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Prognostic Value of PET-Based Metabolic Markers in Nivolumab-Treated NSCLC

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Abstract

Objective: This study aimed to assess the prognostic significance of 18F-FDG PET/CT metabolic parameters in patients with non-small cell lung cancer (NSCLC) receiving nivolumab as second-line therapy. The study also explored associations between these parameters, treatment response, and survival outcomes. **Methods:** A retrospective analysis was performed on 32 patients with stage IV NSCLC who received at least four doses of nivolumab and underwent both baseline and follow-up PET/CT scans. Metabolic parameters, including SUVmax, SUVmean, total metabolic tumor volume (tMTV), and total lesion glycolysis (tTLG), were measured. Treatment response was classified according to EORTC criteria. Kaplan–Meier analysis and log-rank tests were applied for survival comparisons, and non-parametric methods evaluate associations. **Results:** Patients with partial metabolic response demonstrated significantly longer post-nivolumab survival. Post-treatment SUVmax, SUVmean, and tTLG differed significantly among response categories. Pretreatment tMTV and tTLG, and post-treatment SUVmax, SUVmean, and tTLG, were significantly associated with mortality ($p < 0.05$). Lower baseline tMTV and tTLG, and lower post-treatment SUVmax, SUVmean, tMTV, and tTLG were significantly associated with longer overall and post-nivolumab survival ($p < 0.05$). Post-treatment SUVmax and SUVmean were strong predictors of mortality. **Conclusion:** PET/CT-derived metabolic parameters, especially post-treatment SUVmax and SUVmean, offer valuable prognostic insights and may support personalized immunotherapy strategies in advanced NSCLC.

***Keywords*:** *Non-small cell lung cancer, Nivolumab, 18F-FDG PET/CT, Metabolic parameters, Survival.*

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1. Introduction

Lung cancer (LC) is the most commonly diagnosed cancer worldwide, accounting for approximately 2.5 million new cases annually (12.4% of all cancers), and remains the leading cause of cancer-related mortality, with an estimated 1.8 million deaths (18.7%) each year (Bray et al. 2024). The substantial morbidity and mortality associated with LC are largely due to its frequent diagnosis at advanced stages, with approximately 65–70% of patients presenting with stage III or IV disease at the time of initial evaluation. Non-small cell lung cancer (NSCLC) is the most common type of LC, accounting for approximately 80–85% of all cases. Among its subtypes, adenocarcinoma (45–50%) and squamous cell carcinoma (30–35%) are the most frequently observed histologies (Shalata et al. 2024; Travis et al. 2013). Treatment strategies for LC are generally determined based on the patient's clinical condition and disease stage. Standard modalities include surgery, chemotherapy, and radiotherapy, while targeted therapies and immune checkpoint inhibitors (ICIs) are increasingly employed in advanced-stage or molecularly defined subgroups. Immune checkpoint inhibitors, such as antibodies against programmed cell death-1 (anti-PD-1) and its ligand (anti-PDL-1), have significantly improved the treatment outcomes of advanced cancers by enhancing T cell–mediated antitumor immunity. The introduction of immunotherapy in recent years has significantly influenced the treatment approach for selected patients with NSCLC and contributed to better clinical outcomes (Monaco et al. 2021; Zheng et al. 2025). Such ICIs may be administered as monotherapy or in combination with conventional treatments, such as chemotherapy, either in the first- or second-line setting for advanced-stage NSCLC (Saeed et al. 2025).

