Prior curative-intent treatment strategy affects progression outcomes of first-line immunotherapy in metastatic non-small cell lung cancer: A retrospective cohort study

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Abstract. Non-small cell lung cancer (NSCLC) represents the most prevalent histological subtype of lung malignancies, accounting for the vast majority of new diagnoses and remaining a leading cause of oncology-related mortality worldwide. Despite recent therapeutic advancements, the disease maintains a formidable clinical burden, with global incidence rates continuing to rise. Consequently, optimizing treatment sequencing and identifying predictive factors for therapy response remain critical priorities in improving long-term patient outcomes. The present study aimed to evaluate the impact of prior curative-intent treatment strategy on disease progression outcomes during first-line immunotherapy in patients with metastatic NSCLC. The present retrospective, single-center cohort study included 62 patients with advanced NSCLC who developed metastatic disease after receiving curative-intent treatment. Before metastasis, patients had been administered with either adjuvant chemotherapy or definitive chemoradiotherapy. All patients subsequently received first-line immunotherapy after developing metastatic disease. The primary endpoint was disease progression status (presence or absence) during a 24-month follow-up period. Progression-free survival (PFS) was evaluated among patients with disease progression. Results showed that during the 24-month follow-up, disease progression occurred in 33 patients (53.2%). Although not statistically significant, progression was observed more frequently in patients previously treated with adjuvant chemotherapy compared with those who had received definitive chemoradiotherapy (68.0 vs. 43.2%; P=0.055). Among the patients who developed progression, the median PFS was 7.98 months for those in the adjuvant chemotherapy group and 9.82 months for those in the definitive chemoradiotherapy group, with no statistically significant difference observed between the groups. First-line immunotherapy-related adverse events occurred at comparable rates in both groups, with the most frequent toxicities being thyroid dysfunction, pulmonary toxicity and neuropathy. In summary, compared with prior adjuvant chemotherapy, prior definitive chemoradiotherapy demonstrated a potential trend toward a lower risk of disease progression during first-line immunotherapy for metastatic NSCLC, without an associated increase in treatment-related toxicity, such as immune-related adverse events. These findings suggested that previous curative-intent treatment strategies may influence progression outcomes during subsequent immunotherapy.

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Abbreviations: NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RT, radiotherapy; OS, overall survival; PFS, progression-free survival

Key words: nivolumab, immunotherapy, NSCLC, PFS, chemoradiotherapy, immune-related adverse events

Introduction

In recent years, a number of statistical, computational and machine learning-based models have been developed in order to predict the incidence and progression of cancer, the treatment outcomes, and to support screening and prevention strategies (1). However, these models rely on predefined assumptions and may not capture the complexity of individual treatment histories and real-world clinical decision-making. By contrast, clinical protocols and observational studies provide direct evidence of treatment effectiveness and safety in routine practice (2,3). Therefore, real-world analyses complement model-based predictions, particularly when evaluating treatment sequencing and outcomes following different curative-intent strategies in heterogeneous diseases such as non-small cell lung cancer.

Non-small cell lung cancer (NSCLC) remains a significant global health challenge, representing ~85% of all lung cancer cases and serving as a leading cause of cancer-related mortality worldwide (4,5). Recent epidemiological data indicate that the prevalence of the disease continues to rise, with lung cancer accounting for more deaths than colorectal, breast and prostate

cancer combined in certain regions (4). Despite the integration of advanced diagnostic tools and novel therapies, the 5-year survival rate for patients diagnosed with advanced or metastatic stages remains at 25%. This high mortality rate underscores the clinical urgency of optimizing treatment sequencing, particularly in the management of advanced NSCLC without actionable mutations, where first-line therapy typically involves platinum-based chemotherapy or immunotherapy regimens. In the management of advanced NSCLC without actionable mutations, first-line therapy typically involves platinum-based chemotherapy regimens (6). However, the emergence of resistance to initial treatment frequently limits the efficacy of subsequent therapeutic options. Immunotherapies, such as checkpoint inhibitors, demonstrate improved survival outcomes in patients with advanced NSCLC (5). However, despite these advancements, the prognosis for patients is still uncertain, and this highlights the need for further research on the treatment approaches (4).

