

When Brain Metastases Meet Immunotherapy: Real-World Outcomes With First-Line Pembrolizumab in PD-L1-High Metastatic NSCLC

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Submitted: 17 March 2026 Revised: 26 May 2026 Accepted: 24 June 2026 Published: 23 October 2026

Background: Although immune checkpoint inhibitors (ICI) have revolutionized the treatment landscape for patients with non-small cell lung cancer (NSCLC), the impact on brain metastases (BM) remains uncertain, as these patients have often been excluded from or underrepresented in clinical trials. The aim of this study was to investigate the association between metastatic site and response to immunotherapy.

Methods: This retrospective single-center study included 141 consecutive adults with advanced NSCLC, programmed death ligand 1 (PD-L1) tumor proportion score $\geq 50\%$, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and no activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement who received first-line pembrolizumab monotherapy between 2018 and 2022. Patients with BM received stereotactic radiosurgery or whole-brain radiotherapy before or in parallel with pembrolizumab according to multidisciplinary recommendations. Survival was analyzed using Kaplan-Meier estimates, log-rank testing, and Cox proportional hazards models. Because metastatic-site coding was available only for patients with documented distant metastases, the site-specific BM versus other metastatic site comparison was restricted to a 115-patient subset.

Results: The full cohort comprised 141 analyzable patients. In the primary metastatic-site subset ($n = 115$), 28 patients had BM and 87 had other metastatic sites without BM. In this subset, progression-free survival (PFS) was longer in the BM group than in the non-BM metastatic-site group (hazard ratio [HR] 0.42, (95% CI 0.19–0.94; $p = 0.035$)). Median PFS was not reached in the BM group (95% CI 14.0 months to not reached) and was 26.0 months (95% CI 8.0 months to not reached) in the non-BM group. Overall survival (OS) did not differ significantly (HR 0.48, 95% CI 0.21–1.09; $p = 0.080$); the median OS was not reached in the BM group (95% CI 14.0 months to not reached) and was 30.0 months (95% CI 15.0–40.0 months) in the non-BM group.

Conclusion: In this retrospective cohort, patients with BM who received pembrolizumab plus local CNS-directed radiotherapy had longer PFS than patients with other metastatic sites, but no statistically significant OS advantage. These findings should be interpreted cautiously because all BM patients received local radiotherapy and had lower extracranial metastatic burden; the observed PFS difference may reflect treatment-related confounding, selection bias, and baseline prognostic imbalance rather than intrinsic sensitivity of brain metastases to immunotherapy.

Keywords: NSCLC; brain metastases; immunotherapy; pembrolizumab

Introduction

Lung cancer is the malignancy most frequently associated with metastatic spread to the central nervous system (CNS), with nearly 40% of patients with non-small cell lung cancer (NSCLC) developing brain metastases (BM) during the course of their disease. Furthermore, up to 10% of patients present with BM at the time of initial diagnosis, prior to the initiation of systemic oncologic therapy [1]. BM represents a common and clinically challenging complication in NSCLC and are associated with poor prognosis. Standard therapeutic options remain largely pallia-

tive and include surgical resection, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or their combinations. Chemotherapy is rarely used due to limited penetration across the blood–brain barrier [2]. Despite advances in local modalities, these approaches are frequently associated with neurocognitive decline, reduced quality of life, and persistently poor survival outcomes [3].

Immune checkpoint inhibitors (ICI) have transformed the therapeutic landscape of NSCLC, improving survival in selected patient populations and shifting treatment paradigms toward biomarker-driven strategies. Nevertheless, the role of ICI in patients with active CNS disease

remains less clear, as such patients have been systematically excluded from or underrepresented in pivotal clinical trials. For example, the landmark KEYNOTE-024 trial established pembrolizumab as the standard first-line therapy for previously untreated advanced NSCLC with a high programmed death ligand 1 (PD-L1) tumor proportion score, but excluded patients with untreated BM and allowed only those with previously treated, stable disease [4]. Similarly, the OAK trial (atezolizumab vs. docetaxel) and CheckMate 227 (nivolumab plus ipilimumab) reported improved survival with immunotherapy, yet their CNS subgroups were either limited or insufficiently analyzed [5,6].

Emerging evidence suggests that immunotherapy may achieve meaningful intracranial activity in NSCLC, with response rates in BM comparable to those observed at extracranial sites [7]. Retrospective series and pooled analyses have further indicated that patients receiving a combination of local CNS-directed therapy (SRS or WBRT) and ICI may benefit from a synergistic effect, potentially explained by the abscopal phenomenon [8,9]. However, the robustness of these findings is limited by heterogeneous study designs, small sample sizes, and the absence of randomized controlled data specifically addressing this clinical scenario. Given that the immunologic microenvironment may differ across metastatic sites, organ-specific heterogeneity in immunotherapy response is biologically plausible and clinically relevant. Understanding these patterns is critical for treatment optimization and patient selection.

