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Real-World Treatment Patterns and Associated Outcomes in Patients With Resectable Early-Stage Non-Small Cell Lung Cancer: The THASSOS International Study

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ABSTRACT

Background: THASSOS-INTL (NCT04808050), a multinational, retrospective study, evaluated treatment patterns and associated outcomes in patients with early-stage non-small cell lung cancer (NSCLC) from seven countries in the Asia-Pacific and the Middle-East and Africa.

Methods: Eligible adult patients (≥18 years) with resectable clinical stage (CS) IA-IIIB NSCLC (7th AJCC) diagnosed from 01/01/2013 to 31/12/2017 were followed until death, last recorded clinical visit, or 31/12/2020 (data cut-off).

Results: Of 755 patients (CS I: 30.6%, CS II: 35.0%, CS III: 34.2%) with a median age of 62 [range: 56–69] years enrolled, 69.3% were male, and 75.0% were current/ex-smokers. Of 24.2% of patients tested for *EGFR*, 28.4% (52/183) were positive, while 23/44 patients tested (52.3%) had PD-L1 expression (≥1%: 16; unknown: 7). Overall, 82.9% had surgery, of whom 39.1% (245/626) had surgery alone; 21.1% received neoadjuvant therapy, 51.1% received adjuvant therapy, and 5.8% received both; 11.2% (58/519) patients received targeted therapy (adjuvant: 47 patients; neoadjuvant: 11 patients), and 4.6% (24/519) received immunotherapy (adjuvant: 22 patients; neoadjuvant: 2 patients). The 3-year survival was 77.4% with a median overall survival (mOS) of 7.5 (95% confidence interval [CI]: 6.7–NE) years, with the highest mOS recorded with adjuvant therapy (7.5 [95% CI: 7.0–NE] years).

Conclusions: This real-world study showed > 50% use of adjuvant therapy per guideline recommendations but poor use of neoadjuvant therapy. Biomarker testing at diagnosis was low, reflecting the study period being before targeted and immunotherapies. With recent approvals of newer (neo)adjuvant agents, a multidisciplinary approach is needed for better treatment decisions to improve the prognosis of early-stage NSCLC.

1 | Introduction

Lung cancer is the leading cause of cancer-related deaths globally, accounting for 2.5 million cases and 1.8 million deaths in 2022 [1, 2]. Non-small cell lung cancer (NSCLC) predominates all new lung cancer cases and comprises three distinct histological subtypes: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, with adenocarcinoma constituting 50% to

60% of all NSCLC cases [3, 4]. Around 30% to 50% of NSCLC patients are diagnosed in the non-metastatic stage (stage IA to IIIB; as per American Joint Committee on Cancer [AJCC] 7th Ed.) with a 5-year survival rate ranging from 90% for stage IA to <25% in stage IIIB [5, 6]. Treatment of resectable NSCLC depends on disease stage, with approximately 20% to 25% eligible for primary curative surgery [3, 6]. Stage IA patients and stage IB patients without risk factors are predominantly restricted to observation following complete tumor resection. Clinical practice guidelines during the period of this study recommended up to 4 cycles of adjuvant chemotherapy with a platinum-based doublet following surgery for patients with stage IB disease with tumors ≥4 cm or other high-risk factors and for patients with resectable stage IIA–IIIA disease [6–9]. Radiotherapy (RT) is historically recommended for patients with early-stage NSCLC who are not eligible for surgery and for those with significant comorbidities [10–12]. However, the prognosis for early-stage NSCLC undergoing tumor resection remains poor, possibly attributable to inequalities in management and guideline adherence [13]. Greater resource availability and guideline awareness are improving care, particularly in the low-and-middle-income countries [14].

Evidence-based guidelines are continuously evolving, and systemic therapies for advanced NSCLC are currently in various stages of development and regulatory approval for early-stage NSCLC [15]. Several immunotherapies and targeted therapies have shown improved patient outcomes in clinical studies, including the AEGEAN trial (durvalumab treatment plus neoadjuvant chemotherapy (CT) in patients with resectable stage IIA to IIIB NSCLC) [16], the KEYNOTE-671 trial (perioperative pembrolizumab with neoadjuvant CT in patients with resectable, early-stage NSCLC) [17], the Checkmate-77 T trial (perioperative nivolumab in patients with resectable early-stage NSCLC) [18], and the Checkmate-816 trial (nivolumab plus CT in patients with stage IB to IIIA NSCLC) [19]. Notably, the current guidelines strongly recommend testing for PD-L1 status, epidermal growth factor receptor (*EGFR*) mutations, and anaplastic lymphoma kinase (*ALK*) fusions before initiating immunotherapy with CT in eligible patients with stage IB (tumor size [*T*] ≥4 cm) to stage IIIB NSCLC [20]. Adjuvant pembrolizumab significantly improved disease-free survival versus placebo in completely resected, PD-L1-unselected, stage IB-IIIA NSCLC (PEARLS/KEYNOTE-091) [21]. IMpower010 showed improved disease-free survival with adjuvant atezolizumab versus best supportive care in patients with resected stage II-IIIA NSCLC, specifically in those with PD-L1 ≥1% tumors [22]. The ADAURA trial showed significant improvement in disease-free survival and overall survival (OS) with adjuvant osimertinib in patients with surgically resected stage IB to IIIA *EGFR*-mutated NSCLC [23–25]. The ongoing NeoADAURA study is evaluating neoadjuvant osimertinib as monotherapy or in combination with CT versus standard of care CT in patients with *EGFR*-mutated resectable NSCLC (stage II to IIIB) [25]. The ongoing PACIFIC-4 trial is assessing the efficacy and safety of durvalumab following SBRT in patients with unresected stage I/II lymph node negative NSCLC, and osimertinib following SBRT in *EGFR*-mutated patients with unresected stage I/II lymph node negative NSCLC [26].

The application of international guidelines in the management of early-stage (IA to IIIB) resectable NSCLC in routine clinical practice in different regions of the world has not been studied widely. With the high disease burden of lung cancer and the evolving treatment landscape, it is important to identify patient management patterns arising from historical practices and leading to the current standard of care in the real-world setting [27]. Comprehensive databases that include real-world information on diagnosis, treatment patterns, and survival outcomes of patients with early-stage NSCLC are lacking. The THASSOS-INTL study was conducted in non-United States (US) and non-European (EU) countries to collect retrospective data (up to 5 years) from established patients' medical records about a decade before the recent advances in care. The study aimed to consolidate the available information on the historical treatment patterns and their associated clinical outcomes in patients with early-stage resectable NSCLC in the context of the recent developments and evolving guidelines to optimize clinical decision-making and selection of treatment strategies in this patient population.

2 | Methods

2.1 | Study Design

THASSOS (NCT04808050) was a non-interventional, multinational, multicenter, retrospective study determining the treatment patterns and associated survival outcomes in patients with early-stage primary NSCLC. The study was conducted at 33 sites spanning seven countries in the Asia-Pacific (APAC; Australia, Hong Kong, India) and Middle-East and Africa (MEA; Egypt, Kuwait, Turkey, United Arab Emirates) regions (Figure S1). The study protocol was approved by the independent ethics committees/institutional review boards of all participating centers before the enrollment of study participants. The study was conducted per the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practices, and the applicable legislation on non-interventional and observational studies. The reporting of this manuscript has been done following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Supporting Information) [28].

2.2 | Study Population

Adult patients aged ≥18 years or defined as "adults" by the local regulations, at the index date (date of initial diagnosis of early-stage NSCLC), or their next of kin/legal representative (for deceased patients) who provided written/electronic informed consent with availability of at least 12 months of follow-up data from the index date (unless the patient died within 12 months of diagnosis) were enrolled between 01 January 2013 and 31 December 2017. Eligible patients were diagnosed with primary stage IA to IIIB resectable NSCLC as per the AJCC 7th Ed. and followed up until at least 31 December 2020, as per the medical records.

Patients with concomitant cancer diagnosed within 5 years of NSCLC diagnosis (except for non-metastatic nonmelanoma

skin cancers, or in situ or benign neoplasms) or with stage IV NSCLC, and those with small cell lung cancer, neuroendocrine tumors, or mixed histology (small cell and non-small cell) were excluded from the study.