Nivolumab, a human IgG4 monoclonal antibody targeting programmed cell death-1 (PD-1), enhances antitumor immune responses by inhibiting the interaction between PD-1 on T-cells and its ligands expressed on tumor cells (7). This immune checkpoint blockade restores T-cell activity, enabling immune-mediated tumor destruction (8). A previous study demonstrates that nivolumab has an increased efficacy in patients with advanced NSCLC compared with docetaxel, revealing marked improvements in overall survival (OS), progression-free survival (PFS) and overall response rate (9). Despite these promising outcomes, only a subset of patients derive durable benefits from immune checkpoint inhibitors, and reliable predictive biomarkers for response remain limited. Given the heterogeneity of NSCLC and the potential for immune-related resistance or hyperprogression, additional real-world studies are required to further characterize patient subgroups, optimize treatment sequencing and improve long-term outcomes.

Radiotherapy (RT), previously regarded as a local therapy, is now recognized for its ability to produce systemic immune effects, such as the abscopal response in tumors not exposed to radiation. This growing evidence justifies the merging of RT with immune checkpoint inhibitors (10,11). Despite this, questions remain regarding the association between RT and the immune system, optimal treatment regimens and strategies to amplify systemic antitumor responses. Furthermore, the outcomes of lung cancer are still unfavorable and resistance to treatment is prevalent. The clinical management of NSCLC is significantly hindered by treatment resistance, which remains a near-universal challenge. In the setting of first-line immune checkpoint inhibitors, primary resistance is observed in 21-27% of patients, while up to 65% of initial responders eventually develop acquired resistance within 4 years. Similarly, despite high initial response rates in oncogene-driven NSCLC, acquired resistance to targeted therapies occurs in almost all cases, typically within 1 year of treatment initiation. These statistics emphasize the necessity of investigating prior treatment histories to better understand subsequent therapy outcomes (4,12). Therefore, investigating the possible advantages, long-term outcomes and safety aspects of incorporating RT with immunotherapy is key. Further understanding these mechanisms and clinical impacts may possibly improve treatment approaches and enhance outcomes for patients with advanced illness.

As immunotherapy becomes a part of treatment for metastatic NSCLC, it is important to understand how earlier treatments might influence the subsequent outcomes of the patient. Different therapies administered before the development of metastasis, such as adjuvant chemotherapy or definitive chemoradiotherapy, may affect how patients respond to and tolerate immunotherapy. In the present study, the side-effect profiles and 24-month PFS of patients who received first-line immunotherapy after either adjuvant chemotherapy or definitive chemoradiotherapy were compared. By examining these real-world data, the present study aimed to highlight the effects of treatment sequencing and support an informed decision-making for patients with metastatic NSCLC.

Materials and methods

Study design and setting. For the present retrospective, single-center, longitudinal cohort study, the follow-up of patients with advanced NSCLC was carried out. The present study was approved by the Ethics Committee of the University of Okan (Istanbul, Turkey; approval no. 187) and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants for the anonymized use of their medical records, clinical characteristics and treatment-related outcomes for scientific publication.

Patients with advanced NSCLC attending the Oncology Outpatient Clinics of Okan University Hospital (Istanbul, Türkiye) and University of Health Sciences, Sultan Abdulhamid Khan Training and Research Hospital (Istanbul, Türkiye) between December 2020 and December 2024 were included in the present study. The demographic features, chronic diseases and blood parameters of participants were recorded.

Study population. A total of 62 patients with histologically confirmed NSCLC who had received prior curative-intent treatment and subsequently developed metastatic disease were included in the present study. All patients received first-line immunotherapy when metastatic progression was identified. Before the metastatic phase, patients were treated with either adjuvant chemotherapy or definitive chemoradiotherapy.

As a retrospective observational study, the present analyses was based on routinely collected clinical data and assumed comparable clinical management and follow-up within Okan University Hospital and University of Health Sciences, Sultan Abdulhamid Khan Training and Research Hospital. Patients were included if they were: i) Aged ≥18 years; ii) had measurable disease according to RECIST v1.1 criteria (defined as a non-nodal lesion ≥10 mm in the longest diameter or a lymph node with a short axis ≥15 mm on CT or MRI); and iii) had no history of chronic organ failure. Patients were excluded if they: i) Exhibited *de novo* metastatic disease; ii) had not received any treatment before metastatic progression; iii) had a PD-L1 tumor proportion score (TPS) of <50% as determined by immunohistochemistry; or iv) were positive for driver mutations such as EGFR, anaplastic lymphoma kinase (ALK) or ROS proto-oncogene 1.