The aim of this study was therefore to evaluate clinical outcomes and explore the association between metastatic site and response to immunotherapy in a real-world population of patients with advanced NSCLC, with a particular focus on brain metastases.

Patients and Methods

Study Design and Setting

This retrospective, single-center study included 141 consecutive adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC who received first-line ICI monotherapy at the Clinic for Pulmonology, University Clinical Center of Serbia, between 2018 and 2022. Data were obtained from an institutional lung cancer registry, which collects demographic, clinicopathologic, molecular, treatment, and survival data for patients diagnosed and treated at the center.

Patient Population: Inclusion And Exclusion Criteria

Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Only patients with PD-L1 tumor proportion score (TPS) $\geq 50\%$ were included. PD-L1 expression was assessed on contemporaneous tumor biopsy samples using immunohistochemistry (IHC) with the Dako

22C3 pharmDx assay, interpreted by trained pathologists. Patients with tumors harboring activating epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements were excluded, in accordance with current treatment guidelines (Table 1).

Treatment and Radiologic Assessment

All patients received pembrolizumab monotherapy at a dose of 200 mg intravenously every three weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Dose modifications were not permitted, in line with the approved label. Patients with BM received local CNS-directed therapy with stereotactic radiosurgery (SRS) or WBRT prior to or in parallel with ICI initiation, according to multidisciplinary tumor board recommendations. Baseline staging included contrast-enhanced CT of the chest and abdomen and brain MRI when available, or contrast-enhanced brain CT when MRI was unavailable. Tumor assessment was performed at baseline and approximately every 9 weeks thereafter in routine clinical practice. Response was assessed according to the immune Response Evaluation Criteria in Solid Tumors (iRECIST) for systemic disease by institutional radiologists; however, no blinded central review was available. Because a dedicated neuro-oncology adjudication process was not prospectively embedded in the registry, previously irradiated brain lesions were not reassessed using a formal RANO-BM framework. Distinction among pseudoprogression, radiation necrosis, and true intracranial progression therefore relied on routine multidisciplinary clinico-radiologic assessment, and this limitation is acknowledged explicitly. Patients were stratified into two subgroups according to the presence or absence of BM at baseline, and subgroup comparisons were subsequently performed.

Progression-free survival (PFS) was defined as the time from initiation of pembrolizumab to radiologically confirmed disease progression or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Patients alive without progression at the time of analysis were censored at the date of last follow-up.

Statistical Analysis

Descriptive statistics are reported as frequencies and percentages for categorical variables and as medians with interquartile ranges (IQR) or ranges for continuous variables, as appropriate. Continuous variables were assessed for normality using the Shapiro-Wilk test. Continuous variables were compared using the Mann-Whitney U test when non-normally distributed. For categorical comparisons, Pearson's chi-square test was used when expected cell frequencies were adequate (all expected counts ≥ 5 , or no more than 20% of expected counts < 5 and none < 1). For 2×2 tables with a total sample size ≥ 40 and expected counts between 1 and < 5 , the continuity-corrected chi-square test

Table 1. Inclusion and exclusion criteria.

No.	Inclusion criteria	No.	Exclusion criteria
1	Age ≥ 18 years.	1	Age < 18 years.
2	Histologically or cytologically confirmed unresectable locally advanced or metastatic NSCLC.	2	Absence of histologic/cytologic confirmation or a diagnosis other than NSCLC.
3	PD-L1 tumor proportion score $\geq 50\%$.	3	PD-L1 tumor proportion score $< 50\%$ or unavailable.
4	ECOG performance status 0–1.	4	ECOG performance status ≥ 2 .
5	No activating EGFR mutation or ALK rearrangement.	5	Activating EGFR mutation or ALK rearrangement.
6	Pembrolizumab monotherapy as first-line systemic treatment.	6	Prior systemic therapy for advanced disease or a first-line systemic regimen other than pembrolizumab monotherapy.
7	Treatment at the study center between 2018 and 2022, with sufficient baseline, treatment, and follow-up data to determine PFS and OS.	7	Missing essential treatment or follow-up dates that prevented calculation of PFS or OS.
8	For the metastatic-site analysis: documented distant metastasis and classifiable baseline brain-metastasis status.	8	No documented distant metastases: excluded from the site-specific comparison only, but retained in the full cohort if all general criteria were met.

NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PFS, progression-free survival; OS, Overall survival.

was used. Fisher's exact test was used when a cell count was zero, an expected count was < 1 , or the total sample size was < 40 . For multi-category tables with sparse expected counts, the Fisher-Freeman-Halton exact test was used. Survival outcomes were estimated using the Kaplan-Meier method and compared with the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were derived from univariate Cox proportional hazards models with brain-metastasis status as the exposure variable. Because metastatic-site coding was only applicable in patients with documented metastases, site-specific analyses comparing BM with other metastatic sites were restricted to the 115-patient metastatic subset. Missing data were handled by complete-case analysis for the variables entered into each model; no imputation was performed. Follow-up time was calculated from treatment initiation to last contact or death, and median follow-up was estimated using the reverse Kaplan-Meier method. Patients enrolled later in the study period contributed shorter censored follow-up, while earlier-enrolled patients accounted for the longer tail of the KM curves. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA).

Results

Patient Disposition and Analysis Cohorts

A total of 141 patients with locally advanced and metastatic NSCLC treated with first-line ICI monotherapy were included in the analysis. Of these 141 patients, 115 had documented metastases, and 26 had no metastases recorded anywhere. Of them, 28 had CNS metastases, and 87 had other metastatic sites. Since the variable defining the CNS-versus-other-metastatic-site comparison was only ap-

plicable in the metastatic subset, all Kaplan-Meier figures and primary site-specific survival analyses were restricted to 115 patients (28 BM and 87 other metastatic sites). The 26 non-metastatic rows were excluded from that comparison, as shown in the flowchart (Fig. 1).

Baseline Demographic and Clinical Characteristics And Distribution of Metastatic Sites

Baseline characteristics of the 115-patient metastatic subset are summarized in Table 2. Median age and smoking status were similar between groups. The most frequent metastatic site at baseline was, lung metastases were present in 42 patients (36.5%), brain metastases in 28 (24.3%), pleural metastases in 20 (17.4%), bone metastases in 18 (15.7%), adrenal metastases in 16 (13.9%), liver metastases in 13 (11.3%), and other metastatic sites in 11 (9.6%). Because individual patients could have more than one metastatic site, these percentages do not sum to 100%. Among the 115 patients included in the metastatic-site analysis, 28 had brain metastases, and 87 had other metastatic sites without brain metastases. The brain-metastases group had less extracranial metastatic burden than the other-metastatic-sites-without-brain-metastases group, with a median of 0 extracranial involved organs (IQR 0-1) versus 1 (IQR 1-1), respectively ($p < 0.001$). Lung metastases (7.1% vs 46.0%, $p < 0.001$), liver metastases (0.0% vs 14.9%, $p = 0.036$), and pleural metastases (0.0% vs 23.0%, $p = 0.003$) were less frequent in the brain-metastases group, whereas bone metastases were similar between groups (17.9% vs 14.9%, $p = 0.944$). All patients with BM had symptomatic CNS disease, and all received corticosteroids before CNS radiotherapy.

