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Treatment patterns and survival trends among patients with advanced-stage non-small cell lung cancer in Pakistan: a cancer registry-based flexible parametric analysis

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Abstract

This study aimed to describe trends in survival by treatment modality in advanced-stage (III-IV) non-small cell lung cancer (NSCLC) patients. A retrospective observational study was conducted. Patients diagnosed with primary NSCLC stage III-IV were included from the Cancer Registry of the Aga Khan University Hospital, Karachi, Pakistan. A flexible parametric (Royston-Parmar) model was used to estimate survival trends by treatment modality, sex, and age group. Overall, 663 patients were included; 489 (73.76%) were males. Eighty-one (12.22%) received 'radiotherapy only', 217 (32.73%) 'systemic therapy only', 136 (20.51%) 'systemic therapy with radiotherapy', 34 (5.13%) underwent 'surgery $\pm$ additional treatment', and 195 (29.41%) did not receive any treatment. Overall, predicted survival increased across all treatment modalities from 2011 to 2019, including the 'no treatment' group. In stage III disease, the absolute change in 1- and 2-year survival was most pronounced in the 'radiotherapy only' group, at 25.71% and 20.62%, respectively. In stage IV disease, the absolute change in 1-year survival was largest in the 'no treatment' group (24.44%) and in 2-year survival in the 'surgery $\pm$ additional treatment' group (33.46%). For 'surgery $\pm$ additional treatment' in stage III disease, patients aged >60 years had significantly lower odds of receiving surgery [odds ratio (OR) 0.25, 95% confidence interval (CI) 0.09-0.70, $p=0.008$]. Among stage IV patients, those diagnosed in 2017-2019 had significantly lower odds of receiving 'radiotherapy only' (OR 0.46, 95% CI 0.23-0.92, $p=0.027$), while squamous cell carcinoma histology was associated with significantly higher odds of receiving 'radiotherapy only' (OR 2.23, 95% CI 1.06-4.71, $p=0.036$). In conclusion, survival improved across all treatment modalities, including among untreated patients. Survival differences across modalities, including with surgical resection and combined therapy, most likely reflect selection of patients with more favorable prognostic profiles. Therefore, these findings should be interpreted as real-world treatment patterns and associated survival trends rather than evidence of comparative treatment efficacy.

Key words: non-small cell lung cancer, advanced stage, treatment pattern, survival trend, flexible parametric model.

Introduction

Lung cancer is the second most commonly diagnosed malignancy and the leading cause of cancer-associated mortality worldwide [1]. In 2022, lung cancer accounted for approximately 2.5 million incident cases and 1.8 million deaths [2], with incidence rates showing a strong link with the Human Development Index (HDI) [3]. About 85% of all lung cancers are histologically 'non-small cell lung cancer (NSCLC)' [4].

Due to the lack of a population-based cancer registry in Pakistan, a reliable epidemiological landscape for lung cancer is missing [5]. However, according to a GLOBOCAN 2022 statistical report, lung cancer ranks 3rd in the list of leading cancers in Pakistan. In 2022, lung cancer was responsible for 9,464 incident cases, both sexes combined, comprising approximately 5.1% of the overall incidence of cancer. Seven percent of deaths (by cancer site) were attributable to lung cancer during the same year, in Pakistan [6].

In most of the cases, lung cancer is diagnosed at advanced stages [5]. Historically, chemotherapy has been described as the mainstay of treatment for most patients with advanced-stage NSCLC [7]. This pattern is especially relevant to Pakistan, where access to molecular testing, targeted therapy, and immunotherapy remains limited due to constraints in diagnostic infrastructure, drug availability, and affordability [5]. Curative surgery has a limited role in advanced-stage lung cancer. Radiotherapy may be curative for stage III disease, when comorbidities preclude surgical resection, or serve as symptomatic disease control in stage IV disease (metastasis) [5].

Given the frequent occurrence of advanced-stage diagnosis, it is important to describe survival patterns associated with the treatment modalities used in real-world clinical practice. Such data can help contextualize current treatment approaches and highlight gaps in care, particularly in resource-limited settings. To the best of our knowledge, there is currently no evidence from Pakistan describing survival patterns across the various treatment modalities used for advanced-stage primary NSCLC. The objectives of this retrospective study were to: (1) describe trends in treatment modality among patients with advanced-stage (III-IV) primary NSCLC; (2) describe survival outcomes by treatment modality using a flexible parametric (Royston-Parmar) model; and (3) identify predictors of receiving 'radiotherapy only' or 'surgery ± additional treatment'.

Materials and Methods

Ethics statement

Before commencing the study, a research protocol was submitted for exemption and ethical approval was obtained from the Ethical Review Committee of The Aga Khan University, Karachi, Pakistan (Reference # 2024-10764-31703). Informed consent was waived owing to retrospective nature of the research study. The study was performed in agreement with the Declaration of Helsinki.

Study design and setting

A retrospective observational research study was performed at the Aga Khan University Hospital (Main Campus), Karachi, Pakistan. The Aga Khan University Hospital is one of the largest not-for-profit tertiary care hospitals based in Karachi, Pakistan. The hospital caters patients from all over Pakistan; however, a sizable number of patients come from the metropolis (Karachi). The hospital has well-established oncology department with all the required expertise (highly skilled medical oncologists, radiation oncologists, hematologists, nurses, and technicians) and equipment (radiology, laboratory, and blood bank) to assist in cancer diagnosis and management [8].

