] patients with stage III NSCLC who held private insurance in the USA were more likely to be optimally diagnosed and treated; besides, they had twice longer median OS compared with patients uninsured or from Medicare and Medicaid or Veterans Affairs. In Brazil, discrepancies have also been



	Subjects	Event	Censored	Median Survival	95%	CI
Best Supportive Care	25	15	10	3.700	2.067	6.600
Chemotherapy alone	56	39	17	10.20	7.400	17.17
Concomitant Chemoradiation	212	116	96	27.97	20.57	34.13
Radiotherapy alone	26	12	14	28.47	8.433	.
Surgery with/without (neo)adjuvant treatment	76	26	50	64.63	34.43	77.87

A



	Subjects	Event	Censored	Median Survival	95%	CI
Best Supportive Care	25	18	7	3.167	2	3.833
Chemotherapy alone	56	51	5	6.767	4.700	8.933
Concomitant Chemoradiation	212	168	44	11.93	10.80	14.20
Radiotherapy alone	26	18	8	16.60	6.700	28.80
Surgery with/without (neo)adjuvant treatment	76	49	27	22.40	15.97	30.20

B

Figure 5. Impact of treatment type on (*A*) overall survival and (*B*) progression-free survival. Survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. CI, confidence interval.

reported for patients with NSCLC with brain metastasis treated in private or public health institutions. Patients from public institutions were more symptomatic and had higher tumor burden at the time of central nervous system metastases diagnosis, suggesting they were diagnosed later. In addition, the median OS doubled for patients in private care (24.2 versus 12.1 mo; $p < 0.001$).[18] In our cohort, the risk of death was almost twofold (hazard ratio = 1.83) for patients treated in the public health system.

Table 3. Cox Regression Multivariate Model Integrating the Impact of Age, Staging, Histology, Treatment Type, and Health Insurance on OS and PFS

Variable	OS		PFS	
	Hazard Ratio (95% CI)	*p* Value	Hazard Ratio (95% CI)	*p* Value
Treatment		<0.0001		<0.0001
Surgery with or without (neo)adjuvant treatment[a]	1.00		1.00	
Best supportive care	10.26 (5.08-20.72)		12.95 (7.07-23.70)	
Chemotherapy only	4.10 (2.40-6.99)		5.15 (3.29-8.05)	
Concomitant chemoradiation	1.71 (1.09-2.69)		1.70 (1.21-2.40)	
Radiotherapy only	2.00 (0.98-4.03)		1.61 (0.92-2.81)	
Histology		0.051		0.65
Non squamous carcinoma[a]	1.00		1.00	
Squamous cell carcinoma	1.34 (0.98-1.81)		1.09 (0.84-1.40)	
Mixed or Other	2.00 (0.97-4.10)		1.28 (0.67-2.43)	
Stage (AJCC stage - seventh edition)		0.38		0.79
Stage IIIA[a]	1.00		1.00	
Stage IIIB	1.14 (0.84-1.53)		0.97 (0.75-1.25)	
Health insurance		0.0002		0.14
Private[a]	1.00		1.00	
Public (governmental)	1.85 (1.33-2.58)		1.23 (0.94-1.59)	
Age at diagnosis	1.02 (1.00-1.03)	0.052	1.2 (0.99-1.02)	0.34

Note: Adenocarcinoma, bronchioloalveolar carcinoma, and large cell carcinoma were grouped for this analysis.
[a]Reference category.
AJCC, American Joint Committee on Cancer; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Squamous histology has been previously associated with worse outcomes in stage III NSCLC in a retrospective analysis, using propensity matching score, of data from the Taiwan Society of Cancer Registry. In this study, the 5-year survival rate was 27% versus 13% when comparing adenocarcinomas and squamous cell carcinomas.[19] In the current study, squamous histology was associated with a hazard ratio of 1.34 (0.98–1.81) for death.

As pointed out in the Introduction section, consolidation with durvalumab has greatly improved PFS and OS of unresectable stage III NSCLC, and the benefit was maintained at long-term follow-up.[9] Unfortunately, we could not evaluate the impact of consolidation with durvalumab because, in our cohort, only nine patients received this treatment. Because the drug was approved in Brazil in September 2020, these patients might have been included in clinical trials or early access programs.