Study Flowchart

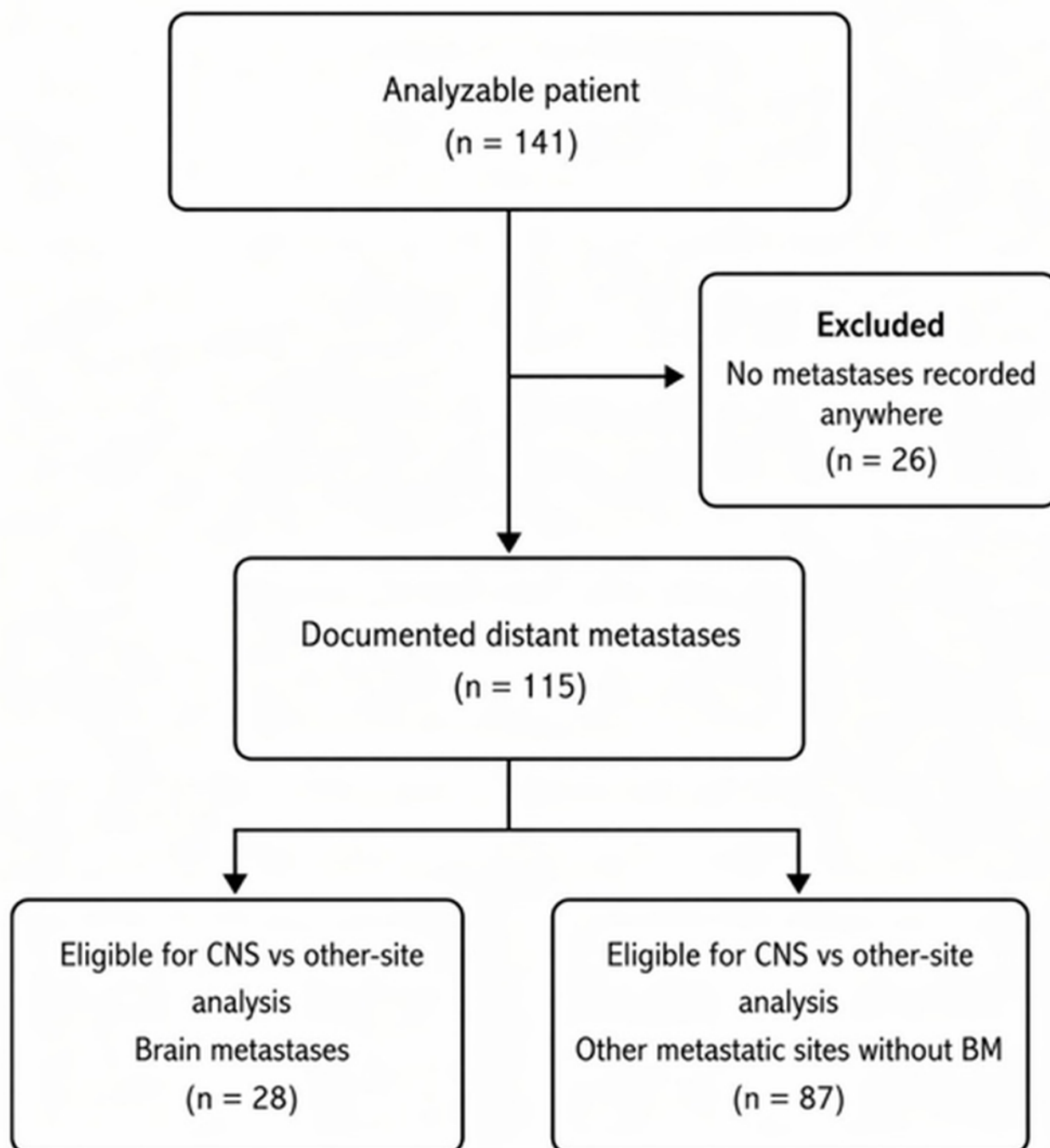


Fig. 1. Study flow diagram.

Progression-Free Survival and Overall Survival in the Metastatic-Site Subset.

In the univariate Cox model, the brain-metastases group had a lower hazard of progression or death than the other-metastatic-sites group (HR 0.42, 95% CI 0.19–0.94; $p = 0.035$). The Kaplan-Meier median PFS was not reached

in the BM group (95% CI 14.0 months to not reached) and was 26.0 months (95% CI 8.0 months to not reached) in the non-BM group (log-rank $p = 0.030$) (Fig. 2). Median follow-up was 16.0 months. The wide confidence interval around the median PFS estimate in the other-metastatic-sites group reflects limited precision and censoring over time. Later portions of the Kaplan-Meier curve should

Table 2. Baseline characteristics and demographics.

Characteristic	Overall (n = 115)	Brain metastases (n = 28)	Other metastatic sites (n = 87)	Statistic	<i>p</i> value
Age, years, median (IQR)	64.0 (58.0–68.0)	64.0 (58.5–67.5)	64.0 (58.0–68.8)	$Z = -0.216$	0.832
Sex				$\chi^2 = 1.277$	0.259
Female	47 (40.9)	14 (50.0)	33 (37.9)		
Male	68 (59.1)	14 (50.0)	54 (62.1)		
Smoking status				$\chi^2 = 2.355$	0.308
Current smoker	63 (54.8)	18 (64.3)	45 (51.7)		
Former smoker	40 (34.8)	9 (32.1)	31 (35.6)		
Never smoker	12 (10.4)	1 (3.6)	11 (12.6)		
Histology				Fisher-Freeman-Halton exact	0.036
Adenocarcinoma	78 (67.8)	20 (71.4)	58 (66.7)		
Squamous cell carcinoma	19 (16.5)	1 (3.6)	18 (20.7)		
Other histology	18 (15.7)	7 (25.0)	11 (12.6)		
Metastatic burden					
Total affected organs at baseline, median (IQR)	1 (1–1)	1 (1–2)	1 (1–1)	$Z = 0.791$	0.431
Extracranial affected organs at baseline, median (IQR)	1 (1–1)	0 (0–1)	1 (1–1)	$Z = -6.467$	<0.001
Metastatic sites					
Lung metastases	42 (36.5)	2 (7.1)	40 (46.0)	$\chi^2 = 13.779$	<0.001
Bone metastases	18 (15.7)	5 (17.9)	13 (14.9)	Continuity-corrected $\chi^2 = 0.005$	0.944
Adrenal metastases	16 (13.9)	2 (7.1)	14 (16.1)	Continuity-corrected $\chi^2 = 0.768$	0.381
Liver metastases	13 (11.3)	0 (0.0)	13 (14.9)	Fisher exact	0.036
Pleural metastases	20 (17.4)	0 (0.0)	20 (23.0)	Fisher exact	0.003
Other metastatic sites	11 (9.6)	1 (3.6)	10 (11.5)	Continuity-corrected $\chi^2 = 0.758$	0.384