Study patients

The study included adult patients (≥ 18 years) diagnosed with advanced-stage (III-IV) primary NSCLC from 2011 to 2019. The data was retrieved from Cancer Registry of the Aga Khan University Hospital, Karachi, Pakistan [9]. Based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), advanced-stage (III-IV) primary NSCLC patients with following codes were included: C34.0 (malignant neoplasm of main bronchus), C34.1 (malignant neoplasm upper lobe, bronchus or lung), C34.2 (malignant neoplasm of middle lobe, bronchus or lung), C34.3 (malignant neoplasm of lower lobe, bronchus or lung), C34.8 (overlapping malignant lesion of bronchus or lung), and C34.9 (malignant neoplasm of bronchus or lung unspecified). For tumor histology/behavior, International Classification of Diseases for Oncology (ICD-O-3) coding was used. Histology of the NSCLC was grouped as adenocarcinoma, squamous cell carcinoma, and other/rare/not otherwise specified (NOS). For the purpose of tumor node metastasis (TNM) staging, 7th Edition of American Joint Committee on Cancer (AJCC) was used from 2011 till 2017, while 8th Edition of AJCC TNM for NSCLC data from 2018 and 2019. Patients were omitted from the dataset if

1) diagnosis was based on autopsy or death certificate, 2) survival time (years) could not be determined, and 3) incomplete data. Overall survival (years) was defined as the time from diagnosis to death or last contact at the hospital, whichever came first.

Treatment modalities

Treatment modalities were organized as: 1) 'no treatment' for patients who remain untreated, 2) 'radiotherapy only' for patients receiving only radiotherapy, 3) 'systemic therapy only' for patients who received chemotherapy and also included patients who received targeted therapy or immunotherapy due to lack of distinct treatment documentation in the registry, 4) 'systemic therapy with radiotherapy' group combined patients receiving chemotherapy, targeted therapy, or immunotherapy along with radiotherapy (concurrent/sequential), and 5) 'surgery ± additional treatment' encompassed surgical resection (sublobar resection, lobectomy, pneumonectomy) with possible adjuvant or neoadjuvant chemotherapy/radiotherapy.

Multidisciplinary decision-making

During the study period, multidisciplinary decision-making formed part of the clinical pathway for patients with NSCLC at our institution. Cases requiring multidisciplinary input, particularly those with potentially resectable or locally advanced disease where treatment selection and sequencing were complex, were discussed at the institutional multidisciplinary tumor board. Treatment recommendations were individualized according to disease stage, resectability, performance status, comorbidities, and available diagnostic information, with consideration of the appropriate sequencing of surgery, systemic therapy, and radiotherapy. However, tumor board participation and the rationale for individual treatment recommendations were not systematically captured in the Cancer Registry.

Statistical analysis

Data management was conducted in Microsoft Excel for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA). After converting raw data into usable format, data was imported into Stata/MP 17.0. All the statistical analyses were performed using Stata/MP 17.0 (Stata Corporation, College Station, TX, USA). Descriptive characteristics of patients diagnosed with advanced-stage primary NSCLC from 2011 to 2019, stratified by treatment modalities, were reported. Chi-Square (χ^2) or Fisher's Exact test, as appropriate, was executed to determine the differences in characteristics among treatment groups. Change in treatment modality between

2011 and 2019 was examined separately for stage III and stage IV disease using multinomial logistic regression, with treatment modality as the outcome, year of diagnosis (continuous) as the predictor, and 'no treatment' as the reference category. A joint Wald test was used to assess the overall trend across treatment categories. Penalized (Firth) logistic regression analysis was performed to determine the factors associated with odds of receiving 'radiotherapy only' or 'surgery $\pm$ additional treatment'. Firth's method was chosen over conventional logistic regression given the small number of 'radiotherapy only' and 'surgery $\pm$ additional treatment' cases and limited representation within certain subgroups, which may otherwise produce biased estimates. The results were shown as odds ratio (OR) with 95% confidence interval (95% CI). For the aforementioned analysis, treatment groups were reorganized as 'radiotherapy only' versus other treatments (reference group) and 'surgery $\pm$ additional treatment' versus other treatments (reference group). Penalized logistic regression was restricted to 'radiotherapy only' and 'surgery $\pm$ additional treatment', as these represent distinct clinical decision points where variation in receipt reflects selection factors of interest such as resectability and performance status.

A flexible parametric (Royston-Parmar) model was utilized to estimate the survival trends by treatment modality, sex, and age group [10,11]. In comparison with conventional survival models such as Cox proportional hazards regression model, flexible parametric model assumes that the risk of an event (or survival pattern) changes over time and therefore it uses a piecewise approach to capture those changing survival trends [12]. We fitted the flexible parametric model using the *stpm2* command suitable for Stata package [11]. The survival model included a prespecified set of covariates selected on clinical and prognostic grounds rather than statistical significance: sex, age at diagnosis, year of diagnosis, tobacco use, tumor histology, and treatment modality. Year of diagnosis and treatment modality were modeled with time-varying effects (i.e., non-proportional hazards). Staging was addressed by conducting separate analyses for stage III and stage IV disease. All covariates were retained regardless of statistical significance, consistent with their plausible prognostic relevance in advanced-stage NSCLC. We also performed sensitivity analysis to optimize degrees of freedom and thereby number of knots based on lowest Akaike Information Criterion (AIC) value [13]. Due to small sample size and relatively shorter median survival time in the study population, only trends in 1- and 2-year survival rates were estimated by treatment modalities, sex, and age group. Stata commands used for *stpm2*, predicting trends in 1- and 2-year survival rate by treatment

modality, sex, and age group, absolute change in survival, and sensitivity analysis to number of knots are detailed in *Supplementary Material*.

Results

Characteristics of patients with advanced-stage primary NSCLC

In the present study, we identified 663 advanced-stage primary NSCLC patients (*Supplementary Figure 1*). Majority were males (n=489, 73.76%). Mean age at diagnosis was 62.14 ± 12.67 years. Tobacco use (current/past) was prevalent amongst 60.48% (n=401) patients. Adenocarcinoma was the most common histological subtype of NSCLC i.e., 55.20% (n=366) of all NSCLC patients. Overall, 81 (12.22%) received 'radiotherapy only', 217 (32.73%) 'systemic therapy only', 136 (20.51%) 'systemic therapy with radiotherapy', 34 (5.13%) underwent 'surgery $\pm$ additional treatment', and 195 (29.41%) did not receive any treatment. Table 1 presents the demographic and clinical characteristics of patients diagnosed with advanced-stage primary NSCLC between 2011 and 2019.