Data collection. The electronic medical records of the study population were accessed and analyzed for research purposes between December 2020 and December 2024 at Okan University Hospital and Sultan Abdulhamid Khan Training and Research Hospital. Collected variables included demographic characteristics, tumor histology, PD-L1 expression levels, prior treatment modalities (adjuvant chemotherapy or definitive chemoradiotherapy) and details of the first-line immunotherapy received by patients after they developed metastatic disease. Comorbidities were recorded as present vs. absent due to the variability in the type and number of chronic conditions affecting patients.

Outcome measurements included PFS over a 24-month follow-up period and treatment-related adverse events. The clinical assessments included the evaluation of patient demographics, ECOG performance status and detailed oncological history. Laboratory parameters specifically focused on PD-L1 TPS and routine oncology follow-up markers. During immunotherapy, patients were systematically monitored for treatment-related toxicities through clinical examination and laboratory tests, including complete blood counts and comprehensive metabolic panels. Specific assessments for immune-related adverse events, such as thyroid function tests for suspected endocrine toxicity and radiological imaging (CT scans) for pulmonary toxicity, were performed in accordance with institutional protocols.

Statistical analysis. R, an open-source software environment for statistical computing and graphics (version 4.4.3; R Development Core Team), was used for all statistical computations and model fitting. Descriptive statistics were used to summarize patient characteristics. Categorical variables are presented as frequencies and percentages, while continuous variables are reported as means ± SD. The Shapiro-Wilk test was used to assess normality. Associations between categorical variables were evaluated using the χ^2 or Fisher's exact test. For continuous variables, due to non-normal distributions, the Mann-Whitney U test was used to compare the continuous variables between independent groups. Multivariable regression analyses were not carried out due to limited sample size and risk of model overfitting. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics. An aim of the present study was to compare disease progression and safety outcomes during first-line immunotherapy between patients previously treated with adjuvant chemotherapy and those treated with definitive chemoradiotherapy. The present study included 62 patients with histologically confirmed NSCLC who had received curative-intent treatment prior to developing metastatic disease. Prior to metastatic progression, 25 patients (40.3%) had undergone adjuvant chemotherapy without radiotherapy, whereas 37 patients (59.7%) had been treated with definitive chemoradiotherapy. All patients started first-line immunotherapy when metastatic disease was diagnosed. Baseline demographic and clinical characteristics were comparable between the adjuvant chemotherapy and definitive chemoradiotherapy groups. No statistically significant differences were observed in the age, sex, smoking status, ECOG performance status, comorbidity or histological subtypes between the two treatment groups (all $P>0.05$; Table I).

Progression status. Across a 24-month follow-up period, disease progression was documented in 33 patients (53.2%). Progression was more frequent among patients who had previously received adjuvant chemotherapy alone, occurring in 17 patients (68.0%), compared with 16 patients (43.2%) in the definitive chemoradiotherapy group. Accordingly, the proportion of patients remaining progression-free was higher in the definitive chemoradiotherapy group compared with the adjuvant chemotherapy group (56.8 vs. 32.0%, respectively; Table II). This difference did not reach statistical significance using the χ^2 test, yielding a borderline result ($P=0.055$). These findings indicated a reduced likelihood of disease progression during first-line immunotherapy in patients who received prior definitive chemoradiotherapy.

PFS. PFS was evaluated among patients who had disease progression. In this subgroup, patients who received adjuvant chemotherapy prior to first-line immunotherapy had a median PFS of 7.98 months (range, 4.53-16.72) compared with 9.82 months (range, 4.17-15.74) for those who received definitive chemoradiotherapy prior to first-line immunotherapy. The mean PFS values were 8.44 and 9.43 months for patients who received adjuvant chemotherapy or definitive chemoradiotherapy prior to first-line immunotherapy, respectively. No statistically significant difference in PFS was observed between the two treatment groups ($P=0.322$; Table III). This suggested that the prior treatment strategy may have influenced the occurrence of disease progression during first-line immunotherapy but not the duration of PFS once disease progression developed.