Nivolumab, a fully human IgG4 monoclonal antibody that inhibits the PD-1 receptor, is one of the most extensively studied ICIs in advanced NSCLC. It is primarily administered as second-line therapy for patients with disease progression after platinum-based chemotherapy, regardless of PD-L1 expression status. Landmark clinical trials, including CheckMate 017 and CheckMate 057, demonstrated that nivolumab significantly improved overall survival, progression-free survival, and response rates compared to docetaxel in both squamous and non-squamous NSCLC histologies, which led to its widespread clinical adoption and regulatory approval. These studies also reported a lower incidence of grade 3–5 treatment-related adverse events in patients treated with nivolumab compared to those receiving docetaxel. These findings positioned nivolumab as a second-line treatment option in patients who have progressed after platinum-based chemotherapy for advanced NSCLC (Borghaei et al. 2015; Brahmer et al. 2015). Subsequent 2- and 3-year follow-up analyses confirmed the durability of clinical benefit, highlighting that a substantial proportion of patients achieved long-term responses (Horn et al. 2017; Vokes et al. 2018).

18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) plays a crucial role in the comprehensive management of NSCLC, particularly in initial staging, restaging, and assessment of treatment response. Beyond its anatomical and diagnostic utility, PET/CT provides quantitative metabolic parameters including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), which reflect tumor biology and aggressiveness. These parameters have been increasingly investigated as prognostic and predictive biomarkers in patients undergoing systemic therapies, including immunotherapy. Recent studies suggest that PET-based metabolic and volumetric indices may aid in predicting treatment outcomes and stratifying patients by survival risk and therapeutic response, thereby providing complementary information to traditional clinical variables (Park et al. 2020; Pellegrino et al.

2025; Zheng et al. 2025). While traditional imaging modalities are primarily based on anatomical assessment, the increasing importance of personalized treatment strategies has led to the increased use of functional imaging techniques such as 18F-FDG PET/CT. These modalities can detect microscopic biological alterations before observable structural changes, facilitating earlier response evaluation, enabling timely therapeutic modifications, and supporting individualized decision-making in NSCLC immunotherapy (Liu et al. 2025).

In this study, we aimed to investigate the prognostic value of baseline and post-treatment metabolic parameters derived from 18F-FDG PET/CT in patients with advanced-stage NSCLC receiving nivolumab as second-line therapy. We also examined the association between these parameters, treatment response, clinical and demographic variables, and survival outcomes.

2. Material and Method

2.1. Patient selection

This retrospective study included 32 patients diagnosed with stage IV NSCLC who received at least four doses of nivolumab monotherapy at a dose of 3 mg/kg via intravenous infusion every two weeks as second-line treatment between January 2022 and December 2024. Patients who had undergone 18F-FDG PET/CT imaging within four weeks before the initiation of immunotherapy and again within 4 to 6 weeks after the final dose were included in the study. A total of 64 PET/CT scans (baseline and post-treatment) were reviewed. Inclusion criteria required histopathologically confirmed NSCLC (adenocarcinoma or squamous cell carcinoma), receipt of first-line platinum-based chemotherapy, and documented disease progression before nivolumab initiation. All treatments were administered within the scope of national insurance reimbursement regulations without exceptional access or legal exemption. EGFR and ALK mutation testing had previously been performed as part of routine clinical practice, and patients with targetable mutations were excluded from the study. Patients with incomplete imaging data, history of other primary malignancies, who did not complete at least four doses of nivolumab, or those demonstrating findings suggestive of pseudoprogression on post-treatment PET/CT were excluded from the study. Demographic and clinical data, including age, sex, smoking history, histological subtype, and follow-up duration, were obtained retrospectively from medical records. The study protocol was approved by the institutional ethics committee (decree number: 20.478.486/2970). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration and its later amendments. Written informed consent was obtained from all patients according to our institution’s rules.