Data were retrospectively extracted from the patients' medical records from the index date to the end of follow-up, that is, until death, the last medical record entry, or the date of data extraction (31 December 2020), whichever was the earliest. Data collection included treatment modalities, sociodemographics, clinicopathological characteristics, and exposure and outcome variables (i.e., medical and treatment history, disease staging, biomarker assessments, radiological findings, concomitant medications, and survival), factor(s) for prescribing neoadjuvant and/or adjuvant treatment, and reason(s) for discontinuation.

2.3 | Study Endpoints

The primary endpoint included the treatment patterns and their associated 3-year survival rate according to clinical and pathologic staging. Treatment patterns were described as patients who underwent surgery only, those receiving neoadjuvant therapy (systemic therapy [ST] +/− radiotherapy [RT]) only, those receiving adjuvant therapy (ST +/− RT) only, and those receiving both neoadjuvant and adjuvant therapies. Systemic therapy included chemotherapy, targeted therapy, and immunotherapy (as monotherapy or in combination).

Secondary endpoints included baseline demographic and clinicopathological characteristics, the real-world OS and survival rates according to clinical stage and treatment patterns, biomarker testing strategies, the prevalence of *EGFR* mutations and PD-L1 expression, and the relationship between OS and age, stage, *EGFR* mutation status, and PD-L1 status.

3 | Bias

Attrition bias (patients may be lost to follow-up due to AEs, lack of efficacy, or other reasons) was minimized using Kaplan–Meier (KM) curves to obtain estimates of survival that considered patient attrition. Selection bias (retrospective data interpretation was dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records) was minimized by choosing Good Clinical Practice-qualified investigators and the sponsor providing protocol training for selecting the right participants as required for the study. The physicians were instructed to randomly select from their pool of patients who fulfilled the selection criteria included in the patient screener of the electronic data clarification form (eDCF). Selection was based on a randomly generated letter for the first letter of the patient's last name. Physicians selected all eligible patients whose last names began with this letter. If no eligible patients were found, they selected all patients whose last name started with the next letter in alphabetical order. This ensured no systematic selection of patients starting with a particular letter of a patient's last name. There was a soft quota around the year of initial NSCLC diagnosis to ensure an equitable distribution of patient charts across the year of NSCLC diagnosis. The physicians were asked to refer to the patient's complete medical record while completing the eDCF and not to answer any question from memory. Information bias was minimized by reporting the study results according to the STROBE checklist.

3.1 | Statistical Analysis

Based on the assumption of exponential survival, the precision shown was the 95% CI of the KM estimate of 3-year OS. At least 5% of surviving patients were assumed to be lost to follow-up in the subsequent 3 years. Enrollment was considered to be uniform from 01 January 2013 to 31 December 2017, with data cut-off on 31 December 2020. All analyses were performed using the Full Analysis Set comprising all the participants who fulfilled the eligibility criteria and were included in the study. Descriptive analyses are presented using SAS Version 9.2 or higher. Data from all participating centers were pooled for analysis and, where applicable, presented by cohort, country, and/or region within the predefined subgroups of interest.

In case of missing data from the original medical records, the analyses were performed using only available data. Categorical variables were summarized as frequencies and 95% confidence intervals (CIs) estimated by the Clopper-Pearson exact method. Continuous variables were reported as the number of observations, arithmetic mean (standard deviation [SD]), and median (range). Estimation of 3-year survival as per clinical and pathologic staging in patients with resectable early-stage (IA to IIIB) NSCLC was done by extrapolating the corresponding 3-year OS from the AJCC 7th Ed. estimates of expected 2-year OS per clinical and pathologic staging and assuming exponential (constant hazard) survival (Table S1). Survival rates were presented using the KM curve.

Correlation analyses were performed to analyze the effect of factors such as age, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, *EGFR* mutation, and PD-L1 expression on OS. No adjustments for multiple comparisons were made as this was a non-interventional study. In the Cox proportional hazards model, used for probability assessment, death from any cause was considered as the end of follow-up, while the last contact date served as the censoring point for patients who were alive at their last recorded visit. Multivariable models were adjusted for age, ECOG performance status, disease stage, *EGFR* mutation, and PD-L1 expression at the index date.

4 | Results

4.1 | Patient Disposition and Baseline Characteristics

A total of 755 patients were included at the index date, with 231 (30.6%) patients at clinical stage (CS) I (IA: 14.0%; IB: 16.6%), 264 (35%) at CS II (IIA: 17.9%; IIB: 17.1%), and 258 (34.2%) at CS III (IIIA: 28.7%; IIIB: 5.4%); the stage of disease was unknown for two patients (Figure 1) (Table 1). The median age (range) at diagnosis was 62.0 (19–88) years, which was similar across all disease stages, with the majority (69.3%) of patients being male ($n = 523$). Most patients

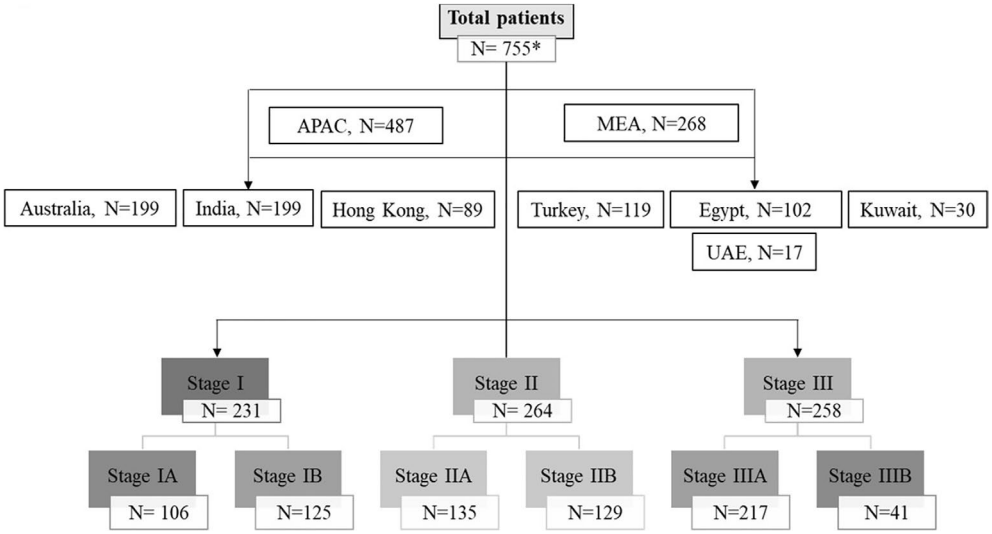

FIGURE 1 | Patient disposition. *All patients included in the study comprised the full analysis set. Two patients had "Unknown" stage. APAC, Asia-Pacific; MEA, Middle-East and Africa; UAE, United Arasb Emirates.

were smokers or ex-smokers (65.2% [$n=492$]). Overall, 42.9% of patients ($n=324$) had tumors classified as T2a–T2b, with no nodal involvement reported in 55.5% ($n=419$). A majority (57.7%, $n=436$) of patients had an ECOG performance status ≤ 1 across all stages. Adenocarcinoma was the predominant (57.5%, $n=434$) histological subtype in all stages, with most tumors located in the right lung (58.1% [$n=439$]).

4.2 | Treatment Modalities

Overall, 82.9% ($n=626$) of patients across all stages underwent curative resection (CS IA: 95.3% [$n=101$]; CS IB: 94.4% [$n=118$]; CS IIA: 88.1% [$n=119$]; CS IIB: 83.7% [$n=108$]; CS IIIA: 77.4% [$n=168$]; CS IIIB: 26.8% [$n=11$]) (Table 2). Lobectomy was the most common surgical procedure (81.6% [$n=511$]) (Figure S2) and 81.6% ($n=511$) of patients reported complete surgical resection (R0) (Table S2). Surgery alone was the primary treatment modality in CS I (64.1% [$n=148$]; CS IA: 75.5% [$n=80$]; CS IB: 54.4% [$n=68$]) while surgery with adjuvant ST +/− RT was recorded in 16.0% (CS IA [$n=17$]) and 34.4% (CS IB [$n=43$]). Neoadjuvant therapy was rare (CS IA: $n=2$; CS IB: $n=6$). Among 17.1% ($n=129$) patients who did not undergo curative surgery, 51.2% ($n=66$) received ST, 3.1% ($n=4$) received RT, and 44.2% ($n=57$) received both ST + RT; 9 patients did not receive any treatment.