Treatment-related adverse events. Treatment-related adverse events were detected in 13 patients (52.0%) in the adjuvant chemotherapy group and in 20 patients (54.1%) in the definitive chemoradiotherapy group, which was not significantly different ($P=0.874$; Table IV). The most frequent immune-related adverse events were pulmonary toxicity (17.7%), neuropathy (16.1%) and thyroid dysfunction (11.3%). Other adverse events, including neutropenia, febrile neutropenia and nephrotoxicity, were infrequent and occurred at similar rates in both treatment groups. No cases of hepatotoxicity, dermatologic toxicity or diarrhea were observed in either treatment group. Overall, the incidence of individual adverse events did not differ significantly between treatment groups.

Discussion

In the present study, the primary aim was to evaluate whether the prior curative-intent treatment strategy influenced progression outcomes and safety during first-line immunotherapy in metastatic NSCLC. The present study indicated a possible trend for a lower risk of disease progression in patients previously treated with definitive chemoradiotherapy compared with those who received adjuvant chemotherapy; however, this was not statistically significant. Furthermore, the results of the present study suggested that prior exposure to definitive

Table I. Baseline demographics and clinical characteristics of the cohort used in the present study (n=62).

	Curative-intent treatment group prior to first-line immunotherapy		
Variable	Adjuvant CT (n=25)	Definitive CRT (n=37)	P-value
Age, years[a]	63.1±8.4	64.5±7.6	0.672[b]
Sex, N (%)			0.074[c]
Female	7 (28.0)	3 (8.1)	
Male	18 (72.0)	34 (91.9)	
Smoking status, N (%)			0.404[d]
Non-smoker	17 (68.0)	20 (54.1)	
Smoker	8 (32.0)	17 (45.9)	
ECOG performance status, N (%)			0.573[d]
0	20 (80.0)	26 (70.3)	
1	5 (20.0)	11 (29.7)	
Comorbidity, N (%)			0.749[d]
Absent	12 (48.0)	15 (40.5)	
Present	13 (52.0)	22 (59.5)	
Histological subtype, N (%)			0.404[d]
Squamous cell carcinoma	8 (32.0)	17 (45.9)	
Adenocarcinoma	17 (68.0)	20 (54.1)	

[a]Mean ± SD. [b]Mann-Whitney U test. [c]Fisher's exact test. [d]χ^2 test. ECOG, Eastern Cooperative Oncology Group; CT, chemotherapy; CRT, chemoradiotherapy.

Table II. Disease progression status according to the different curative-intent treatment groups.

Variable	Disease progression present, n (%)	Disease progression absent, n (%)	P-value
Prior treatment group			0.055[a]
Adjuvant CT (n=25)	17 (68.0)	8 (32.0)	
Definitive CRT (n=37)	16 (43.2)	21 (56.8)	
Total patients (n=62)	33 (53.2)	29 (46.8)	-

[a]χ^2 test. CT, chemotherapy; IT, immunotherapy; CRT, chemoradiotherapy.

chemoradiotherapy may modify subsequent immunotherapy responsiveness without increasing toxicity. In the current study, all patients had a PD-L1 TPS of ≥50%, a threshold clinically defined as high PD-L1 expression. This high expression level is a key predictive biomarker for enhanced response to pembrolizumab or nivolumab monotherapy in the first-line setting. By focusing on this specific subgroup, the study aimed to minimize biomarker-driven heterogeneity and focus on the impact of prior curative treatments on immunotherapy outcomes. While this approach reduced heterogeneity and potential confounding from targeted therapies, it limited the generalizability of the present findings. In real-world practice, a notable proportion of patients with metastatic NSCLC present with lower PD-L1 expression levels or harbor driver alterations such as EGFR or ALK mutations. Therefore, the present results may only be applicable to a selected subgroup of patients (those who received first-line immunotherapy and had high PD-L1 expression levels), instead of the broader NSCLC population.

The potential trend of a lower overall progression rate in the definitive chemoradiotherapy group and the absence of a significant difference in PFS among patients who experienced disease progression suggested that prior definitive chemoradiotherapy may influence the likelihood of achieving durable disease control instead of prolonging PFS once resistance to immunotherapy develops. Within this context, previous locoregional treatment may act as a modifier of initial immunotherapy responsiveness instead of a determinant of post-progression disease kinetics.