Characteristics of advanced-stage primary NSCLC patients by treatment modality

Table 2 demonstrates the demographic and clinical characteristics of primary NSCLC stage III patients based on treatment modality. Age at diagnosis differed significantly across treatment groups ($p < 0.001$): younger patients (≤ 60 years) were more likely to receive 'surgery $\pm$ additional treatment' (68.42%) or 'systemic therapy with radiotherapy' (50.00%), whereas older patients (> 60 years) predominantly received 'radiotherapy only' (85.71%) or 'no treatment' (82.50%). Histology also varied significantly by treatment modality ($p = 0.011$): adenocarcinoma was most common among patients receiving 'systemic therapy only' (52.94%) and 'surgery $\pm$ additional treatment' (52.63%), while squamous cell carcinoma predominated among those receiving 'radiotherapy only' (71.43%) and 'no treatment' (52.50%). No significant differences were observed by sex, period of diagnosis, tobacco use, alcohol use, or survival status across treatment groups.

For stage IV patients (Table 3), age at diagnosis differed significantly across treatment groups ($p = 0.004$), with younger patients (≤ 60 years) more frequently receiving 'surgery $\pm$ additional treatment' (53.33%) or 'systemic therapy with radiotherapy' (52.83%), while older patients (> 60 years) had higher proportion of 'no treatment' (69.03%) or 'radiotherapy only' (64.18%). Histology differed significantly by treatment modality ($p < 0.001$). Adenocarcinoma was the predominant histological subtype among patients who received 'systemic therapy with

radiotherapy' (70.75%) and 'systemic therapy only' (70.49%). In contrast, patients who received 'no treatment' had a comparatively higher proportion of other/rare/NOS histology (39.35%), while those who received 'radiotherapy only' had a comparatively higher proportion of squamous cell carcinoma (32.84%). No significant differences were observed across treatment modalities for sex, period of diagnosis, tobacco use, alcohol use, or survival status.

Trends of treatments in advanced-stage primary NSCLC patients

The change in treatment modality trends between 2011 and 2019 among stage III patients was assessed (*Supplementary Table 1*). The overall trend across treatment modalities was not statistically significant (overall p for trend = 0.149). However, when trends were assessed individually for each modality, the proportion of patients receiving 'radiotherapy only' declined significantly over the study period (from 23.81% in 2011 to 6.25% in 2017; p trend = 0.010). No other treatment modality showed a statistically significant individual trend.

Supplementary Table 2 presents treatment modality trends among stage IV patients from 2011 to 2019. While the omnibus trend test across all five modalities did not reach statistical significance ($p=0.077$), modality-specific analysis revealed a notable exception: use of radiotherapy alone fell steadily over the study period, from 17.39% of patients in 2011 to 12.82% in 2019 ($p=0.017$). Trends for the remaining treatment modalities did not reach statistical significance over the study period.

Trends in survival rate by treatment modalities, sex, and age group

Trends in 1- and 2-year survival by treatment modality among patients with stage III NSCLC from 2011 to 2019 are shown in Figure 1. Overall, predicted survival increased across all treatment modalities from 2011 to 2019, including the 'no treatment' group. The absolute change in 1-year survival was most pronounced in the 'radiotherapy only' group (25.71%), followed by 'systemic therapy only' group (10.11%). A similar pattern was observed for 2-year survival, with the largest absolute change in the 'radiotherapy only' (20.62%) and 'surgery ± additional treatment' (19.57%) groups. *Supplementary Table 3* shows the absolute change in 1- and 2-year survival from 2011 to 2019 by treatment modality for stage III disease.

Among patients with stage IV NSCLC, predicted survival also improved across all treatment groups between 2011 and 2019, including those who received no treatment (Figure 2; *Supplementary Table 4*). The absolute change in 1-year survival was largest in the 'no treatment' group (24.44%), followed by 'surgery ± additional treatment' (19.71%). For 2-year

survival, the largest absolute change was observed in the 'surgery $\pm$ additional treatment' group (33.46%), followed by the 'no treatment' group (26.35%), 'systemic therapy with radiotherapy' (21.81%), and 'systemic therapy only' (20.21%).

Supplementary Figure 4 depicts trends in 1- and 2-year survival by sex and age group from 2011 to 2019 for patients with stage III NSCLC. Survival improved only among patients aged >60 years, regardless of sex: 1-year survival rose by 14.16% in males and 2-year survival rose by 12.99% in females and 12.00% in males. In contrast, survival declined among patients aged $\leq$ 60 years for both sexes, with the largest drop seen in 2-year survival among females (-10.24%, based on 2012-2019 data, as no cases were diagnosed in this subgroup in 2011). *Supplementary Table 5* presents the absolute change in 1- and 2-year survival from 2011 to 2019 by sex and age group for stage III disease.

For patients with stage IV NSCLC, survival improved across all sex and age subgroups between 2011 and 2019, though the extent of improvement varied considerably (*Supplementary Figure 3*; *Supplementary Table 6*). Males aged >60 years experienced the greatest gains, with 1-year survival rising by 28.51% and 2-year survival by 30.88%. A similar pattern was seen in males aged $\leq$ 60 years (17.87% and 21.02% for 1- and 2-year survival, respectively). Improvements among females were modest by comparison: 8.24% ($\leq$ 60 years), 4.33% (>60 years), 10.90% ($\leq$ 60 years), and 8.99% (>60 years).