2.2. 18F-FDG PET/CT Imaging Protocol

All patients fasted for 4–6 hours prior to imaging, and blood glucose levels were confirmed to be below 200 mg/dL before tracer injection. Each patient received an intravenous dose of 370–555 MBq (10–15 mCi) of 18F-FDG. After a resting period of approximately 60 minutes in a quiet, dimly lit room, patients were asked to void to minimize bladder activity. PET/CT imaging was performed using a General Electric Discovery IQ 3-Ring hybrid PET/CT system (GE Healthcare, Milwaukee, USA). Initially, a low-dose CT scan (16-slice; 120 kVp; 90 mA) was acquired for attenuation correction and anatomical localization. This was followed by PET acquisition in

the supine position from the mid-thigh to the skull base, with an acquisition time of 2 minutes per bed position (8–10 bed positions, depending on patient height).PET images were reconstructed using the Q.Clear algorithm (penalized-likelihood reconstruction) with a β-value of 500. Reconstruction parameters included a matrix size of 192 × 192, a field of view (FOV) of 70 cm, and a slice thickness of 3.26 mm, yielding a voxel volume of approximately 11.88 mm^3. Attenuation correction was applied using the corresponding CT images. All images were reviewed in axial, sagittal, and coronal planes using attenuation-corrected and maximum intensity projection (MIP) datasets. All metabolically active lesions were semi-automatically segmented using the PET VCAR software (GE Healthcare), with a 41% SUVmax threshold applied to define the volume of interest. Total metabolic tumor volume (tMTV) and total lesion glycolysis (tTLG) were calculated by summing individual MTV and TLG values from each lesion. An example of this lesion segmentation process is shown in Fig. 1.

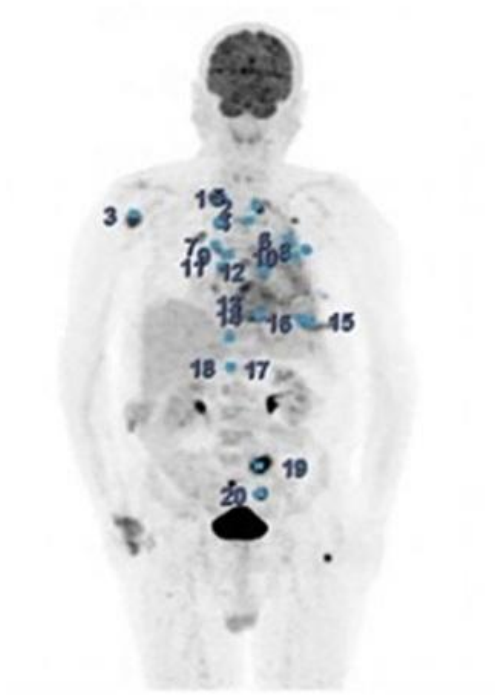

Figure 1. Lesion segmentation in a patient with multiple metastases performed using Volume Computer-Assisted Reading (VCAR) software.

2.3. Clinical Follow-up and Response Assessment

All patients were monitored clinically throughout the course of treatment and follow-up to evaluate disease progression, therapeutic response, and survival outcomes. Treatment response was assessed using post-

treatment 18F-FDG PET/CT images according to the EORTC criteria (European Organization for Research and Treatment of Cancer) (Young et al. 1999). A ≥25% increase in SUVmax or the emergence of new FDG-avid lesions was considered progressive metabolic disease (PMD), while a complete resolution of FDG uptake in all lesions was defined as complete metabolic response (CMR). A reduction of ≥25% in SUVmax was considered a partial metabolic response (PMR), and changes that did not meet the criteria for PMR or PMD were classified as stable metabolic disease (SMD). Overall survival (OS) was defined as the time from the initiation of nivolumab treatment to the date of death or the last clinical follow-up. All deceased patients were included in the survival analysis, with their date of death recorded accordingly.

2.4. Statistical analysis

The Shapiro-Wilk test showed that the data were not normally distributed. Therefore, the relationships of metabolic parameters with clinical data were evaluated with non-parametric tests. Response to nivolumab treatment was evaluated on 18F-FDG PET/CT images according to EORTC criteria. According to these criteria, patients were divided into three groups: partial metabolic response to treatment, stable metabolic disease, and progressive metabolic disease. When comparing the measurement values obtained from 18F-FDG PET/CT images, the Mann–Whitney U test was used to compare two independent groups, and the Kruskal–Wallis H test was used to compare three or more independent groups. Patients were divided into two groups based on the median values of metabolic parameters, and survival analysis was performed. Survival curves were estimated using the Kaplan–Meier analysis, and differences between groups were examined with the log-rank test. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0, IBM Corp., Armonk, New York, USA). For all analyses, a $P < 0.05$ was considered statistically significant.