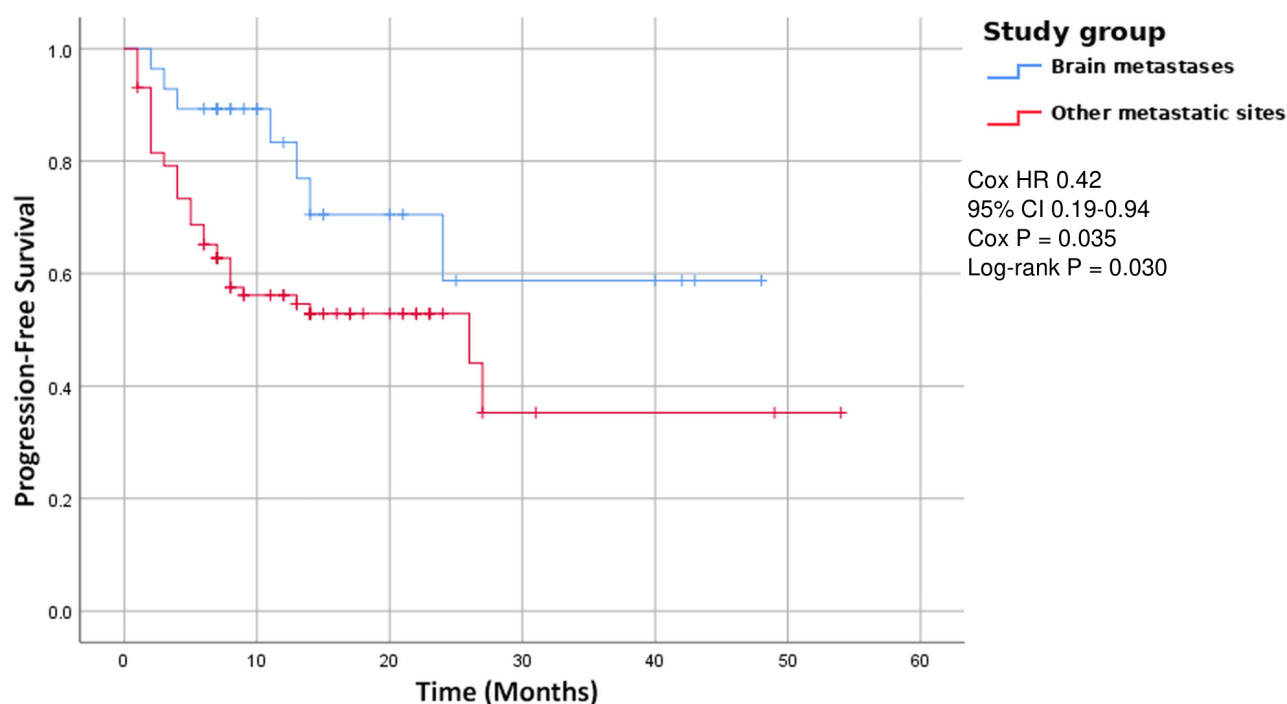
Note: Values are n (%) unless otherwise specified. Percentages are calculated within each column denominator. Pearson chi-square tests were used when expected frequencies were adequate; continuity-corrected chi-square tests were used for 2×2 tables with expected frequencies between 1 and <5; Fisher exact tests were used for zero cells or very sparse 2×2 comparisons; the Fisher-Freeman-Halton exact test was used for the histology comparison; and *Z* values are shown for Mann-Whitney U tests. Brain-metastasis status was not tested as a separate metastatic-site variable because it defined the study groups.

therefore be interpreted cautiously, as they are based on progressively smaller numbers of patients remaining at risk.

In contrast, for OS the univariate Cox model did not show a statistically significant difference between groups (HR 0.48, 95% CI 0.21–1.09; $p = 0.080$). The Kaplan-Meier median OS was not reached in the brain-metastases group (95% CI 14.0 months to not reached) and was 30.0 months (95% CI 15.0–40.0 months) in the other-metastatic-sites-without-brain-metastases group (log-rank $p = 0.074$) (Fig. 3). In the full 141-patient cohort, the association remained significant for PFS (HR 0.41, 95% CI 0.19–0.89; $p = 0.025$) but not for OS (HR 0.53, 95% CI 0.24–1.16; $p = 0.112$). Because the full cohort included 26 patients without documented distant metastases, these results were considered exploratory, while the 115-patient metastatic-site subset was used as the primary analytic population for site-specific comparisons.