Predictors of 'radiotherapy only' and 'surgery $\pm$ additional treatment'

Predictors of receiving 'radiotherapy only' or 'surgery $\pm$ additional treatment' were assessed separately for stage III and stage IV disease (*Supplementary Tables 7-10*). Among stage III patients, no factors were significantly associated with receiving 'radiotherapy only', although patients aged >60 years showed a non-significant trend toward higher odds (OR 3.00, 95% CI 0.73-12.43, $p=0.129$). For 'surgery $\pm$ additional treatment' in stage III disease, patients aged >60 years had significantly lower odds of receiving surgery compared with those $\leq$ 60 years (OR 0.25, 95% CI 0.09-0.70, $p=0.008$). Among stage IV patients, those diagnosed in 2017-2019 had significantly lower odds of receiving 'radiotherapy only' (OR 0.46, 95% CI 0.23-0.92, $p=0.027$), while squamous cell carcinoma histology was associated with significantly higher odds of receiving 'radiotherapy only' (OR 2.23, 95% CI 1.06-4.71, $p=0.036$). No significant predictors of 'surgery $\pm$ additional treatment' were identified among stage IV patients.

Discussion

In this retrospective cancer registry-based research study on patients with advanced-stage (III-IV) primary NSCLC, we did not observe a significant change in the pattern of treatment modality use from 2011 to 2019 in either stage III or stage IV disease. However, specific modality-level shifts were noted: the use of 'radiotherapy only' declined over the study period in both stage III and stage IV disease. Survival improved across all treatment modalities, including the 'no treatment' group, over the study period in both stages, though the magnitude and pattern of improvement varied: 'radiotherapy only' showed the greatest absolute gains in stage III disease, while 'surgery ± additional treatment' and 'no treatment' showed the largest gains in stage IV disease. Survival trends by age and sex were similarly heterogeneous, with more consistent improvement among patients aged >60 years. Interestingly, age >60 years was associated with significantly lower odds of receiving 'surgery ± additional treatment' in stage III disease.

Radiotherapy is administered for NSCLC management across all stages, both with curative and palliative intent [14]. The recent guideline by American Society for Radiation Oncology (ASTRO) recommends that stage III NSCLC patients unfit for a concurrent chemoradiotherapy must be managed by either sequential chemotherapy followed by radiotherapy or by dose-adjusted or hypofractionated radiotherapy alone [15]. On the other hand, in stage IV disease its role is predominantly palliative or directed toward selected sites of disease [16]. In the present study, 'radiotherapy only' showed improved survival from 2011 to 2019 in both stage III and stage IV disease. Notably, in stage III disease, the absolute improvement in 1- and 2-year survival was greatest for the 'radiotherapy only' group compared with other treatment modalities, whereas in stage IV disease, the survival gains were the lowest among the treatment groups. Changes over time in patient selection, staging, radiotherapy techniques, supportive care, and referral patterns may have contributed to the observed survival trends. Therefore, the improvement in survival with radiotherapy alone should be interpreted cautiously and does not establish improved efficacy of radiotherapy over time.

The decline in use of 'radiotherapy only' was observed in both stage III and stage IV disease, and in stage IV disease this decline was also reflected in our predictor analysis, where patients diagnosed in 2017-2019 had significantly lower odds of receiving 'radiotherapy only' compared with 2011-2013 (OR 0.46, 95% CI 0.23-0.92, $p=0.027$). This trend could be reflective of a transition toward multimodal disease management and increasing use of systemic treatments. However, several alternative explanations cannot be excluded such as

shifts in referral patterns (e.g., patients with better performance status being preferentially referred for systemic therapy), evolving stage composition, or simply improved access to systemic agents over time could each independently produce this pattern. During the latter part of the study period, immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab, atezolizumab) were becoming available in Pakistan, but their use was likely limited by cost and access. Therefore, we cannot attribute the decline in 'radiotherapy only' use, or the survival gains in systemic therapy groups, specifically to targeted therapy or immunotherapy uptake, as we lack individual-level data on molecular testing or drug receipt to support this explanation.

Consolidation durvalumab following definitive chemoradiotherapy became a standard treatment for eligible patients with unresectable stage III NSCLC following the PACIFIC trial [17]. More recently, osimertinib following chemoradiotherapy has emerged as a treatment option for unresectable EGFR-mutated stage III NSCLC based on the LAURA trial [18]. However, these developments are unlikely to explain most of the survival improvement observed in our 2011-2019 cohort, particularly because molecular data and individual systemic treatment details were unavailable. Radiotherapy alone remains clinically relevant for patients who are unsuitable for combined modality treatment because of performance status, comorbidity, frailty, or other patient and treatment related factors [5]. This may explain why patients aged >60 years in our stage III cohort showed a non-significant trend toward higher odds of receiving 'radiotherapy only' (OR 3.00, 95% CI 0.73-12.43, $p=0.129$). This is consistent with its continued role for patients not fit for surgical resection or combination treatment, local disease control, and palliation [19,20]. In contrast, patients with stage IV disease showed comparatively greater survival gains in the 'systemic therapy only' and 'systemic therapy with radiotherapy' groups, which may reflect a greater relative reliance on systemic disease control, given that curative-intent local therapies such as radiotherapy or surgery play a more limited role in metastatic disease.

Nearly 30% of our cohort received no treatment at all. Several structural barriers likely contribute to this pattern in Pakistan. Financial toxicity is a well-documented driver of treatment discontinuation and non-initiation among cancer patients in low- and middle-income countries, where out-of-pocket expenditure dominates healthcare financing and can exceed patients' ability to pay even for potentially curative treatment [21]. Referral pathways for advanced-stage NSCLC in resource-limited settings are often fragmented [22]. Patients may be diagnosed at peripheral centers without timely onward referral for oncologic management,

or may receive treatment at outside facilities not captured in our institutional registry. This suggests that our 'no treatment' category may, in part, reflect incomplete capture of care received elsewhere rather than a true absence of treatment. Diagnostic and molecular testing capacity remains limited nationally, which may delay definitive diagnosis and staging [5]. These access-related factors likely explain a meaningful proportion of the untreated population, and should be considered when interpreting survival trends. The improvement in survival observed even among patients with 'no treatment' recorded in the registry suggests that the survival gains cannot be attributed mainly to changes in anti-cancer treatment. Changes in case mix, staging, supportive care, referral patterns, follow-up ascertainment, or treatment received outside our institution may also have contributed.