Surgery alone was recorded in 24.2% ($n=64$) patients in CS II (CS IIA: 26.9% [$n=32$]; CS IIB: 29.6% [$n=32$]). Surgery with adjuvant ST was the primary treatment modality for patients with CS II disease (50.8% [$n=134$]; CS IIA: 57.0% [$n=77$]; CS IIB: 44.2% [$n=57$]); adjuvant RT was received by 6 patients, while 19 patients (7.2%) received both. Neoadjuvant ST was received by 13.6% of patients ($n=36$; CS IIA: 11.1% [$n=15$]; CS IIB: 16.3% [$n=21$]) and both neoadjuvant and adjuvant therapy was recorded for 11 (4.2%) patients. Among patients with CS III disease, 50.0% ($n=129$) received adjuvant ST +/− RT (CS IIIA: 51.2% [$n=111$]; CS IIIB: 43.9% [$n=18$]) and 24.0% ($n=62$) received neoadjuvant therapy (CS IIIA: 20.3% [$n=44$]; CS IIIB: 43.9% [$n=18$]); 11.6% [$n=30$] received both. Surgery alone was recorded in 12.8% ($n=33$) of patients with CS III, most of whom belonged to CS IIIA ($n=31$) (Table 2, Figure 2).

Overall, 68.7% ($n=519$) patients received ST, 48.1% ($n=363$) in the adjuvant setting, and 20.7% ($n=156$) in the neoadjuvant setting. Neoadjuvant ST had a higher compliance rate with 92.3% ($n=144$) patients completing planned treatment versus 87.5% ($n=317$) patients who received adjuvant ST. The median (range) duration of adjuvant ST was 71 (0–2613) days and of neoadjuvant ST was 70 (0–2244) days. In total, 11.2% ($n=58$) patients received targeted therapy (adjuvant: 47 patients; neoadjuvant: 11 patients), and 4.6% ($n=24$) patients received immunotherapy (adjuvant: 22 patients; neoadjuvant: 2 patients) with or without chemotherapy. The main reasons for discontinuation of treatment were treatment-related toxicity (in 26 patients receiving adjuvant therapy) and patient refusal (in 4 patients receiving neoadjuvant therapy). About a quarter of the patients (23.0% [$n=174$]) received RT overall, 15.6% ($n=118$) in the adjuvant setting, and 7.4% ($n=56$) in the neoadjuvant setting. The dose range for adjuvant RT varied from 0.1 to 200.0 Gy (mean [SD] 45.2 [56.9] Gy) and that for neoadjuvant RT varied from 1.8 to 220.0 Gy (mean [SD] 25.2 (43.3) Gy) depending on individual patient needs (Table 3). Upon disease progression, 29.9% ($n=226$) patients received ST, and 22.0% ($n=166$) patients received RT (Figure S3).

4.3 | Survival Outcomes

In the overall population, the median (95% CI) OS time calculated using the Kaplan–Meier curve was 7.5 (6.7–NE) years with a 3-year survival probability rate (95% CI) of 77.4% (74.3%–80.6%) (Figure 3A, Table 4). A total of 34.8% ($n=263$) of patients died during the study. Patients with CS I disease had a median OS of 8.1 (7.6–not estimable [NE]) years (CS IA: 8.1 [6.7–NE]; CS IB: 8.0 [7.8–NE]) and a 3-year survival rate of 86.9% (82.5%–91.6%) (Figure 3B, Table 4). Among patients with CS II disease, the median OS was 7.2 (6.6–NE) years (CS IIA: 7.7 [6.9–NE]; CS IIB:

TABLE 1 | Baseline characteristics.

Characteristic	Overall[a] *N* = 755	CS IA *N* = 106	CS IB *N* = 125	CS IIA *N* = 135	CS IIB *N* = 129	CS IIIA *N* = 217	CS IIIB *N* = 41
Demographics							
Age (years)							
Median (range)	62.0 (19.0, 88.0)	62.0 (57.0, 68.8)	65.0 (57.0, 71.0)	61.0 (55.0, 68.0)	62.0 (56.0, 68.0)	62.0 (56.0, 68.0)	58.0 (52.0, 66.0)
Sex, *n* (%)							
Female	232 (30.7)	48 (45.3)	46 (36.8)	44 (32.6)	34 (26.4)	52 (24.0)	8 (19.5)
Male	523 (69.3)	58 (54.7)	79 (63.2)	91 (67.4)	95 (73.6)	165 (76.0)	33 (80.5)
Smoking status, *n* (%)							
Current smoker	244 (32.3%)	40 (37.7%)	32 (25.6%)	45 (33.3%)	42 (32.6%)	71 (32.7%)	14 (34.1%)
Ex-smoker	248 (32.8%)	36 (34.0%)	36 (28.8%)	38 (28.1%)	43 (33.3%)	83 (38.2%)	11 (26.8%)
Never smoker	164 (21.7%)	22 (20.8%)	42 (33.6%)	34 (25.2%)	29 (22.5%)	32 (14.7%)	5 (12.2%)
Unknown	99 (13.1%)	8 (7.5%)	15 (12.0%)	18 (13.3%)	15 (11.6%)	31 (14.3%)	11 (26.8%)
Number of pack-years, median (range)	40 (0.0, 90.0)	40 (0.0, 70.0)	43 (10.0, 65.0)	40 (10.0, 60.0)	40 (5.0, 81.0)	40 (3.0, 60.0)	40 (6.0, 90.0)
Ethnicity, *n* (%)							
Caucasian	244 (32.3)	42 (39.6)	45 (36.0)	41 (30.4%)	32 (24.8)	65 (30.0)	19 (46.3)
Indian	195 (25.8)	20 (18.9)	35 (28.0)	31 (23.0%)	41 (31.8)	58 (26.7)	10 (24.4)
Arabic	131 (17.4)	12 (11.3)	14 (11.2)	26 (19.3)	25 (19.4)	44 (20.3)	9 (22.0)
East Asian	57 (7.5)	8 (7.5)	11 (8.8)	11 (8.1)	10 (7.8)	16 (7.4)	1 (2.4)
Chinese	35 (4.6)	5 (4.7)	10 (8.0)	5 (3.7)	6 (4.7)	9 (4.1)	0 (0.0)
Health insurance coverage, *n* (%)							
No	114 (15.1)	10 (9.4)	18 (14.4)	22 (16.3)	23 (17.8)	34 (15.7)	7 (17.1)
Yes	309 (40.9)	53 (50.0)	48 (38.4)	53 (39.3)	47 (36.4)	84 (38.7)	24 (58.5)
Unknown	332 (44.0)	43 (40.6)	59 (47.2)	60 (44.4)	59 (45.7)	99 (45.6)	10 (24.4)
Health insurance type, *n* (%)							
Employer-provided	31 (4.1)	1 (0.9)	2 (1.6)	5 (3.7)	2 (1.6)	11 (5.1)	10 (24.4)
Private insurance	18 (2.4)	6 (5.7)	3 (2.4)	2 (1.5)	3 (2.3)	4 (1.8)	0 (0.0)

(Continues)

TABLE 1 | (Continued)