Previous studies suggest a potential synergistic interaction between radiotherapy and immune checkpoint inhibition in metastatic NSCLC (13,14). In a real-world analysis by

Table III. PFS among patients with disease progression during IT.

Variable	Median PFS, months	Mean PFS, months	Min-max, months	P-value
Curative-intent treatment group prior to first-line IT				0.322
Adjuvant CT (n=17)	7.98	8.44	4.53-16.72	
Definitive CRT (n=16)	9.82	9.43	4.17-15.74	

PFS, progression-free survival; CT, chemotherapy; IT, immunotherapy; CRT, chemoradiotherapy.

Table IV. Immune-related adverse events according to adjuvant CT (n=25) or definitive CRT (n=37) treatment prior to first-line IT.

	Curative-intent treatment group prior to first-line IT		
Adverse event	Adjuvant CT, n (%)	Definitive CRT, n (%)	P-value
Any adverse event	13 (52.0)	20 (54.1)	0.874
Thyroid dysfunction (hypo/hyper)	3 (12.0)	5 (13.5)	>0.999
Febrile neutropenia	3 (12.0)	2 (5.4)	0.385
Neutropenia	2 (8.0)	4 (10.8)	>0.999
Nephrotoxicity	1 (4.0)	2 (5.4)	>0.999
Pulmonary toxicity	4 (16.0)	6 (16.2)	>0.999
Neuropathy	4 (16.0)	5 (13.5)	>0.999
Hepatotoxicity	0 (0.0)	0 (0.0)	-
Dermatologic toxicity	0 (0.0)	0 (0.0)	-
Diarrhea	0 (0.0)	0 (0.0)	-

CT, chemotherapy; IT, immunotherapy; CRT, chemoradiotherapy.

Li *et al* (14), the addition of radiotherapy to first-line immunotherapy was associated with a markedly prolonged PFS and OS compared with immunotherapy alone, without a notable increase in treatment-related toxicity. The aforementioned findings support the hypothesis that radiotherapy may enhance antitumor immune responses through mechanisms such as increased antigen release and modulation of the tumor microenvironment. The present results suggested a potential clinical trend, as patients with a prior history of definitive chemoradiotherapy demonstrated a lower numerical likelihood of disease progression during follow-up compared with the adjuvant chemotherapy group (43.2 vs. 68.0%, respectively). While this comparison yielded a borderline P-value (P=0.055) and did not reach the threshold for formal statistical significance, it suggests a biological rationale that prior radiotherapy may modulate subsequent immunotherapy responsiveness. However, there was a difference in the treatment sequencing between the present study and that by Li *et al* (14). In the previous study by Li *et al* (14), radiotherapy was administered concurrently or in close temporal proximity to immunotherapy; however, in the present study, radiotherapy was delivered with curative intent before the onset of metastatic disease. This difference suggests that the immunomodulatory effects of radiotherapy may persist beyond the immediate treatment period and potentially influence responses to subsequent systemic immunotherapy.

Additionally, a meta-analysis by Fiorica *et al* (15) reports that combined radiotherapy and immunotherapy improves the OS and PFS compared with either treatment alone in advanced-stage NSCLC. However, in the aforementioned meta-analysis, marked heterogeneity is observed across studies regarding radiotherapy dose, fractionation and timing relative to immunotherapy. In contrast to concurrent or planned combination approaches, the present study examined a clinical scenario that focused on the effect of prior definitive chemoradiotherapy on first-line immunotherapy outcomes in the metastatic setting. This approach reduced confounding associated with radiotherapy timing during metastatic disease and suggested that previous locoregional treatment may have a lasting immunomodulatory effect that influenced subsequent immunotherapy response.

Although not statistically significant, a higher proportion of patients remained progression-free in the definitive chemoradiotherapy group compared with the adjuvant chemotherapy group. However, PFS among patients who developed disease progression was similar between the two treatment groups. This finding differs from the results of the PACIFIC trial, which reported an improvement in the median PFS with immunotherapy following chemoradiotherapy (16). One possible explanation is that prior definitive chemoradiotherapy may lower the overall risk of progression by inducing lasting

immune activation or modifying tumor biology, instead of prolonging PFS once resistance to immunotherapy has developed. Therefore, prior chemoradiotherapy may affect the likelihood of achieving benefit from immunotherapy as opposed to the duration of benefit after progression. However, these results should be interpreted with caution, as the retrospective design and clinical heterogeneity of the present study limits causal interpretation.