3. Results

A total of 32 patients with histopathologically confirmed stage IV NSCLC were included in the study. The cohort comprised three females (9.4 %) and 29 males (90.6%), with a mean age of 64 ± 6.5 years (range: 52–77). The histological subtypes included adenocarcinoma (n = 15, 46.9%) and squamous cell carcinoma (n = 17, 53.1%). Twenty-three patients had a history of smoking, whereas nine patients had never smoked. The mean body mass index (BMI) of the cohort was 27.04 ± 4.47. According to the treatment response evaluation based on PET/CT images, partial metabolic response was observed in 8 patients (25%), stable disease in 15 patients (46.9%), and progressive metabolic disease was observed in 9 patients (28.1%). The median follow-up duration after diagnosis was 24.9 months (range: 7.7–122.2 months). Twenty-three patients (71.9%) died during the follow-up period. The mean overall survival time from diagnosis was 35.7 ± 25.8 months, while the mean post-nivolumab survival time was 13.4 ± 9.1 months. No statistically significant relationships were observed between baseline or post-treatment PET-derived metabolic parameters (SUVmax, SUVmean, tMTV, and tTLG) and clinical variables such as histological subtype, age, body mass index (BMI), or smoking history ($p > 0.05$). Similarly, no statistically significant associations were found between clinical variables (histological subtype, age, body mass index, and smoking history) and either overall survival or post-nivolumab survival ($p > 0.05$). Significant differences were observed in post-treatment SUVmax ($p < 0.001$), SUVmean ($p < 0.001$), and tTLG ($p = 0.018$) among the response categories defined by post-nivolumab PET/CT evaluation. Statistical analysis

revealed that pretreatment tMTV and tTLG values, as well as post-treatment SUVmax, SUVmean, and tTLG values, were significantly associated with mortality ($p < 0.05$). Post-nivolumab survival significantly differed across response categories defined by EORTC criteria, with patients showing a partial metabolic response (PMR) exhibiting longer survival than those with stable metabolic disease (SMD) or progressive metabolic disease (PMD) (Fig. 2).

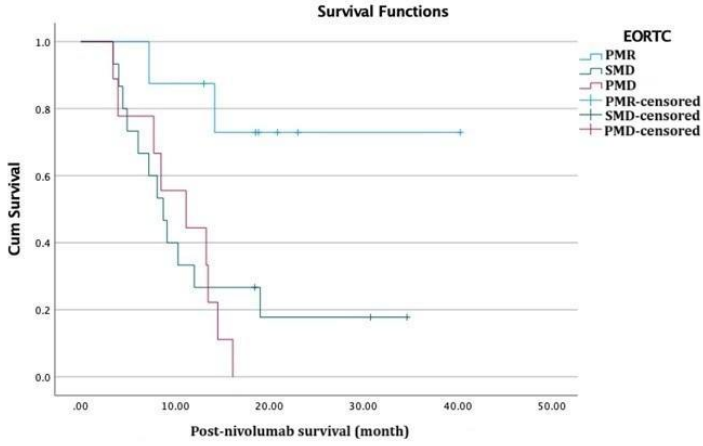

Figure 2. Kaplan–Meier survival curves for post-nivolumab survival according to metabolic response assessed by the European Organization for Research and Treatment of Cancer (EORTC) criteria. Patients with partial metabolic response (PMR) showed significantly better post-treatment survival than those with stable metabolic disease (SMD) or progressive metabolic disease (PMD) (log-rank $p < 0.05$). Censored cases are marked with plus signs.