Characteristic	Overall[a] *N* = 755	CS IA *N* = 106	CS IB *N* = 125	CS IIA *N* = 135	CS IIB *N* = 129	CS IIIA *N* = 217	CS IIIB *N* = 41
Public governmental	258 (34.2)	46 (43.4)	43 (34.4)	44 (32.6)	42 (32.6)	69 (31.8)	14 (34.1)
Clinical characteristics							
ECOG, *n* (%)							
0/1	436 (57.7)	58 (54.7)	73 (58.4)	74 (54.8)	83 (64.3)	133 (61.3)	15 (36.6)
2	31 (4.1)	3 (2.8)	4 (3.2)	6 (4.4)	7 (5.4)	8 (3.7)	3 (7.3)
3/4	6 (0.8)	1 (0.9)	1 (0.8)	1 (0.7)	2 (1.6)	1 (0.5)	0 (0.0)
Unknown	282 (37.4)	44 (41.5)	47 (37.6)	54 (40.0)	37 (28.7)	75 (34.6)	23 (56.1)
Tumor stage (as per AJCC 7th Ed), *n* (%)							
T1a	77 (10.2)	56 (52.8)	0 (0.0)	13 (9.6)	0 (0.0)	6 (2.8)	2 (4.9)
T1b	95 (12.6)	50 (47.2)	0 (0.0)	22 (16.3)	0 (0.0)	21 (9.7)	2 (4.9)
T2a	217 (28.7)	0 (0.0)	125 (100.0)	41 (30.4)	0 (0.0)	46 (21.2)	5 (12.2)
T2b	107 (14.2)	0 (0.0)	0 (0.0)	59 (43.7)	22 (17.1)	24 (11.1)	2 (4.9)
T3	201 (26.6)	0 (0.0)	0 (0.0)	0 (0.0)	107 (82.9)	89 (41.0)	5 (12.2)
T4	56 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (14.3)	25 (61.0)
Unknown	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Regional lymph node stage, *n* (%)							
N0	419 (55.5)	106 (100.0)	125 (100.0)	59 (43.7)	107 (82.9)	22 (10.1)	0 (0.0)
N1	142 (18.8)	0 (0.0)	0 (0.0)	76 (56.3)	22 (17.1)	44 (20.3)	0 (0.0)
N2	172 (22.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	151 (69.6)	21 (51.2)
N3	20 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (48.8)
Unknown	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor site, *n* (%)							
Left–unspecified	9 (1.2)	0 (0.0)	1 (0.8)	3 (2.2)	2 (1.6)	2 (0.9)	1 (2.4)
Left lingula	4 (0.5)	0 (0.0)	1 (0.8)	2 (1.5)	0 (0.0)	1 (0.5)	0 (0.0)
Left lower lobe	104 (13.8)	11 (10.4)	23 (18.4)	19 (14.1)	21 (16.3)	27 (12.4)	3 (7.3)

(Continues)

TABLE 1 | (Continued)

Characteristic	Overall[a] *N* = 755	CS IA *N* = 106	CS IB *N* = 125	CS IIA *N* = 135	CS IIB *N* = 129	CS IIIA *N* = 217	CS IIIB *N* = 41
Left upper lobe	189 (25.0)	29 (27.4)	20 (16.0)	34 (25.2)	34 (26.4)	64 (29.5)	8 (19.5)
Right–Unspecified	20 (2.6)	2 (1.9)	3 (2.4)	0 (0.0)	5 (3.9)	7 (3.2)	2 (4.9)
Right lower lobe	123 (16.3)	20 (18.9)	22 (17.6)	22 (16.3)	21 (16.3)	30 (13.8)	8 (19.5)
Right middle lobe	38 (5.0)	6 (5.7)	8 (6.4)	11 (8.1)	2 (1.6)	9 (4.1)	2 (4.9)
Right pancoast	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.9)	0 (0.0)
Right upper lobe	255 (33.8)	38 (35.8)	46 (36.8)	43 (31.9)	41 (31.8)	71 (32.7)	16 (39.0)
Unknown	10 (1.3)	0 (0.0)	1 (0.8)	1 (0.7)	2 (1.6)	4 (1.8)	1 (2.4)
Histology, *n* (%)							
Adenocarcinoma	434 (57.5)	72 (67.9)	77 (61.6)	78 (57.8)	66 (51.2)	118 (54.4)	23 (56.1)
Squamous cell carcinoma	193 (25.6)	20 (18.9)	31 (24.8)	37 (27.4)	33 (25.6)	58 (26.7)	14 (34.1)
Adenosquamous cell carcinoma	16 (2.1)	1 (0.9)	4 (3.2)	5 (3.7)	3 (2.3)	3 (1.4)	0 (0.0)
Comorbidities, *n* (%)							
Yes	459 (60.8)	75 (70.8)	76 (60.8)	76 (56.3)	75 (58.1)	137 (63.1)	19 (46.3)
HTN	266 (58.0)	51 (68.0)	45 (59.2)	40 (52.6)	41 (54.7)	79 (57.7)	9 (47.4)
T2D	131 (28.5)	18 (24.0)	21 (27.6)	25 (32.9)	17 (22.7)	43 (31.4)	6 (31.6)
COPD	86 (18.7)	20 (26.7)	16 (21.0)	13 (17.1)	15 (20.0)	18 (13.1)	4 (21.0)

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; CS, clinical stage; ECOG, Eastern Cooperative Oncology Group; HTN, hypertension; PTB, pulmonary tuberculosis; SD, standard deviation; T2D, type 2 diabetes.
[a]Two patients had "Unknown" stage.

TABLE 2 | Treatment patterns.

Treatment, *n* (%)	Overall *N* = 755	CS IA *N* = 106	CS IB *N* = 125	CS IIA *N* = 135	CS IIB *N* = 129	CS IIIA *N* = 217	CS IIIB *N* = 41
Surgery	626 (82.9)	101 (95.3)	118 (94.4)	119 (88.1)	108 (83.7)	168 (77.4)	11 (26.8)
Surgery only	245 (39.1)	80 (79.2)	68 (57.6)	32 (26.9)	32 (29.6)	31 (18.5)	2 (18.2)
NT	159 (21.1)	8 (7.5)	11 (8.8)	21 (15.6)	26 (20.2)	71 (32.7)	21 (51.2)
ST	103 (64.8)	4 (50.0)	10 (90.9)	16 (76.2)	20 (76.9)	45 (63.4)	8 (38.1)
RT	3 (1.9)	3 (37.5)	0	0	0	0	0
ST + RT	53 (33.3)	1 (12.5)	1 (9.1)	5 (23.8)	6 (23.1)	26 (36.6)	13 (61.9)
AT	386 (51.1)	20 (18.9)	47 (37.6)	85 (63.0)	74 (57.4)	138 (63.6)	21 (51.2)
ST	268 (69.4)	15 (75.0)	37 (78.7)	77 (90.6)	57 (77.0)	69 (50.0)	12 (57.1)
RT	23 (6.0)	3 (15.0)	5 (10.6)	1 (1.2)	5 (6.8)	8 (5.8)	1 (4.8)
ST + RT	95 (24.6)	2 (10.0)	5 (10.6)	7 (8.2)	12 (16.2)	61 (44.2)	8 (38.1)
NT + AT	44 (5.8)	2 (1.9)	1 (0.8)	6 (4.4)	5 (3.9)	27 (12.4)	3 (7.3)

Abbreviations: AT, adjuvant therapy; CS, clinical stage; NT, neoadjuvant therapy; RT, radiotherapy; ST, systemic therapy.