The PACIFIC trial, a previous large prospective analysis investigating the impact of immune checkpoint inhibitors in patients with NSCLC previously treated with chemoradiotherapy evaluates the effect of treatment sequencing on survival outcomes (16). The aforementioned trial demonstrates that administering immunotherapy after definitive chemoradiotherapy may provide meaningful disease control and survival benefit. This supports the concept that prior locoregional treatment does not compromise, and may even enhance, subsequent immunotherapy efficacy. However, the trial focused on survival endpoints and treatment feasibility within a controlled trial framework, without comparing different types of curative-intent pretreatment (16). By contrast, the present study offered a granular comparison between patients who received adjuvant chemotherapy and those treated with definitive chemoradiotherapy before developing metastatic disease. By isolating the type of prior curative treatment as the differentiating factor, the findings of the present study suggested that definitive chemoradiotherapy may be associated with a lower probability of disease progression during first-line immunotherapy, while maintaining a comparable safety profile. This added to the existing evidence by suggesting that not all curative-intent strategies exert equivalent downstream effects on immunotherapy responsiveness in the metastatic setting (16,17).

A recent large real-world multicenter retrospective study by Li *et al* (14) evaluates treatment sequencing in unresectable stage III NSCLC. The aforementioned study reports an improved PFS and OS in patients who received neoadjuvant immunotherapy and chemotherapy before definitive chemoradiotherapy compared with those treated with chemoradiotherapy followed by adjuvant immunotherapy. Although the aforementioned study focuses on locally advanced disease and a different treatment setting, it supports the concept that treatment sequencing may influence immunotherapy outcomes. The findings of the present study extended this concept to the metastatic setting and suggested that prior definitive chemoradiotherapy given with curative intent may affect the subsequent response to first-line immunotherapy.

The CORRELATE study is a recent real-world, retrospective analysis that compares outcomes of first-line immunotherapy-based regimens in patients with metastatic NSCLC to outcomes in randomized clinical trials (18). The aforementioned study reveals that real-world OS and PFS are shorter compared with those in clinical trials, reflecting differences in patient characteristics and treatment patterns in routine practice compared with controlled settings. The aforementioned study differs from the present study as its aim is to compare real-world outcomes with clinical trial results for immunotherapy with or without chemotherapy, as opposed to investigating the impact of prior curative-intent treatment on subsequent immunotherapy effectiveness. While the previous CORRELATE study highlights the efficacy-effectiveness gap in metastatic NSCLC treated with first-line immunotherapy, the present study focused on how definitive chemoradiotherapy before metastasis may influence progression outcomes and safety during first-line immunotherapy. Taken together, this highlights the importance of real-world evidence in understanding immunotherapy performance and suggests that prior treatments and patient selection can markedly affect outcomes outside clinical trials.

Furthermore, a recent real-world propensity score-matched analysis by Kim *et al* (19) compares long-term survival outcomes of immunotherapy vs. chemotherapy in patients with metastatic NSCLC. The aforementioned study demonstrates a survival advantage for immunotherapy compared with chemotherapy in routine clinical practice, supporting the effectiveness of immune checkpoint inhibitors beyond randomized clinical trials. Unlike the present study, the study by Kim *et al* (19), focuses on treatment modality comparison in the metastatic setting and did not evaluate the impact of prior curative-intent treatments on subsequent immunotherapy outcomes. Taken together, these findings indicate the value of real-world evidence in metastatic NSCLC and suggests that both treatment selection and prior treatment history may be important factors shaping immunotherapy outcomes in routine practice.