Survival trends by age and sex differed by stage. In stage III disease, survival marginally declined among patients aged ≤ 60 years for both sexes, while it generally improved among patients aged >60 years. In stage IV disease, survival improved across all age and sex subgroups, with the largest absolute gains observed among males aged >60 years and the smallest among females. This pattern of better outcomes among older patients is notable, as elderly patients with advanced lung cancer have previously been reported to face higher mortality risk and lower odds of receiving anti-cancer treatment, irrespective of comorbidity and performance status [23]. Females demonstrated higher overall survival than males in our cohort, consistent with a prior report that females with NSCLC tend to have better prognosis, potentially due to differences in tumor biology and a higher prevalence of driver mutations [24]. These findings may underscore the age- [23,25-27] and sex-associated [28,29] discrepancies in selection of treatments, emphasizing the importance of identifying driving factors, particularly for elderly patients who may remain undertreated owing to risk of treatment complication, multiple health issues, frailty, physician referral practices, or physician treatment preferences. We would like to emphasize that the heterogeneous survival trends by age and sex should be interpreted cautiously because the study was not designed primarily to evaluate these subgroup differences, and important potential confounders including performance status, comorbidity, molecular alterations, and treatment details were not available.

Patients who underwent surgical resection (sublobar resection, lobectomy, or pneumonectomy) with or without other modalities had the highest 1- and 2-year survival rates in our stage IV cohort. Surgical resection is not routinely indicated in metastatic NSCLC but may form part of a multimodal strategy in highly selected patients with limited metastatic

disease. Accordingly, the favorable survival observed in the small stage IV surgical subgroup likely reflects careful patient selection, typically younger, with better performance status, fewer comorbidities, and more limited disease burden, rather than a direct benefit from surgery [30-34]. According to a retrospective research study from our center, only 2.3% of the initially presented NSCLC patients were eligible and underwent curative surgical resection [35]. Rates of surgery in our cohort were low across both stages (n=19 in stage III, n=15 in stage IV), consistent with broader reports of declining surgical utilization in advanced NSCLC despite favorable outcomes in selected patients. While systemic therapies, including third-generation EGFR-tyrosine kinase inhibitors, have been shown to improve survival in molecularly selected advanced-stage NSCLC populations [36,37], we cannot confirm whether or to what extent this contributed to outcomes in our surgical subgroup. This attribution remains speculative given the absence of individual-level molecular and detailed treatment data. As this is a retrospective, none of the treatment comparisons presented here should be interpreted as evidence of a direct treatment effect; observed survival differences most likely reflect a combination of treatment selection and unmeasured prognostic factors. Given the promising prospect of multimodal disease management in carefully selected patients, comprehensive multidisciplinary assessment remains important for identifying appropriate surgical candidates among patients with stage III and IV NSCLC.

Strengths and limitations

The main strength of the present research study is that we utilized flexible parametric model to describe trends in overall survival by treatment modality, sex, and age group in patients with advanced-stage primary NSCLC. This advanced survival analysis technique can efficiently handle non-proportional hazards and capture changes in survival trajectories by estimating the time-varying effect of the treatment modality [12]. The study also provides a descriptive overview of survival patterns across treatment modalities in a real-world cohort of advanced-stage NSCLC, offering context on current treatment practices and outcomes in a resource-limited setting.

There are also limitations of this research study which need to be acknowledged and discussed. First, we relied on a retrospective dataset from the Cancer Registry which is subject to inherent biases, and we may not have been able to account for all the relevant covariates. Second, it was a single-center research study and therefore findings may not be applicable beyond the study setting. As a single-center cohort, our results cannot reliably represent national treatment

patterns or survival outcomes in Pakistan, and should be interpreted as reflective of practice at our institution. Third, information regarding Eastern Cooperative Oncology Group (ECOG) performance status, cost preferences, and choices between patients and providers were not available. Therefore, we were not able to account for its prognostic influence on survival outcomes. Fourth, the lack of molecular data was another key limitation and this omission might confound treatment selection and survival outcomes, particularly for 'systemic therapy', 'systemic therapy with radiotherapy' and 'surgery $\pm$ additional treatment' cohorts. Fifth, small sample size of patients with surgical resection precluded subgroup analysis and therefore all patients who underwent surgery were pooled together. Sixth, patients in 'systemic therapy only' and 'systemic therapy with radiotherapy' groups included patients who also received targeted therapy and immunotherapy which could partly explain the survival gains observed in these groups. Moreover, we were not able to measure treatment intent, as curative and palliative therapies may impact survival estimates contrarily. Eighth, treatment decisions for stage III and IV NSCLC patients, particularly the choice between surgery, chemoradiation, and multimodal therapy, are typically informed by multidisciplinary team discussion, and the absence of standardized documentation of this pathway in the Cancer Registry limits our ability to characterize how treatment recommendations were formulated. Finally, due to relatively shorter median survival time and sensitivity of the flexible parametric model to follow-up time, we only reported 1- and 2-year survival trend estimates.

Conclusions

To conclude, treatment modality use did not change significantly for stage III or stage IV NSCLC between 2011 and 2019, though 'radiotherapy only' use declined in both stages for reasons that could not be determined from our data. Predicted survival improved across all treatment modalities, including among untreated patients, suggesting factors beyond treatment itself may have contributed to these trends. Survival differences across modalities, including with surgical resection and combined therapy, most likely reflect selection of patients with more favorable prognostic profiles rather than a direct treatment effect. As an observational study lacking key prognostic factors, these findings should be interpreted as real-world treatment patterns and associated survival trends rather than evidence of comparative treatment efficacy.