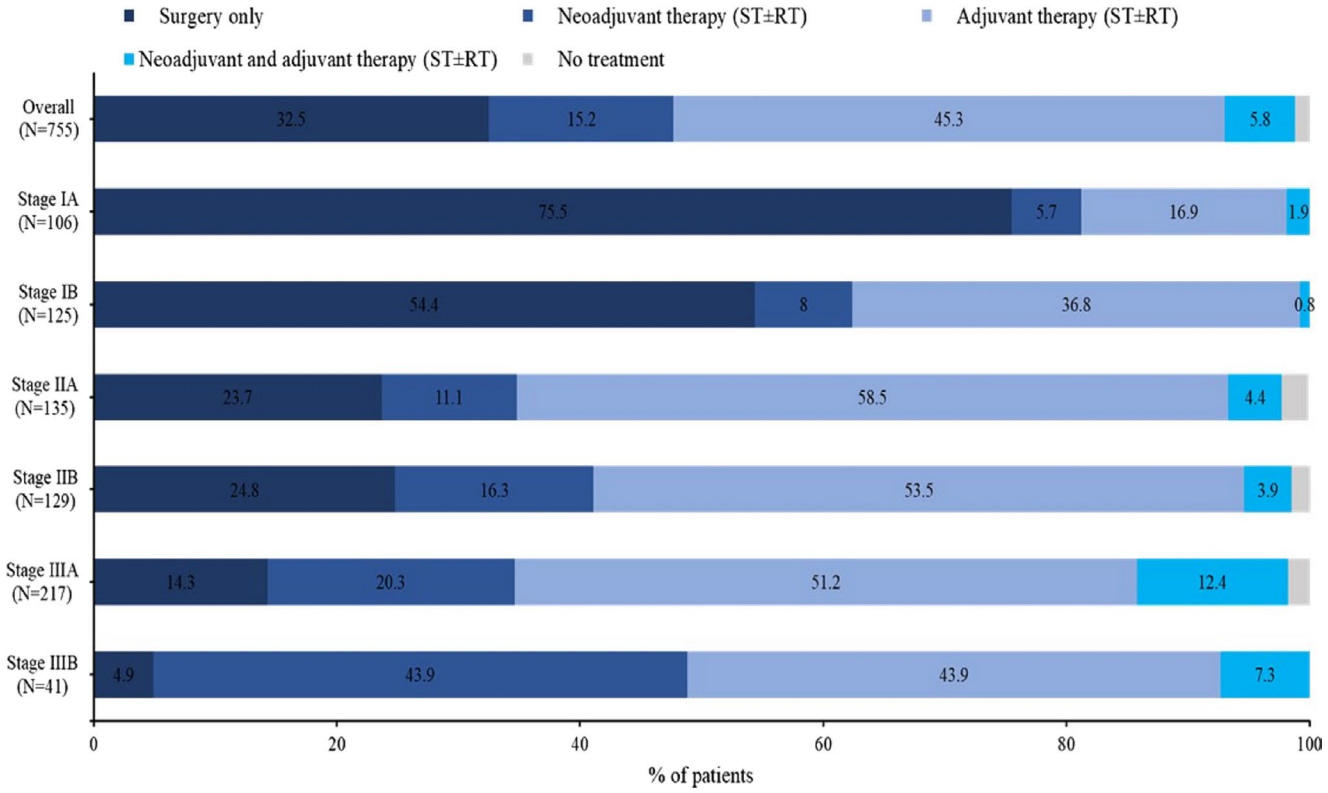

FIGURE 2 | Treatment patterns. RT, radiotherapy; ST, systemic therapy.

6.7 [4.2–NE]) with a 3-year survival rate of 79.1% (74.1%–84.4%). Patients with CS III disease had a median OS of 6.0 (4.8–NE) years (CS IIIA: 6.2 [5.0–NE]; CS IIIB: 3.7 [1.8–NE]) with a 3-year survival rate of 66.7% (60.7%–73.2%). Regardless of disease stage, the median OS was 7.4 [6.7–NE] years for patients who received surgery and 7.5 (7.0–NE) years for those who received adjuvant ST, while the median OS for patients receiving any RT was 4.5 (3.6–NE) years in the adjuvant setting and 6.2 (3.9–NE) years in the neoadjuvant settings (Table 4, Figure S4).

4.4 | Molecular Testing Patterns, EGFR Mutation and PD-L1 Expression

About one-fourth of patients (24.2% $n = 183$) underwent testing for *EGFR* mutation and 5.8% ($n = 44$) for PD-L1 expression at the local laboratory (Table 5). Of the patients tested, 28.4% (52/183) were found to harbor *EGFR* mutations. The proportion of patients with *EGFR* mutations was equally distributed, with 30.1% ($n = 19$) in CS I (CS IA: 11; CS IB: 8), 25% ($n = 14$)

TABLE 3 | Treatment compliance.

	Neoadjuvant therapy							Adjuvant therapy						
	Overall	**CS IA**	**CS IB**	**CS IIA**	**CS IIB**	**CS IIIA**	**CS IIIB**	**Overall**	**CS IA**	**CS IB**	**CS IIA**	**CS IIB**	**CS IIIA**	**CS IIIB**
	***N* = 159**	***N* = 8**	***N* = 11**	***N* = 21**	***N* = 26**	***N* = 71**	***N* = 21**	***N* = 386**	***N* = 20**	***N* = 47**	***N* = 85**	***N* = 74**	***N* = 138**	***N* = 21**
Systemic therapy														
N (%)	156 (98.1)	5 (62.5)	11 (100)	21 (100)	26 (100)	71 (100)	21 (100)	363 (94.0)	17 (85.0)	42 (89.3)	84 (98.8)	69 (93.2)	130 (94.2)	20 (95.2)
DoT (days), mean (SD)	70.0 (0–2244)	48.0 (1–50)	42 (0–170)	70.0 (0–2244)	74.5 (0–233)	70.0 (0–794)	77.0 (1–487)	71.0 (0–2613)	77.0 (0–1515)	71.0 (0–1117)	75.0 (0–1180)	70.0 (0–2613)	70.0 (0–1279)	83.0 (0–1889)
Completed treatment, *n* (%)	144 (90.6)	5 (62.5)	11 (100)	20 (95.2)	23 (88.5)	63 (88.7)	21 (100)	317 (82.1)	17 (85.0)	36 (76.6)	73 (85.9)	59 (79.7)	114 (82.6)	17 (81.0)
Reasons for discontinuation														
Toxicity	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)	0 (0.0)	26 (6.7)	0 (0.0)	3 (6.4)	6 (7.1)	5 (6.8)	11 (8.0)	1 (4.8)
Disease progression	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	0 (0.0)	7 (1.8)	0 (0.0)	2 (4.3)	1 (1.2)	0 (0.0)	2 (1.4)	2 (9.5)
Physician decision	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (1.4)	0 (0.0)	5 (1.3)	0 (0.0)	0 (0.0)	3 (3.5)	2 (2.7)	0 (0.0)	0 (0.0)
Patient refusal	4 (2.5)	0 (0.0)	0 (0.0)	1 (4.8)	2 (7.7)	1 (1.4)	0 (0.0)	7 (1.8)	0 (0.0)	1 (2.1)	0 (0.0)	3 (4.1)	3 (2.2)	0 (0.0)
Unknown	4 (2.5)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	24 (6.2)	3 (15.0)	5 (10.6)	2 (2.4)	5 (6.8)	8 (5.8)	1 (4.8)
Radiotherapy														
N	56 (35.2)	4 (50.0)	1 (0.9)	5 (23.8)	6 (23.1)	26 (36.6)	13 (61.9)	118 (30.6)	5 (25.0)	10 (21.3)	8 (9.4)	17 (23.0)	69 (50.0)	9 (42.9)
Duration of treatment (days), mean (SD)	43.0 (0.0, 416.0)	17.0 (9.3, 28.0)	416.0 (416.0, 416.0)	54.0 (37.0, 405.0)	26.5 (0.0, 52.0)	43.5 (2.0, 168.0)	40.0 (2.0, 58.0)	42.0 (0.0, 3695.0)	43.0 (34.0, 44.0)	43.0 (1.0, 92.0)	41.5 (0.0, 261.0)	41.0 (2.0, 50.0)	41.0 (1.0, 3695.0)	47.0 (22.0, 53.0)
Dose (Gy), mean (SD)	25.2 (43.3)	40.1 (25.6)	2.0 (NA)	21.2 (27.3)	18.4 (27.7)	22.6 (41.1)	31.6 (68.7)	45.2 (56.9)	91.6 (101.3)	73.0 (76.0)	28.0 (27.7)	42.0 (48.4)	44.5 (55.6)	14.1 (19.3)
Completed treatment, *n* (%)	53 (33.3)	3 (37.5)	1 (9.1)	5 (23.8)	4 (15.4)	26 (36.6)	13 (61.9)	108 (28.0)	5 (25.0)	9 (19.1)	8 (9.4)	14 (18.9)	64 (46.4)	8 (38.1)

Abbreviations: CS, clinical stage; DoT, duration of therapy; RT, radiotherapy; SD, standard deviation; ST, systemic therapy.