Discussion

BM occur in up to one third of patients with NSCLC [10] and are associated with poor prognosis [11] due to their immunosuppressive microenvironment and limited drug penetration across the blood–brain barrier [12]. It is well known that the immunologic microenvironment of metastatic disease can vary by specific organ, with a possible impact on the response to immunotherapy, as well as prognosis [13,14,15]. Consequently, patients with BM have been largely excluded or underrepresented in pivotal ICI trials, resulting in scarce data on intracranial efficacy [16]. Nevertheless, our results demonstrated the efficacy of pembrolizumab for BM in patients with previously untreated NSCLC with high tumor PD-L1 expression. Our data suggest a PFS signal in the BM subgroup along with numerically longer overall survival, although the latter did not reach statistical significance.



No. at Risk (months)	0	10	20	30	40	50	60
Brain metastases	28	17	8	4	4	0	0
Other metastasis sites	87	39	17	3	2	1	0

Fig. 2. Kaplan-Meier analysis of progression-free survival in patients with brain metastases (blue line) and patients with other metastatic sites without brain metastases (red line).

Several mechanisms may explain this finding. All patients with BM in our cohort received local radiotherapy (SRS or WBRT) in addition to immunotherapy. Radiotherapy not only provides local control but can enhance systemic immune responses through antigen release, cross-priming of tumor-specific CD8⁺ T cells, and disruption of the blood–brain barrier, facilitating immune cell trafficking into the CNS. This interaction may generate an abscopal effect, which has been reported to have a higher frequency when RT is combined with ICIs [17,18,19,20]. The combination of radiation and immunotherapy may increase the occurrence of the abscopal effect [21,22,23,24], with rates ranging from 25% to 52% with immune checkpoint inhibitors [21,23]. Recent reviews further consolidate that combining RT with ICI enhances the durability of response via immune modulation, especially in CNS metastases [25,26,27]. For example, a recent comprehensive review on radiation immunotherapy highlighted updated mechanisms, timing strategies, and clinical experiences across cancer types, including BM settings [26].

Supporting evidence comes from Tozuka et al. [28], who demonstrated that patients with BM receiving local treatment plus ICIs had significantly longer OS and PFS

compared with those treated with ICIs alone. A similar result was observed in a retrospective study, which found that patients receiving ICIs plus brain RT tended to have longer OS compared with those receiving ICI alone, although the difference was not statistically significant ($p = 0.201$). Wu et al. [29] reported that irradiation of brain lesions induced stronger systemic immune activation compared with RT to other metastatic sites. They assumed that this may be due to the fact that the blood–brain barrier was breached by RT, thereby amplifying ICI efficacy [29]. Findings by Sumodhee et al. [30] suggest that RT may help extend the ICI benefit even after progression. Among 32 patients with advanced melanoma or NSCLC who were treated with RT at the time of progression on ICI therapy, an abscopal effect had been observed in 2 patients with almost complete response across all target lesions [30].

Recent data in NSCLC specifically also support the benefit of RT + ICI in BM. A recently published retrospective analysis showed that concurrent radiotherapy with ICI in NSCLC patients with BM was associated with improved outcomes compared with non-concurrent strategies [31,32]. Another study reported improved survival outcomes of patients with brain metastases treated with ICI + RT versus