In addition, Kaplan–Meier survival analysis revealed that lower pretreatment tMTV and tTLG, as well as lower post-treatment SUVmax, SUVmean, tMTV, and tTLG values, were significantly associated with prolonged overall and post-nivolumab survival ($p < 0.05$ for all comparisons). Receiver operating characteristic (ROC) curve analysis demonstrated that post-treatment SUVmax and SUVmean were strong predictors of mortality. The area under the curve (AUC) was 0.961 for SUVmax (95% CI: 0.899–1.000, $p < 0.001$) and 0.947 for SUVmean (95% CI: 0.867–1.000, $p < 0.001$), indicating excellent discriminative ability. The optimal cut-off values were 12.035 for SUVmax (sensitivity: 82.6%, specificity: 100%) and 6.430 for SUVmean (sensitivity: 82.6%, specificity: 88.9%) (Fig. 3).

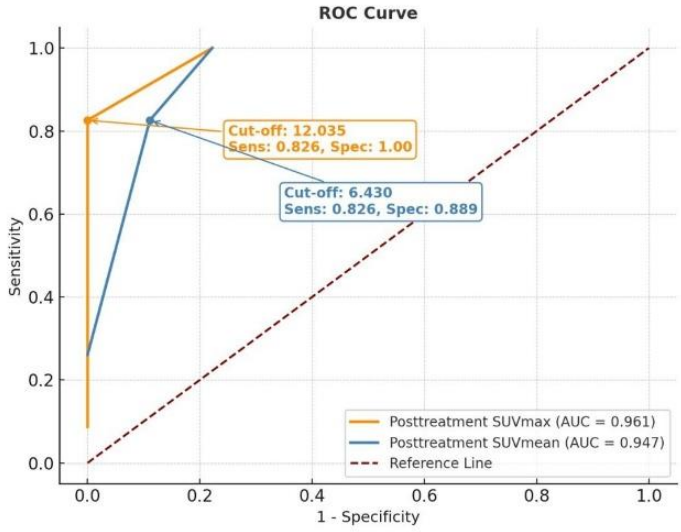

Figure 3. Receiver operating characteristic (ROC) curves of posttreatment maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean) for predicting mortality. The area under the curve (AUC) was 0.961 for SUVmax and 0.947 for SUVmean, indicating high diagnostic performance. Optimal cut-off values were determined using the Youden Index and were 12.035 for SUVmax (sensitivity: 0.826, specificity: 1.00) and 6.430 for SUVmean (sensitivity: 0.826, specificity: 0.889).

4. Discussion

The introduction of ICIs has reshaped the treatment paradigm for advanced NSCLC, particularly in the second-line setting. Nivolumab, a PD-1 inhibitor, has demonstrated consistent survival benefits across both squamous and non-squamous NSCLC subtypes in previously treated patients, as shown in the CheckMate 017 and CheckMate 057 trials (Borghaei et al. 2015; Brahmer et al. 2015). In CheckMate 017, which enrolled patients with squamous histology, nivolumab achieved a median overall survival (OS) of 9.2 months compared to 6.0 months with docetaxel (HR: 0.59; $p < 0.001$), whereas in CheckMate 057, targeting non-squamous NSCLC, median OS was 12.2 versus 9.4 months (HR: 0.73; $p = 0.002$). These results solidified nivolumab's role as a second-line therapy in advanced NSCLC, regardless of histological subtype. Long-term follow-up analyses have reinforced the durability of the clinical benefit observed with nivolumab. In the 2-year follow-up of the CheckMate 017 and 057 trials, overall survival rates continued to favor nivolumab over docetaxel, 23% versus 8% in squamous NSCLC and 29% versus 16% in non-squamous NSCLC, respectively. These outcomes further support the sustained benefit of immune checkpoint inhibition in NSCLC. The relative reduction in the risk of death was 28% with nivolumab, and the incidence of grade 3–4 treatment-related adverse events remained markedly lower compared to chemotherapy (10% vs. 55%) (Horn et al. 2017). After a minimum follow-up of 40.3 months, nivolumab continued to provide a survival advantage over docetaxel, with an estimated 3-year overall survival rate of 17% versus 8% in the pooled population with squamous or non-squamous NSCLC (Vokes et al. 2018). While ICIs, such as nivolumab, have demonstrated substantial clinical efficacy in advanced