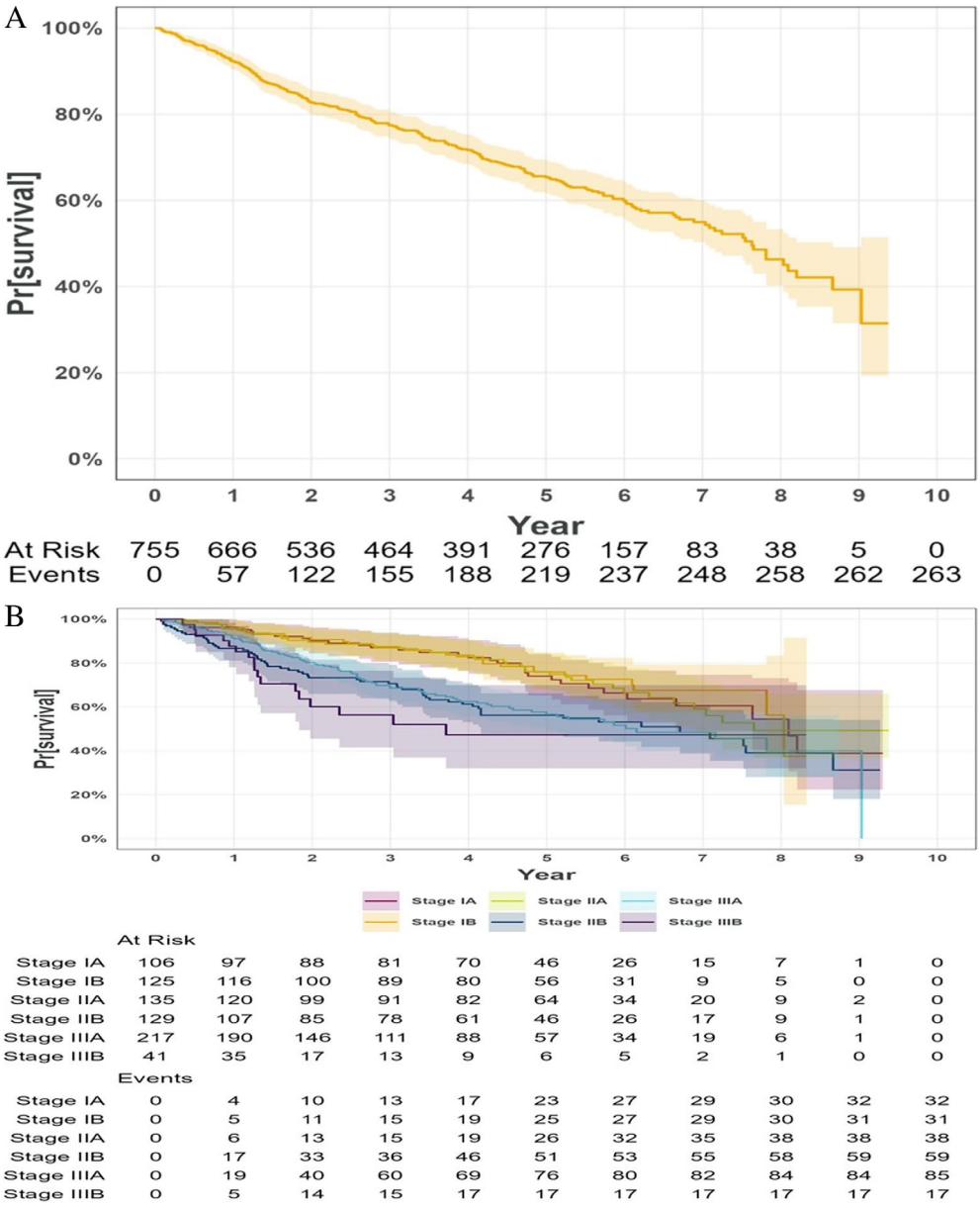

FIGURE 3 | (A) KM curve for overall survival. (A) Kaplan–Meier survival curves for overall survival for all patients. mOS for the entire cohort was 7.6 (95% CI: 7.0–8.7) years. (B) KM curve for overall survival by stage. (B) Kaplan–Meier survival curves for overall survival by disease stage. Kaplan–Meier survival curves for CS IA (maroon), CS IB (orange), CS IIA (yellow), CS IIB (indigo), CS IIIA (blue), CS IIIB (purple). mOS (95% CI) for CS IA, 8.1 (6.7–NE) years; CS IB, 8.0 (7.8–NE) years; CS IIA, 7.7 (6.9–NE); CS IIB, 6.7 (4.2–NE); CS IIIA, 6.2 (5.0–NE); CS IIIB, 3.7 (1.8–NE). CI, confidence interval; mOS, median overall survival; NE, not estimable.

in CS II (CS IIA: 8; CS IIB: 6), and 29.7% ($n = 19$) in CS III (CS IIIA: 17; CS IIIB: 2). Of 44 patients who underwent PD-L1 testing, 23 (52.3%) were found to have tumors with PD-L1 expression ≥ 1%, of whom 8 patients (34.8%) had PD-L1 ≥ 50%. The most used antibodies for PD-L1 testing were DAKO22C3 (22/44 [50%]) and Ventana SP263 (10/44 [22.7%]). Other genetic alterations (*AKT1, ALK, BRAF, HER2, KRAS, MEK1, MET, ROS1, PI3KCA, RET, KIF5B*, and *NTRK*) were found in 5.0% of patients (38/755). However, the total number of patients tested for each genetic alteration was not available. The most frequent genetic alterations were *KRAS* (18/755) and *ALK* (11/755) (Table S3).

4.5 | Correlation Analysis

No correlation between age or stage of disease and OS was found. There was a weak negative correlation (correlation coefficient of −0.07) between OS and ECOG status, indicating that patients with higher ECOG scores (worse performance status) had slightly worse survival outcomes than those with lower ECOG scores. A weak negative correlation (correlation coefficient of −0.12) was also found between *EGFR* mutation status and OS. There was a moderate positive correlation (correlation coefficient of 0.32) between OS and disease recurrence, indicating that patients who experienced disease

TABLE 4 | Overall and 3-year survival.

Survival			mOS (95% CI), years	3-year rate (%)
Stage	Overall ($N=755$)		7.5 (6.7–NE)	77.4 (74.3–80.6)
	CS I ($N=231$)		8.1 (7.6–NE)	86.9 (82.5–91.6)
	CS IA ($N=106$)		8.1 (6.7–NE)	87.0 (80.6–93.8)
	CS IB ($N=125$)		8.0 (7.8–NE)	86.9 (80.9–93.3)
	CS II ($N=264$)		7.2 (6.6–NE)	79.1 (74.1–84.4)
	CS IIA ($N=135$)		7.7 (6.9–NE)	87.5 (81.8–93.7)
	CS IIB ($N=129$)		6.7 (4.2–NE)	70.6 (63.0–79.2)
	CS III ($N=258$)		6.0 (4.8–NE)	66.7% (60.7–73.2)
	CS IIIA ($N=217$)		6.2 (5.0–NE)	68.5 (62.2–75.6)
	CS IIIB ($N=41$)		3.7 (1.8–NE)	56.3 (41.5–76.5)
Treatment patterns	Surgery ($N=626$)		7.4 (6.7–NE)	—
	Neoadjuvant therapy ($N=159$)	ST ($n=156$)	NE (6.2–NE)	
		RT ($n=56$)	6.2 (3.9–NE)	
	Adjuvant therapy ($N=386$)	ST ($n=363$)	7.5 (7.0–NE)	
		RT ($n=118$)	4.5 (3.6–NE)	
	Neoadjuvant + Adjuvant ($N=44$)	ST ($n=36$)	NA (6.2–NE)	
		RT ($n=2$)	NE	

Abbreviations: CI, confidence interval; mOS, median overall survival; NE, not estimable.

TABLE 5 | EGFR mutation and PD-L1 expression rate.