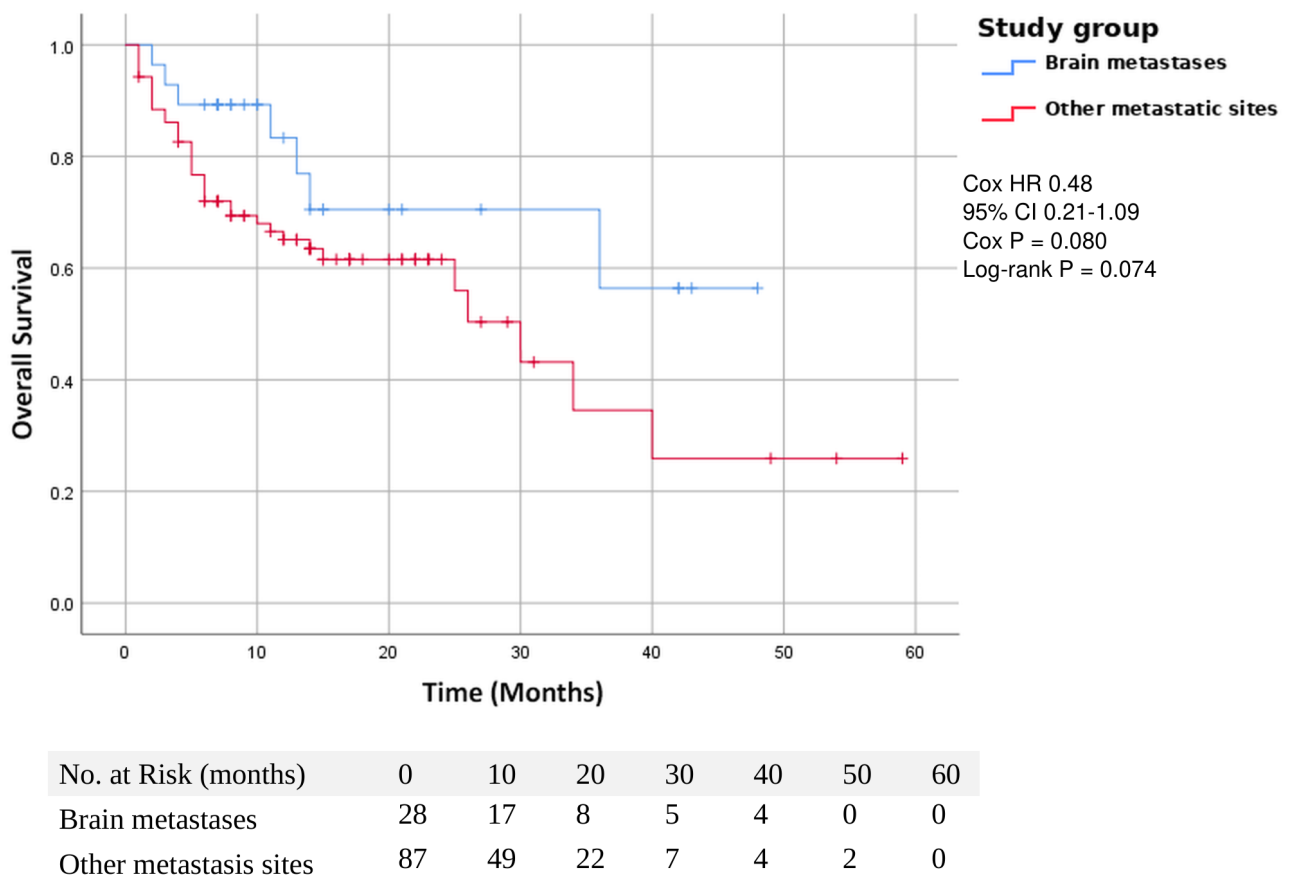


Fig. 3. Kaplan-Meier analysis of overall survival in patients with brain metastases (blue line) and patients with other metastatic sites without brain metastases (red line).

ICI alone in a larger cohort [27]. In brain metastasis settings, systematic reviews indicate that abscopal effects after RT occur, though variably, and combinations with ICI may increase their incidence [8,25].

The clinical relevance of immunotherapy in BM is further supported by Nannini et al. [1], who observed a median PFS of 8.3 months in NSCLC patients with high PD-L1 expression treated with pembrolizumab, regardless of whether local BM treatment was administered. Additionally, a meta-analysis confirmed that PD-1/PD-L1 inhibitors reduce the risk of progression and death in NSCLC patients with BM, particularly when lesions are asymptomatic or previously treated with local therapy [33]. Moreover, recent real-world evidence suggests that integrating brain RT with immunotherapy improves intracranial control and survival outcomes in NSCLC [31,32].

Patient selection for SRS or WBRT was based on multidisciplinary assessment rather than randomization, so patient selection may have favored those with lower overall disease burden or more controllable intracranial disease. In contrast, patients with non-CNS metastases, particularly bone lesions, may require prolonged corticosteroid use, potentially diminishing ICI efficacy. Notably, only pa-

tients with BM in our cohort received curative RT, whereas those with painful bone metastases were treated with single-fraction palliative RT. In addition, the BM subgroup had a lower extracranial metastatic burden and fewer lung, liver, and pleural metastases, suggesting a more favorable systemic disease distribution. Taken together, these factors offer a plausible explanation for the superior PFS observed in the BM subgroup.

Moreover, the presence of liver metastases consistently correlates with diminished survival and inferior response to systemic therapies [34,35]. As noted, the tumor microenvironment plays a critical role in response to ICIs. Similar to the brain, the liver harbors a profoundly immunosuppressive microenvironment, imposing a higher threshold of immune suppression that must be overcome for effective antitumor immunity [36]. Preclinical models suggest that combining liver-directed radiotherapy with immunotherapy may promote systemic antitumor immunity [37]. A recent real-world analysis in NSCLC patients with liver metastases found that the addition of RT to immunochemotherapy was associated with significantly improved survival outcomes compared with immunochemotherapy alone or with chemotherapy + RT

[38]. This finding provides further translational justification for combining RT and immunotherapy, not only in BM settings but across metastatic compartments.