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Online supplementary material

Supplementary Figure 1. Flow diagram for primary non-small cell lung cancer patient inclusion.

Supplementary Figure 2. Trends in 1-year and 2-year survival rate by sex and age group in patients with primary non-small cell lung cancer stage III.

Supplementary Figure 3. Trends in 1-year and 2-year survival rate by sex and age group in patients with primary non-small cell lung cancer stage IV.

Supplementary Table 1. Trends of treatment modalities in primary non-small cell lung cancer stage III patients (2011 to 2019).

Supplementary Table 2. Trends of treatment modalities in primary non-small cell lung cancer stage IV patients (2011 to 2019).

Supplementary Table 3. Absolute change in 1-year and 2-year survival from 2011 to 2019 by treatment modality in patients with primary non-small cell lung cancer stage III.

Supplementary Table 4. Absolute change in 1-year and 2-year survival from 2011 to 2019 by treatment modality in patients with primary non-small cell lung cancer stage IV.

Supplementary Table 5. Absolute change in 1-year and 2-year survival from 2011 to 2019 by sex and age group in patients with primary non-small cell lung cancer stage III.

Supplementary Table 6. Absolute change in 1-year and 2-year survival from 2011 to 2019 by sex and age group in patients with primary non-small cell lung cancer stage IV.

Supplementary Table 7. Predictors of receiving radiotherapy only for patients with primary non-small cell lung cancer stage III (2011 to 2019).

Supplementary Table 8. Predictors of receiving radiotherapy only for patients with primary non-small cell lung cancer stage IV (2011 to 2019).

Supplementary Table 9. Predictors of receiving surgery $\pm$ additional treatment for patients with primary non-small cell lung cancer stage III (2011 to 2019).

Supplementary Table 10. Predictors of receiving surgery $\pm$ additional treatment for patients with primary non-small cell lung cancer stage IV (2011 to 2019).

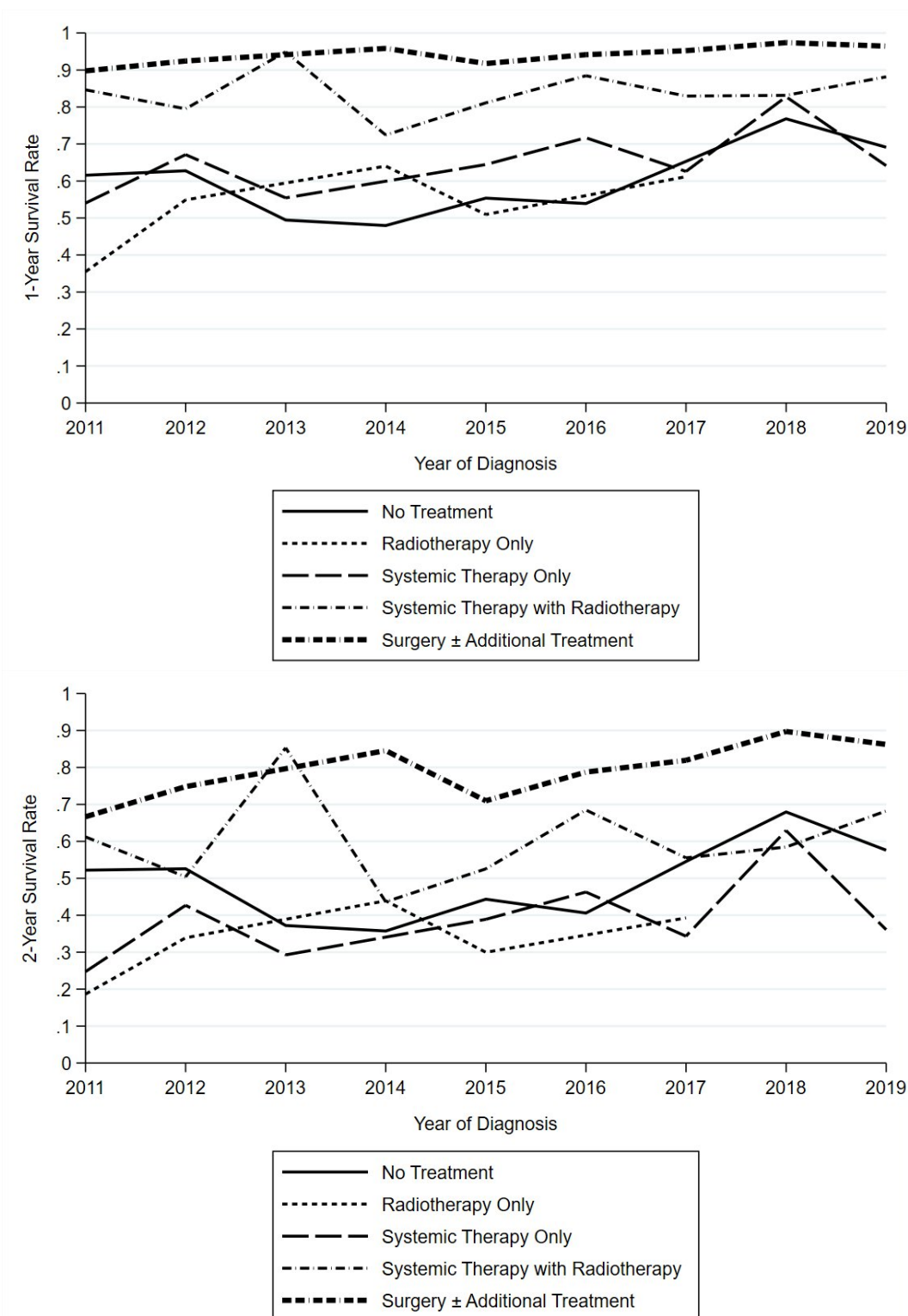


Figure 1. Trends in 1-Year and 2-year survival rate by treatment modality in patients with primary NSCLC stage III. Note: no cases were observed for 'Radiotherapy Only' in 2018 and 2019; these years are represented as gaps in the corresponding trend line.