	Overall ($N=755$)	CS IA ($N=106$)	CS IB ($N=125$)	CS IIA ($N=135$)	CS IIB ($N=129$)	CS IIIA ($N=217$)	CS IIIB ($N=41$)
EGFR mutations, *n* (%)							
Tested	183 (24.2)	34 (32.1)	29 (23.2)	31 (23.0)	25 (19.4)	49 (22.6)	15 (36.6)
Positive	52 (28.4.1)	11 (32.4)	8 (27.6)	8 (25.8)	6 (24.0)	17 (34.7)	2 (13.3)
PD-L1, *n* (%)							
Tested	44 (5.8)	4 (3.8)	6 (4.8)	10 (7.4)	3 (2.3)	17 (7.8)	4 (9.8)
Positive	23 (52.3)	1 (25.0)	5 (83.3)	6 (60.0)	0 (0.0)	9 (52.9)	2 (50.0)
≥ 1% to < 50%	8 (34.8)	0 (0.0)	2 (40.0)	3 (50.0)	0 (0.0)	3 (33.3)	0 (0,0)
≥ 50%	8 (34.8)	1 (100)	1 (20.0)	1 (16.7)	0 (0.0)	5 (55.6)	0 (0.0)
Unknown	7 (30.4)	0 (0.0)	2 (40.0)	2 (33.3)	0 (0.0)	1 (11.1)	2 (100)

recurrence had worse survival outcomes (Table 6). Overall, the correlations observed were weak, indicating that none of the factors above had a strong impact on OS in patients with early-stage NSCLC. In the multivariable regression model adjusted for potential confounders and risk factors, the hazard of death was increased with age (HR: 1.03; 95% CI: 1.02–1.04, $p < 0.001$). Disease stage at index date was strongly associated with poorer OS, reaching a two-fold increase in the hazards of death in patients with CS IIIA (HR 1.91 [95% CI: 1.26–2.92, $p < 0.003$]) and CS IIIB (HR 2.73 [95% CI: 1.47–5.08, $p = 0.001$]) disease (Table 7).

5 | Discussion

The treatment landscape of early-stage resectable NSCLC is dynamic and constantly evolving. To the best of our knowledge, this retrospective real-world study of stage IA to IIIB

TABLE 6 | Correlation analyses for overall survival.

Positive correlation	
Parameter	**Overall *R***
Age (< 60 years)	0.09
Stage (IA, IB, IIA, IIB, IIIA, IIIB)	0.04
PD-L1 status (≥ 50%)	0.08
Disease recurrence	0.32
Negative correlation	
Parameter	**Overall *R***
EGFR mutation status (positive/negative)	−0.12
Lymph node metastasis Status (N0, N1, N2, N3)	−0.05
ECOG status	−0.07

Note: Correlation coefficient (R) represents: +1.0: Perfect positive (+) association; +0.8 to 1.0: very strong + association; +0.6 to 0.8: strong + association; +0.4 to 0.6: moderate + association; +0.2 to 0.4: weak + association; 0.0 to +0.2: very weak + or no association. 0.0 to −0.2: very weak negative (−) or no association; −0.2 to – 0.4: weak–association; −0.4 to −0.6: moderate–association; −0.6 to −0.8: strong–association; −0.8 to −1.0: very strong–association; −1.0 perfect negative association.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed cell-death ligand 1.

patients with NSCLC is the first of its kind to be conducted in several countries from the non-US, non-European regions. Our data provide insights into the treatment approaches and the survival outcomes for this patient population between 2013 and 2020 before the approval of (neo)adjuvant targeted therapy and (neo)adjuvant immunotherapy. The baseline characteristics were consistent with those reported for patients with NSCLC in previously published real-world studies [27, 29–31]. At the index date, 14.0% of patients were at CS IA while more patients presented with CS IB to IIIA disease (CS IB: 16.6%; CS IIA: 17.9%; CS IIB: 17.1%; CS IIIA: 28.7%); only 5.4% of the patients were at CS IIIB. The distribution of patients across the initial treatment types by disease stage reported in this study aligns with other recent retrospective dataset analyses in the US, Canada, and Europe [13, 27, 29, 32]. Surgery was common in CS I with two-thirds of the patients receiving surgery alone (64.1%; CS IA: 79.2%; CS IB: 57.6%) while only about a quarter of the patients in CS II (24.2%; CS IIA: 26.9%; CS IIB: 29.6%) and < 15% of patients in CS III (12.8%; CS IIIA: 18.5%; CS IIIB: 18.2%) received curative surgery. This trend is consistent with the selection of patients for surgical resection according to lymph node involvement status, which is usually absent in CS I to IIA [19, 33, 34]. Other studies have also reported 68% to 79% of CS I NSCLC patients receiving curative surgery while the proportions drop to between 10.3% and 17.5% in CS III patients [32].

Within the surgically resected population, adjuvant ST +/− RT was most commonly used in CS II and III, and neoadjuvant ST was most commonly used in CS III, possibly to shrink the tumor before surgery. Overall, 68.7% of patients received ST, 48.1% in the adjuvant setting, and 20.7% in the neoadjuvant setting. Adjuvant ST +/− RT was the primary treatment modality for patients with CS II (56.1%; CS IIA: 58.5%; CS IIB: 53.5%) and CS III (50.0%; CS IIIA: 51.2%; CS IIIB: 43.9%) disease, which is consistent with guideline recommendations at the time of the study [32, 33, 35, 36]. The use of ST was higher in our study than that reported in comparable populations (24.2% and 28.3%) [32, 37–39]. However, although the use of adjuvant ST in stage II and III patients was high in this study, it was used in only about half of the patients despite guideline recommendations, which may be due to the modest survival advantage offered by ST in the pre-immunotherapy era, thus demonstrating a need for more effective treatments. For patients with CS IIIA or IIIB NSCLC, concurrent RT is a recommended standard of care [31, 33]. Only about a quarter of the patients received RT, which was comparable with that reported in similar real-world populations (17%–37%) [31, 40]. The use of targeted therapies (11.2%) and immunotherapy (4.6%) was limited in accordance with the study having been conducted before the introduction of targeted therapies and immunotherapies as the standard of care for patients with NSCLC [32, 33, 35, 36]. Understanding historical real-world treatment patterns in this population is important in the context of the recent introduction of targeted therapies and immunotherapies for managing early-stage disease.

Median OS was 7.5 years and decreased with increasing stage (CS I, 8.1 years; CS II, 7.2 years; CS III, 6.0 years) highlighting the unmet need for improved therapeutic approaches in the later stages of the disease. Other studies on comparable populations have reported median OS varying from 7 to 4 years for patients with CS I disease and from 3 to 2.5 years for patients with CS II disease, which are shorter than that recorded in our study [13, 31, 40–43]. Even among patients with CS III disease (CS IIIA, 6.2 years; CS IIIB, 3.7 years), we reported longer median OS from diagnosis than that reported in recent studies from Spain, Sweden, and Portugal (CS IIIA, 1.5 to 3 years; CS IIIB, 2.5 to 1 year) [31, 40, 44]. The 3-year survival rate as recorded in this study was 77.4% and declined with advancing stages (CS I: 86.9; CS II: 79.1%; CS III: 66.7%). However, the 3-year survival rates were higher than that reported in similar populations, which ranged from 70% in CS I to 50% in CS III [13, 31, 40–43].

Across all disease stages, OS outcomes were high in patients who received surgery, either alone (7.4 years) or with adjuvant ST (7.5 years). This likely reflects the larger number of patients at earlier stages of disease receiving treatment. Many trials before and during the period of this study have investigated the effects of adjuvant ST in resectable NSCLC [45–48]. The addition of adjuvant systemic CT after surgery for patients with resectable NSCLC improved survival, irrespective of whether systemic CT was adjuvant to surgery alone or adjuvant to surgery plus RT [45–48]. However, the use of ST is impacted by socioeconomic disparities and other barriers that warrant additional study to ensure all patients have equal access to new treatment options that are expected to further improve survival [32, 49]. We assessed the OS rates at predefined landmark time points for surgery only, neoadjuvant therapy, adjuvant therapy, and a combination of neoadjuvant and adjuvant therapies. In our study, OS was found to be negatively associated with age, and higher disease stage at the index date had lower survival. Similar results with lower survival have been reported by another study from central and eastern Europe in patients with early-stage NSCLC who were older and had more advanced tumor stage at diagnosis [50]. We also explored the correlation between the

TABLE 7 | Cox proportional hazard analyses for overall survival.