NSCLC, the ability to predict individual treatment responses and long-term outcomes remains an area of active investigation. In this study, we aimed to explore whether metabolic parameters derived from 18F-FDG PET/CT could serve as prognostic or predictive markers in this context. Specifically, we assessed the relationship between these imaging biomarkers and treatment response, clinical variables, and mortality outcomes in patients with stage IV NSCLC who received nivolumab as second-line therapy.

In our study, both baseline and post-treatment volumetric PET parameters, including total metabolic tumor volume (tMTV) and total lesion glycolysis (tTLG), demonstrated significant associations with mortality as well as overall and post-nivolumab survival. These relationships underscore the prognostic relevance of tumor burden and metabolic activity throughout the treatment course. Elevated pre-treatment volumetric indices may reflect aggressive tumor biology, while persistent post-treatment metabolic activity may indicate suboptimal immunologic response. These findings position tMTV and tTLG as valuable integrative biomarkers for risk stratification and treatment monitoring in patients receiving immunotherapy. Our findings are also consistent with previous studies demonstrating the prognostic significance of PET-derived metabolic parameters in NSCLC patients undergoing immunotherapy. Monaco et al. evaluated 92 patients treated with either nivolumab or pembrolizumab and reported that lower baseline MTV and TLG were associated with longer overall survival, while early reductions in SUVmax after treatment initiation predicted favorable clinical outcomes (Monaco et al. 2021). Similarly, Hashimoto et al. found that elevated baseline MTV and TLG were correlated with poor survival, whereas SUVmax lacked independent prognostic value (Hashimoto et al. 2020). In contrast, our study highlights the powerful prognostic utility of post-treatment PET-derived parameters, especially SUVmax and SUVmean, which demonstrated excellent predictive accuracy for mortality with AUCs of 0.961 and 0.947, respectively. These results suggest that post-treatment metabolic activity may provide superior real-time insight into immunologic response and survival risk compared to baseline measurements alone. Moreover, our study benefits from a homogeneous cohort exclusively treated with nivolumab, minimizing therapeutic heterogeneity and strengthening the specificity of our conclusions.

The prognostic value of treatment response assessed by FDG PET/CT has been increasingly recognized in patients receiving ICIs. In our study, patients who achieved a partial metabolic response (PMR) according to EORTC criteria experienced significantly longer post-treatment survival compared to those with stable metabolic disease (SMD) or progressive metabolic disease (PMD). These results highlight the clinical utility of metabolic response evaluation in the immunotherapy setting, where conventional anatomical imaging may fall short in detecting early biological changes. Our findings are in line with previous studies, such as Park et al., who observed that only patients with complete or partial metabolic responses derived clinical benefit, while none of the patients with PMD experienced favorable outcomes (Park et al. 2020). Similarly, Ayati et al. demonstrated that metabolic responders, as defined by multiple criteria (PERCIST, imPERCIST, RECIST, and iRECIST), had significantly longer progression-free and overall survival (Ayati et al. 2021). These observations are further supported by a recent meta-analysis by Wu et al., which confirmed the prognostic significance of metabolic response in patients treated with ICIs across different cancers, including NSCLC. The pooled results demonstrated that PET responders had significantly improved progression-free survival (HR: 0.27) and overall survival (HR: 0.56) compared to non-responders. Importantly, the predictive power of PET response was evident even at early follow-up intervals, reinforcing its potential role in guiding early treatment decisions and optimizing patient selection for ongoing immunotherapy (Wu et al. 2020). Recent studies continue to underscore the importance of FDG PET/CT in assessing early treatment response and predicting prognosis in