From a translational perspective, organ-specific heterogeneity in immune landscapes and genomic alterations may influence responsiveness to ICI + RT. Differences in tumor-infiltrating lymphocytes, myeloid cell populations, checkpoint expression, and mutational signatures between intracranial and extracranial lesions may guide future stratification. Paired intracranial and systemic biopsies or CSF ctDNA profiling could yield biomarkers predictive of intracranial efficacy. Radiomic or imaging biomarkers may also aid in distinguishing pseudoprogression from true progression in irradiated lesions under iRECIST. However, our findings must be interpreted in light of limitations. The retrospective, single-center nature of the study restricts causal inference, and sample size limits robustness of subgroup analyses. All BM patients received radiotherapy, whereas the comparator group did not receive a corresponding CNS-directed intervention. Radiotherapy in the BM cohort was administered after multidisciplinary consultation rather than randomization, creating substantial indication bias. We could not uniformly capture data on steroid use, RT dosimetry (dose, fractionation, timing relative to ICI), or comprehensive molecular profiling beyond EGFR/ALK. Detailed selection criteria for SRS versus WBRT were not uniformly recorded, preventing modality-specific subgroup analyses. Guarantee-time bias may favor the BM cohort (i.e., those surviving long enough to receive RT). Also, radiotherapy completion dates were unavailable, which precluded a formal landmark analysis to address guarantee-time bias. Although we used iRECIST and regular imaging intervals, distinguishing intracranial pseudoprogression or radionecrosis remains a challenge, especially in previously irradiated BM. For these reasons, the observed PFS difference should be interpreted as an association within a selected retrospective cohort rather than proof of an absopal or site-specific immunologic effect. Future prospective studies with standardized protocols, molecular correlates, and longer follow-up are needed.

Clinically, these findings suggest that selected patients with brain metastases who receive CNS-directed radiotherapy may still derive disease-control benefit from pembrolizumab-based treatment. Prospective trials should investigate optimal sequencing (RT before vs. during vs. after ICI), fractionation schedules, and translational biomarkers to identify patients most likely to benefit intracranially. In particular, future studies might stratify patients by intracranial tumor burden, molecular immune markers, and prior local therapy history.

Study Limitations

This study has several limitations. First, it was a retrospective, single-center analysis with a relatively small number of patients in the brain-metastases subgroup, which lim-

its statistical power and generalizability. Second, all patients with brain metastases received CNS-directed radiotherapy, whereas patients with other metastatic sites did not receive an equivalent site-directed intervention. Therefore, the observed difference in PFS cannot be attributed to brain-metastasis status alone and may reflect the combined effect of pembrolizumab and local radiotherapy. Third, treatment allocation was not randomized but based on multidisciplinary clinical decision-making, introducing confounding by indication and selection bias. Fourth, the brain-metastases subgroup had a lower extracranial metastatic burden and fewer liver and pleural metastases, suggesting baseline prognostic imbalance. Fifth, detailed data on radiotherapy timing, dose, fractionation, corticosteroid exposure, and intracranial response assessment were not uniformly available, precluding landmark analyses and modality-specific subgroup analyses. Finally, because previously irradiated brain lesions were assessed in routine clinical practice without formal prospective RANO-BM adjudication, distinction between true progression, pseudoprogression, and radiation necrosis may have been imperfect. For these reasons, the findings should be considered hypothesis-generating and interpreted as associations rather than evidence of a causal site-specific benefit of immunotherapy.

Conclusion

In this real-world cohort of patients with advanced NSCLC and high PD-L1 expression treated with first-line pembrolizumab, patients with brain metastases who received CNS-directed radiotherapy showed longer PFS than patients with other metastatic sites without brain metastases, whereas OS was longer, but not significantly different. However, this finding should be interpreted cautiously. Because all patients with brain metastases received non-randomized CNS-directed radiotherapy and had lower extracranial metastatic burden, the observed PFS difference may reflect treatment-related confounding, selection bias, and baseline prognostic imbalance rather than intrinsic sensitivity of brain metastases to immunotherapy. These results are therefore hypothesis-generating and support the need for prospective studies evaluating optimal sequencing of immunotherapy and radiotherapy in patients with NSCLC and brain metastases.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding authors upon reasonable request.

Author Contributions

AR, NN, and AG contributed to clinical data collection and data curation. SP performed the statistical analysis

and contributed to the interpretation of the results. MK designed the research study and supervised the research. AR drafted the initial manuscript, and all authors critically revised it for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of University Clinical Center of Serbia (No. 455/15). Given the retrospective design of the study and the use of de-identified data, the Institutional Ethics Committee waived the requirement for informed consent.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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