In 2022, neoadjuvant chemoimmunotherapy for resectable stage IB to IIIA NSCLC was approved in Brazil based on the randomized phase 3 trial CHECKMATE 816 results. This trial revealed that combining chemotherapy and nivolumab increased the pathologic complete response rate and improved event-free survival compared with chemotherapy only as neoadjuvant treatment, especially for stage IIIA disease.[20] The NADIM II trial compared the same strategy in patients with stages IIIA and IIIB NSCLC and revealed a fivefold improvement in complete pathologic response rate with the combined treatment (36.8% versus 6.9%; $p = 0.068$).[21] These results will probably increase the enthusiasm to take patients with stage III NSCLC to surgery shortly.

Sadly, neither consolidation with durvalumab after CCRT nor neoadjuvant chemotherapy plus nivolumab as neoadjuvant therapy is reimbursed in the public health system in Brazil, further broadening the outcome disparities between patients with public versus private health care.

Our study has several limitations. One-third of patients could not be staged according to the eighth AJCC edition; however, most of the data available for comparison come from trials that used the seventh or earlier editions. We could not identify the patients who received sequential chemotherapy and radiotherapy from those treated with radiotherapy. This might have resulted in the patients treated with radiotherapy reaching a median OS close to that observed for patients treated with CCRT. We did not have access to the original images, so there is a chance that a proportion of the patients were staged down or staged up, especially in public institutions where access to PET-CT, magnetic resonance imaging, and invasive mediastinal staging is more limited.

In conclusion, Brazilian patients diagnosed with having stage III NSCLC have outcomes comparable with those reported in pivotal trials if they have access to adequate treatment. Patients eligible for surgical

Table 4. Comparison Between Patients With Private and Public Health Insurance

Characteristics	Total (N = 403)	Private Insurance (n=131)	Public Governmental (n=272)	*p* Value[a]
Median age, y (min-max)	66 (27-90)	69 (29-86)	65 (27-90)	0.0529
Sex				0.0288
Male	258 (64.02)	74 (56.49)	184 (67.65)	
Female	145 (35.98)	57 (43.51)	88 (32.35)	
Smoking status				0.0003
Never smoker	51 (12.66)	28 (21.37)	23 (8.46)	
Former smoker	224 (55.58)	77 (58.78)	147 (54.04)	
Current smoker	123 (30.52)	22 (16.79)	101 (37.13)	
Unknown	5 (1.24)	4 (3.05)	1 (0.37)	
Race				0.3483
White	127 (31.51)	33 (25.19)	94 (34.56)	
Black	17 (4.22)	4 (3.05)	13 (4.78)	
Brown	77 (19.11)	14 (10.69)	63 (23.16)	
Hispanic	19 (4.71)	7 (5.34)	12 (4.41)	
Unknown	163 (40.45)	73 (55.72)	90 (33.09)	
Histology				<0.0001
Squamous cell carcinoma	182 (45.16)	39 (29.77)	143 (52.57)	
Adenocarcinoma	203 (50.37)	88 (67.18)	115 (42.28)	
Bronchioloalveolar carcinoma	1 (0.25)	1 (0.76)	0 (0.00)	
Large cell carcinoma	1 (0.25)	0 (0.00)	1 (0.37)	
Mixed	3 (0.74)	2 (1.53)	1 (0.37)	
Other	13 (3.23)	1 (0.76)	12 (4.41)	
ECOG performance status				<0.0001
0 or 1	304 (75.43)	112 (27.79)	192 (47.64)	
≥2	99 (20.60)	8 (1.99)	75 (18.61)	
Unknown	16 (3.97)	11 (2.73)	5 (1.24)	
Examination for diagnosis of lung cancer				0.0447
Chest radiograph	66 (16.38)	14 (10.69)	52 (19.12)	
CT scan	304 (75.43)	100 (76.34)	204 (75.00)	
MRI scan	2 (0.50)	1 (0.76)	1 (0.37)	
PET scan (incl. PET-CT)	28 (6.95)	14 (10.69)	14 (5.15)	
Unknown	3 (0.74)	2 (1.53)	1 (0.37)	
Type of treatment				0.0005
Surgery with or without (neo)adjuvant treatment	77 (19.11)	38 (29.01)	39 (14.34)	
Chemotherapy only	56 (13.90)	13 (9.92)	43 (15.81)	
Radiotherapy only	28 (6.95)	7 (5.34)	21 (7.72)	
Concomitant chemoradiation	214 (53.10)	69 (52.67)	145 (53.31)	
Best supportive care	28 (6.95)	4 (3.05)	24 (8.82)	
T (seventh edition)				<0.0001
TX	6 (1.49)	3 (2.29)	3 (1.10)	
T1	25 (6.20)	17 (12.98)	8 (2.94)	
T2	94 (23.33)	38 (29.01)	56 (20.59)	
T3	122 (30.27)	39 (29.77)	83 (30.51)	
T4	135 (33.50)	24 (18.32)	111 (40.81)	
Unknown	21 (5.21)	10 (7.63)	11 (4.04)	
N (seventh edition)				0.4228
N0	39 (9.68)	11 (8.40)	28 (10.29)	
N1	34 (8.44)	9 (6.87)	25 (9.19)	
N2	237 (58.81)	75 (57.25)	162 (59.56)	
N3	53 (13.15)	23 (17.56)	30 (11.03)	
NX	19 (4.71)	3 (2.29)	16 (5.88)	
Unknown	21 (5.21)	10 (7.63)	11 (4.04)	
Stage (AJCC stage - seventh edition)				0.2353
Stage IIIA	251 (62.28)	87 (66.41)	164 (60.29)	
Stage IIIB	152 (37.72)	44 (33.59)	108 (39.71)	