the context of immunotherapy. Kitajima et al. evaluated NSCLC patients undergoing 4–8 cycles of nivolumab or pembrolizumab, demonstrating high concordance between metabolic criteria (EORTC and PERCIST) and highlighting PET's superiority over conventional CT (RECIST1.1) in prognostic stratification. Notably, patients with CMR, PMR, or SMD had significantly better outcomes compared to those with PMD, supporting the predictive power of metabolic response assessment (Kitajima et al. 2021). Complementing these findings, Thunold et al. investigated mesothelioma patients treated with ipilimumab and nivolumab, with or without UV1 vaccine. Their study showed that early changes in PET parameters (especially TLG, SUVmax, and SUVpeak) at week 5 correlated strongly with treatment response, emphasizing the role of early PET imaging in identifying responders even in tumors with atypical immunologic dynamics (Thunold et al. 2025). Similarly, our study contributes to this growing evidence base by demonstrating that NSCLC patients with a partial metabolic response after four doses of nivolumab exhibit significantly longer post-treatment survival. This aligns with the broader literature and further establishes FDG PET/CT as a valuable tool for early therapeutic evaluation and patient selection in the immunotherapy era. Our analysis revealed no statistically significant associations between survival outcomes or PET-derived metabolic parameters and clinical variables such as age, histologic subtype, body mass index (BMI), or smoking history. These results suggest that functional imaging biomarkers may offer prognostic value independent of traditional clinical and demographic factors. Accordingly, metabolic parameters such as SUVmax, tMTV, and tTLG may enhance treatment monitoring and improve outcome prediction, particularly in heterogeneous patient populations where conventional metrics may be insufficient for effective risk stratification.

Several limitations of this study should be considered. First, the retrospective design and relatively small sample size limit the generalizability of the findings. Second, patients with pseudoprogression were excluded to avoid misclassification, which may have introduced a selection bias and affected survival estimates. Third, the optimal timing for post-treatment PET/CT imaging in the context of immunotherapy remains undefined; hence, the temporal dynamics of metabolic response could not be fully captured. Lastly, although robust statistical methods were applied, our results require validation in larger, prospective, multicenter studies to confirm the prognostic value of FDG PET/CT–derived metabolic parameters in this patient population. Future research should focus on prospective validation of metabolic biomarkers in larger, multicenter cohorts to determine their reproducibility and clinical applicability. Comparative studies examining the prognostic performance of PET/CT-based parameters against emerging molecular and immunological biomarkers may further clarify their complementary role. Additionally, integrating longitudinal PET/CT data and exploring adaptive imaging strategies could enhance our understanding of treatment dynamics and enable more personalized approaches in NSCLC immunotherapy.

5. Conclusion

In conclusion, our study reinforces the clinical value of nivolumab in the treatment of advanced-stage NSCLC and highlights the prognostic significance of FDG PET/CT–derived metabolic parameters. Notably, post-treatment SUVmax and SUVmean demonstrated excellent predictive accuracy for survival outcomes, underscoring their potential as reliable imaging biomarkers in patients receiving ICIs. Furthermore, partial metabolic response according to the EORTC criteria was significantly associated with prolonged post-nivolumab survival and overall survival, indicating that early metabolic response may serve as a predictive

marker of long-term benefit. Volumetric PET parameters such as total metabolic tumor volume (tMTV) and total lesion glycolysis (tTLG) also emerged as significant prognostic indicators. Given their ability to reflect both disease burden and metabolic behavior, these markers function as integrative tools for risk stratification and treatment monitoring in the immunotherapy setting. Collectively, these findings support the integration of functional imaging into routine clinical practice to guide early therapeutic decisions and to tailor immunotherapy approaches more precisely. Future prospective studies are warranted to validate these results and explore the role of PET-guided adaptive treatment strategies in the management of advanced NSCLC.

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Authorship Contributions

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