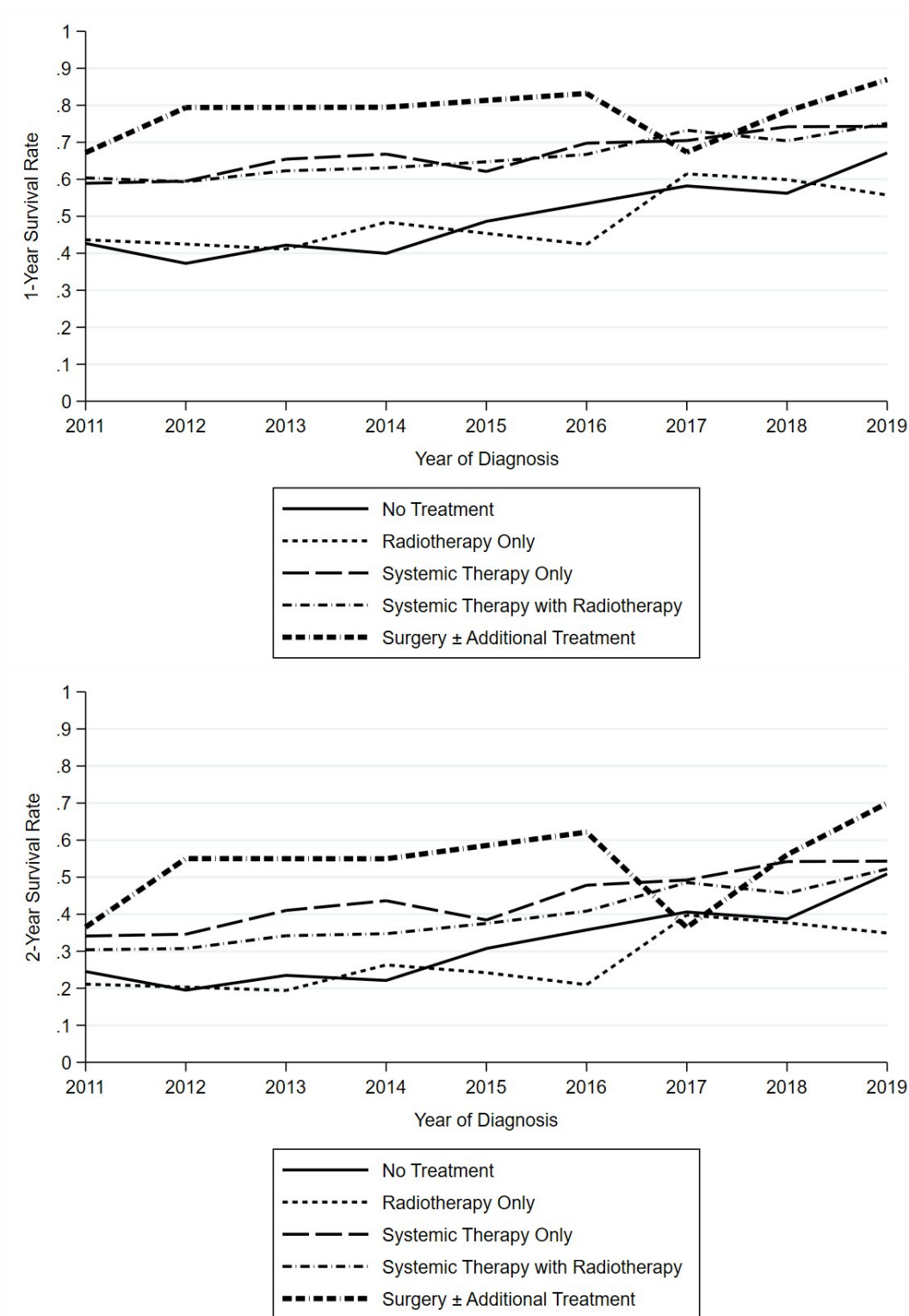


Figure 2. Trends in 1-year and 2-year survival rate by treatment modality in patients with primary NSCLC stage IV.

Table 1. Characteristics of patients diagnosed with primary non-small cell lung cancer, stratified by advanced-stage (2011 to 2019).

	Total		Stage III		Stage IV		p-value
	n=663		n=137		n=526		
	n	(%)	n	(%)			
Sex							0.001
Female	174	(26.24)	21	(15.33)	153	(29.09)	
Male	489	(73.76)	116	(84.67)	373	(70.91)	
Age at Diagnosis (Years)							0.459
≤60	270	(40.72)	52	(37.96)	218	(41.44)	
>60	393	(59.28)	85	(62.04)	308	(58.56)	
Period of Diagnosis							0.431
2011-2013	193	(29.11)	46	(33.58)	147	(27.95)	
2014-2016	235	(35.44)	45	(32.85)	190	(36.12)	
2017-2019	235	(35.44)	46	(33.58)	189	(35.93)	
Tobacco (Current/Past)							<0.001
No	262	(39.52)	33	(24.09)	229	(43.54)	
Yes	401	(60.48)	104	(75.91)	297	(56.46)	
Alcohol (Current/Past)							0.273 [†]
No	630	(95.02)	133	(97.08)	497	(94.49)	
Yes	33	(4.98)	4	(2.92)	29	(5.51)	
Histology							<0.001
Other/Rare/NOS	143	(21.57)	24	(17.52)	119	(22.62)	
Squamous Cell Carcinoma	154	(23.23)	66	(48.18)	88	(16.73)	
Adenocarcinoma	366	(55.20)	47	(34.31)	319	(60.65)	
Treatment Modalities							<0.001
No Treatment	195	(29.41)	40	(29.20)	155	(29.47)	
Radiotherapy Only	81	(12.22)	14	(10.22)	67	(12.74)	
Systemic Therapy Only	217	(32.73)	34	(24.82)	183	(34.79)	
Systemic Therapy with Radiotherapy	136	(20.51)	30	(21.90)	106	(20.15)	
Surgery ± Additional Treatment	34	(5.13)	19	(13.87)	15	(2.85)	
Event							0.030
Alive/Censored	442	(66.67)	102	(74.45)	340	(64.64)	
Died	221	(33.33)	35	(25.55)	186	(35.36)	

NSCLC, non-small cell lung cancer; NOS, not otherwise specified. [†]Fisher's Exact Test.