Dependent variable OS (months)	X	All	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
Age	Mean (SD)	61.8 (10.4)	1.03 (1.02–1.04)	$p<0.001$	1.03 (1.02–1.04)	$p<0.001$
CS	IA	106 (14.0)	—		—	
	IB	125 (16.6)	0.86 (0.52–1.41)	$p=0.546$	0.95 (0.57–1.57)	$p=0.831$
	IIA	135 (17.9)	0.98 (0.61–1.57)	$p=0.939$	1.15 (0.71–1.86)	$p=0.570$
	IIB	129 (17.1)	1.83 (1.19–2.82)	$p=0.006$	1.99 (1.28–3.11)	$p=0.002$
	IIIA	217 (28.7)	1.72 (1.14–2.58)	$p=0.009$	1.91 (1.26–2.92)	$p=0.003$
	IIIB	41 (5.4)	2.32 (1.29–4.19)	$p=0.005$	2.73 (1.47–5.08)	$p=0.001$
	Unknown	2 (0.3)	1.49 (0.20–10.94)	$p=0.696$	7.07 (0.93–53.90)	$p=0.059$
ECOG PS	0	169 (22.4)	—		—	
	1	267 (35.4)	1.49 (1.06–2.10)	$p=0.022$	1.23 (0.86–1.75)	$p=0.259$
	2–4	37 (4.9)	1.58 (0.87–2.86)	$p=0.131$	1.14 (0.61–2.13)	$p=0.675$
	Unknown	282 (37.4)	1.36 (0.97–1.91)	$p=0.074$	1.36 (0.96–1.93)	$p=0.087$
Disease progression	False	424 (56.2)	—		—	
	True	331 (43.8)	2.52 (1.96–3.25)	$p<0.001$	2.31 (1.77–3.02)	$p<0.001$
EGFR-mutation	Negative	128 (17.2)	—		—	
	Positive	52 (7.0)	0.93 (0.57–1.51)	$p=0.767$	0.87 (0.53–1.45)	$p=0.599$
	Not tested	563 (75.8)	0.80 (0.59–1.09)	$p=0.152$	0.98 (0.71–1.37)	$p=0.922$
PD-L1 expression	Negative (< 1%)	21 (2.8)	—		—	
	Positive	23 (3.0)	0.59 (0.23–1.52)	$p=0.275$	0.69 (0.26–1.79)	$p=0.442$
	Not tested	567 (75.1)	0.72 (0.39–1.32)	$p=0.291$	1.12 (0.59–2.11)	$p=0.738$
	Unknown	144 (19.1)	0.45 (0.23–0.87)	$p=0.018$	0.68 (0.33–1.41)	$p=0.306$

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell-death ligand 1.

factors influencing survival rates, such as patient characteristics, tumor characteristics, and treatment modalities, and found a weak negative correlation between *EGFR* mutation status and OS ($R=-0.12$). Further analyses are required to explore the impact of associated factors on the survival rates of patients with NSCLC in the real world.

The current NCCN guidelines recommend upfront testing for molecular biomarkers before initiating targeted therapy and immunotherapy for NSCLC [20]. In the present study, *EGFR* mutation-positive status was tested in a small proportion of patients (24.2%) of whom about a third were found to be positive (28.4%) with the highest prevalence observed in CS IA (32.4%). The data concur with other retrospective studies on early-stage IB to IIIA NSCLC patients that report an *EGFR* mutation rate of 30%–35% [24,51,52]. It has been hypothesized that *EGFR* mutation is an early event that plays a significant role in the pathogenesis of NSCLC. Since *EGFR* mutations are significantly associated with female sex, non-smoker, and adenocarcinoma subtypes, the considerable number of *EGFRm+* individuals among those tested in our study could be due to the inclusion of more female patients and non-smokers [53]. The ADAURA trial has demonstrated improved OS rate with the EGFR tyrosine kinase inhibitor osimertinib as adjuvant therapy in patients with completely resected CS IB to IIIA NSCLC harboring *EGFR exon-19* deletions or *exon-21 L858R* mutations compared with placebo (5-year OS rate: 88% versus 78%; hazard ratio: 0.20; 95% CI: 0.14 to 0.30; $p<0.001$) [54]. Osimertinib is recommended as an adjuvant therapy option for eligible patients with R0 CS IB-IIIA and CS IIIB (only T3, N2) *EGFR* mutation-positive NSCLC who have previously received adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy [23]. However, the low testing rate in our study precluded proper estimation of the *EGFR* mutation status in this population. PD-L1 expression was tested in only 44 patients, of whom more than half (52.3%) were found positive, with 34.8% having PD-L1 ≥ 50%. Although studies have reported that PD-L1 overexpression indicated poor patient prognosis, the extremely low testing rate in our study population prevents proper estimation of patient prognosis based on PD-L1 status [55,56]. The NSCLC treatment landscape has evolved rapidly since the period of this study. While historically, surgery followed by adjuvant therapy was the standard of care, neoadjuvant and perioperative approaches are becoming more prevalent based on the encouraging results from multiple phase 3 trials [10]. Neoadjuvant nivolumab plus CT was approved for the treatment of patients with stage IB to IIIA NSCLC

based on the results of the CHECKMATE-816 trial [18,19,57]. Both perioperative durvalumab and pembrolizumab with neoadjuvant CT significantly improved survival and patient response versus neoadjuvant CT alone in patients with resectable, early-stage NSCLC in patients with resectable NSCLC [16,17,58]. The NSCLC treatment landscape in the adjuvant setting has also evolved dramatically with the advent of novel immunotherapies and targeted therapies [13,21,57,59,60]. Thus, clinical decision-making requires a multidisciplinary team approach and incorporation of biomarker testing in diagnostic algorithms to offer the best therapy and improve patient outcomes. Our study highlights a lack of biomarker testing in the real-world setting during the study period, potentially impacting treatment decisions based on current evidence. Furthermore, multispecialty collaboration, widely recognized as the optimal approach to diagnostic and treatment decisions in NSCLC, is now more crucial than ever for this patient population. Rapid advances in novel treatments have created significant knowledge gaps necessitating an examination of the factors that optimize their utilization.

This study provides insights into historical treatment patterns for early-stage NSCLC and identifies areas for improving the implementation of current treatment guidelines for better patient outcomes. The data, spanning diverse racial, socioeconomic, and ethnic populations, is broadly applicable. Additionally, the results highlight unmet needs for biomarker testing to include novel treatment options in the treatment strategies and better use of systemic chemotherapy in the adjuvant setting.

The limitations of this study are mostly related to the retrospective design of the study. Since data collection was limited to the availability of existing health records, resulting in missing data, many patients could have been lost to routine clinical follow-up. Additionally, real-world data on progression-free survival, the time from the completion of neoadjuvant therapy to surgery or from surgery to initiating adjuvant therapy, were not collected. Lastly, the results presented for *EGFR* mutation and PD-L1 positivity may not be representative of actual prevalence rates in early-stage NSCLC, as they were collected as part of routine clinical practice and reported only for patients who were tested.

6 | Conclusion

This retrospective, population-based, real-world cohort study provides insights into treatment patterns and outcomes for patients with early-stage resectable NSCLC in the period before the availability of newer therapies. Although adjuvant therapy was used in > 50% as per guideline recommendations, median OS was highest in patients receiving adjuvant ST, while the use of neoadjuvant therapy remained low. Biomarker testing was also limited with < 25% tested for *EGFR* and < 10% for PD-L1. With the recent approvals of newer neoadjuvant and adjuvant (targeted and immunotherapy) agents and emerging data, a multidisciplinary approach is essential to improve biomarker testing and facilitate biomarker-directed treatment selection for better prognosis of early-stage NSCLC. The real-world data may provide a baseline to evaluate the impact of immune checkpoint inhibitors and tyrosine kinase inhibitors as they are incorporated into routine clinical practice.

Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published. All authors were involved in data collection, conceptualization, and drafting of the manuscript. All authors provided significant intellectual input and reviewed, edited, and approved the final draft of the manuscript.

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Ethics Statement

The study protocol (NCT04808050) was approved by the independent ethics committees/institutional review boards of all participating centers before the enrollment of study participants. Written informed consent was obtained from all patients (or next of kin/legal representatives) before data collection.

Conflicts of Interest

K.P. reports grants or contracts from Janssen, Aurigene, and Roche outside the submitted work. R.M. reports travel and meeting support from MSD, BMS, AstraZeneca, Roche, and Novartis. JSFN reports participation in an advisory board for Takeda and leadership or fiduciary role (in other board, society, committee, or advocacy group, paid or unpaid) in The Hong Kong SBRT Study Group. F.G., E.M., P.K., and F.S. are employees of AstraZeneca. The other authors declare no conflicts of interest.

Data Availability Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.