Note: *p* values were calculated disregarding the unknown category (noninformative).
[a]*p* value was calculated excluding the "Unknown" category.
AJCC, American Joint Committee on Cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; incl., including; max, maximum; min, minimum; MRI, magnetic resonance imaging; PET, positron emission tomography.

treatment have excellent OS. Notwithstanding, Brazilian patients treated in the public health system are diagnosed later, as reflected by larger tumors at diagnosis and poorer performance status, and have poorer OS compared with patients with private health insurance even after adjusting by other prognostic variables. The recent approval of immunotherapy as consolidation and neoadjuvant treatment will deepen this gap further. A complete revision of the procedures available in the public system for patients with lung cancer is urgently needed to make earlier diagnoses, offer adequate treatment for each clinical scenario, and guarantee the best outcome possible.

CRediT Authorship Contribution Statement

Vladmir C. Cordeiro de Lima: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Roles/Writing—original draft, Investigation, Writing—review and editing.

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Gustavo Gössling: Data curation, Supervision, Roles/Writing—original draft, Investigation, Writing—review and editing.

Clarissa Baldotto: Data curation, Methodology, Project administration, Supervision, Investigation, Writing—review and editing.

Gilberto de Castro, Jr.: Methodology, Project administration, Investigation, Writing—review and editing.

Clarissa Mathias: Methodology, Project administration, Investigation, Writing—review and editing.

Ricardo M. Terra: Methodology, Project administration, Investigation, Writing—review and editing.

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Rosely Yamamura: Investigation, Writing—review and editing.

Caroline Kawamura: Investigation, Writing—review and editing.

Eldsamira Mascarenhas: Investigation, Writing—review and editing.

Disclosure

Dr. Cordeiro de Lima reports receiving research grant from Bristol-Myers Squibb (for the institution); payment or honoraria from AstraZeneca, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Serono, and Novartis; support for attending meetings from AstraZeneca and Roche; and having participation on data safety monitoring board or advisory board in AstraZeneca, Daiichi Sankyo, Amgen, Pfizer, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, Merck Serono, and Janssen. Dr. De Castro Jr., reports having consulting or advisory roles from Boehringer Ingelheim, Pfizer, Bayer, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Yuhan, Merck Serono, Janssen, Libbs, Sanofi, Novartis, Eli Lilly, Amgen, and Takeda; receiving payment or honoraria from AstraZeneca, Pfizer, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, Roche, Amgen, Janssen, Merck Serono, Bayer, and Takeda; receiving support for attending meetings from Boehringer Ingelheim, Pfizer, Bayer, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Merck Serono, Novartis, Eli Lilly, and Amgen; and having participation on data safety monitoring board or advisory board in Boehringer Ingelheim, Pfizer, Bayer, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Yuhan, Merck Serono, Janssen, Libbs, Sanofi, Novartis, Eli Lilly, Amgen, and Takeda. Dr. Werutsky reports receiving grants or contracts from Novartis, Roche/Genentech, AstraZeneca/MedImmune, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Bristol-Myers Squibb Brazil, Merck Sharp & Dohme, Merck, Bayer, Janssen, Bristol-Myers Squibb, Astellas, Libbs, Takeda, Celgene, and GlaxoSmithKline; consulting fees from Merck; and payment or honoraria for lectures from Pfizer, AstraZeneca/MedImmune, Libbs, and Merck. The remaining authors declare no conflict of interest.

Acknowledgments

This work was supported by AstraZeneca. The authors thank AstraZeneca for sponsoring the study. We acknowledge SAS Institute Inc. for supporting our study by providing access to SAS statistical products. We thank all the LACOG staff for logistical and statistical support of

the study and Matheus Soares Rocha for the help with the submission process.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100646.

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