Cancer progression and treatment responses are influenced by a number of biological mechanisms, including tumor-immune system interactions, molecular biomarkers such as tumor mutational burden and PD-L1 expression levels, and host-related factors such as patient performance status (ECOG) and nutritional health. Understanding these markers provides a biological framework for evaluating immunotherapy efficacy. In NSCLC, biomarkers such as the PD-L1 expression levels serve a role in guiding immunotherapy selection. Immune checkpoint inhibitors aim to restore antitumor immune responses by targeting inhibitory pathways. In addition, supportive factors such as nutritional status affect treatment tolerance and overall outcomes in patients with advanced cancer (8,9,20). Understanding these mechanisms may provide a biological framework for evaluating immunotherapy strategies, such as nivolumab, in different clinical settings. While these mechanisms may provide biological context, the present study was not designed to evaluate the impact of biomarkers or nutritional status on outcomes. However, future studies addressing these aspects may provide a further understanding of their potential role in optimizing immunotherapy outcomes in patients with NSCLC.

In addition, the present study period overlapped with the coronavirus disease 2019 (COVID-19) pandemic, which may have influenced the delivery of care for patients with cancer as well as outcomes worldwide. However, COVID-19-specific data, such as infection status or COVID-related mortality, were not consistently available in the present retrospective cohort and therefore could not be analyzed separately. However, as all patients were treated within the same healthcare system and during the same time frame, any pandemic-related effects were likely similar between the treatment groups. Despite this, the potential impact of the COVID-19 pandemic should be considered when interpreting the results of the present study.

The present study had a number of limitations that should be considered when interpreting the present results. The retrospective, single-center design may have

introduced selection bias and limits the generalizability of the findings. Furthermore, the small sample size may have reduced the statistical power for detecting differences in certain outcomes, particularly the differences in the PFS among patients who experienced disease progression. This prevented the use of multivariable regression analyses due to the risk of model overfitting. In addition, prior treatments were not standardized, as radiotherapy dose, treatment field size, chemotherapy regimens and number of chemotherapy cycles varied among patients and could not be adjusted for in the statistical analysis. OS was not evaluated due to limited follow-up duration and an insufficient number of mortality events at the time of analysis, which restricted the conclusions regarding long-term treatment benefit. Additionally, multivariable regression analyses were not carried out due to the limited number of patients and progression events, as such analyses could have led to model overfitting. Furthermore, treatment-related adverse events were assessed based on incidence instead of severity and detailed toxicity grading or treatment discontinuation data were not available. Molecular factors beyond the predefined criteria, such as tumor mutational burden, were not consistently available and therefore were not analyzed. As a result, the safety profile may not reflect the clinical impact of severe adverse events.

Despite these limitations, the present study has several strengths. To the best of our knowledge, this is the first study to directly compare different curative-intent treatment strategies used before metastasis and to evaluate their association with first-line immunotherapy outcomes in metastatic NSCLC. The use of first-line immunotherapy in all patients and the clear definition of treatment groups allowed for an evaluation of prior treatment effects. All participants received standard first-line monotherapy with anti-PD-1 agent, nivolumab, at conventional doses. Treatment was continued until disease progression, unacceptable toxicity or completion of the 2-year planned course. Furthermore, the assessment of treatment-related adverse events provided good evidence that previous definitive chemoradiotherapy does not increase immunotherapy-associated toxicity. Overall, the present study indicated a real-world insight into how prior treatment strategies may influence immunotherapy outcomes in the metastatic setting.

In conclusion, the present findings suggested a clinically relevant trend, in which, compared with prior adjuvant chemotherapy, prior definitive chemoradiotherapy may be associated with a lower risk of disease progression during first-line immunotherapy in patients with metastatic NSCLC, without an increase in treatment-related toxicity. Although PFS among patients who developed disease progression was similar between groups, the higher proportion of progression-free patients in the definitive chemoradiotherapy group indicated a potential long-term modulatory effect of prior radiotherapy on immunotherapy responsiveness. These results suggested the importance of considering previous curative-intent treatment strategies when interpreting immunotherapy outcomes in the metastatic setting. However, additional prospective, multicenter studies with large patient populations are needed to validate the present findings and to investigate the mechanisms underlying this association.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RC and SA conceptualized the present study. RC was responsible for the methodology. RC used the software and validated the data of the present study and conducted a formal analysis of the data. RC and DS conducted the investigation. RC, DS, AO and SA contributed to data acquisition and provision of study materials. RC and AO conducted data curation. RC prepared the original manuscript draft. RC, DS, AO and SA reviewed and edited the manuscript. RC and DS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in line with the principles of the Declaration of Helsinki. The Ethics Committee of the University of Okan (Istanbul, Turkey; approval no. 187) approved the present research. Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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