Table 2. Characteristics of patients with primary non-small cell lung cancer stage III, stratified by treatment modalities (2011 to 2019).

	No Treatment		Radiotherapy Only		Systemic Therapy Only		Systemic Therapy with Radiotherapy		Surgery ± Additional Treatment		p-value
	n=40		n=14		n=34		n=30		n=19		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Sex											
Female	5	(12.50)	1	(7.14)	6	(17.65)	5	(16.67)	4	(21.05)	0.818 [†]
Male	35	(87.50)	13	(92.86)	28	(82.35)	25	(83.33)	15	(78.95)	
Age at Diagnosis (Years)											
≤60	7	(17.50)	2	(14.29)	15	(44.12)	15	(50.00)	13	(68.42)	<0.001 [†]
>60	33	(82.50)	12	(85.71)	19	(55.88)	15	(50.00)	6	(31.58)	
Period of Diagnosis											
2011-2013	11	(27.50)	7	(50.00)	13	(38.24)	9	(30.00)	6	(31.58)	0.344 [†]
2014-2016	11	(27.50)	6	(42.86)	9	(26.47)	11	(36.67)	8	(42.11)	
2017-2019	18	(45.00)	1	(7.14)	12	(35.29)	10	(33.33)	5	(26.32)	
Tobacco (Current/Past)											
No	7	(17.50)	3	(21.43)	8	(23.53)	7	(23.33)	8	(42.11)	0.382 [†]
Yes	33	(82.50)	11	(78.57)	26	(76.47)	23	(76.67)	11	(57.89)	
Alcohol (Current/Past)											
No	39	(97.50)	13	(92.86)	33	(97.06)	30	(100.00)	18	(94.74)	0.602 [†]
Yes	1	(2.50)	1	(7.14)	1	(2.94)	-	-	1	(5.26)	
Histology											
Other/Rare/NOS	12	(30.00)	2	(14.29)	2	(5.88)	5	(16.67)	3	(15.79)	0.011[†]
Squamous Cell Carcinoma	21	(52.50)	10	(71.43)	14	(41.18)	15	(50.00)	6	(31.58)	
Adenocarcinoma	7	(17.50)	2	(14.29)	18	(52.94)	10	(33.33)	10	(52.63)	
Event											
Alive/Censored	31	(77.50)	10	(71.43)	23	(67.65)	24	(80.00)	14	(73.68)	0.806 [†]
Died	9	(22.50)	4	(28.57)	11	(32.35)	6	(20.00)	5	(26.32)	

NSCLC, non-small cell lung cancer; NOS, not otherwise specified. [†]Fisher's Exact Test.

Table 3. Characteristics of patients with primary non-small cell lung cancer stage IV, stratified by treatment modalities (2011 to 2019).

	No Treatment		Radiotherapy Only		Systemic Therapy Only		Systemic Therapy with Radiotherapy		Surgery ± Additional Treatment		p-value
	n=155		n=67		n=183		n=106		n=15		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Sex											
Female	44	(28.39)	15	(22.39)	60	(32.79)	31	(29.25)	3	(20.00)	0.539 [†]
Male	111	(71.61)	52	(77.61)	123	(67.21)	75	(70.75)	12	(80.00)	
Age at Diagnosis (Years)											
≤60	48	(30.97)	24	(35.82)	82	(44.81)	56	(52.83)	8	(53.33)	0.004
>60	107	(69.03)	43	(64.18)	101	(55.19)	50	(47.17)	7	(46.67)	
Period of Diagnosis											
2011-2013	38	(24.52)	25	(37.31)	48	(26.23)	31	(29.25)	5	(33.33)	0.107 [*]
2014-2016	54	(34.84)	27	(40.30)	60	(32.79)	45	(42.45)	4	(26.67)	
2017-2019	63	(40.65)	15	(22.39)	75	(40.98)	30	(28.30)	6	(40.00)	
Tobacco (Current/Past)											
No	70	(45.16)	18	(26.87)	87	(47.54)	47	(44.34)	7	(46.67)	0.061
Yes	85	(54.84)	49	(73.13)	96	(52.46)	59	(55.66)	8	(53.33)	
Alcohol (Current/Past)											
No	151	(97.42)	65	(97.01)	170	(92.90)	97	(91.51)	14	(93.33)	0.147 [†]
Yes	4	(2.58)	2	(2.99)	13	(7.10)	9	(8.49)	1	(6.67)	
Histology											
Other/Rare/NOS	61	(39.35)	14	(20.90)	26	(14.21)	13	(12.26)	5	(33.33)	<0.001[*]
Squamous Cell Carcinoma	17	(10.97)	22	(32.84)	28	(15.30)	18	(16.98)	3	(20.00)	
Adenocarcinoma	77	(49.68)	31	(46.27)	129	(70.49)	75	(70.75)	7	(46.67)	
Event											
Alive/Censored	108	(69.68)	46	(68.66)	118	(64.48)	57	(53.77)	11	(73.33)	0.093 [†]
Died	47	(30.32)	21	(31.34)	65	(35.52)	49	(46.23)	4	(26.67)	

NSCLC, non-small cell lung cancer; NOS, not otherwise specified. [†]Fisher's Exact Test. ^{*}Pearson's χ^2 reported; Fisher's exact not computable due to small cell counts.