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Molecular Response Assessment with Immune Adaptive PERCIST in Lung Cancer Patients Treated with Nivolumab: Is It Better Than iRECIST?

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Abstract

Aims We compared the immune response evaluation criteria in solid tumors (iRECIST) with immune adaptive positron emission tomography response criteria in solid tumors (imPERCIST) in lung cancer patients treated with nivolumab.

Materials and Methods Twenty lung cancer patients underwent fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) scan at baseline (PET-0), after four cycles (PET-1) and six to eight cycles (PET-2) of nivolumab were included. Kappa coefficient (*k*) was derived to see the level of agreement in two response criteria. Progression-free survival (PFS) curves were computed by the Kaplan–Meier method and compared with the Log Rank test. Univariate and multivariate regression for the percentage change in the sum of diameters (SoD), standard uptake value maximum (SUVmax), sum of metabolic tumor volume (SoMTV), and sum of total lesion glycolysis (SoTLG) was computed. A *p*-value less than 0.05 was considered significant.

Results Kappa coefficient showed a substantial level of agreement (k 0.769) in two response criteria. Mean PFS in partial response, stable disease, and progressive disease (PD) patients in iRECIST and imPERCIST was 27.3, 17.7, 4.2, and 23.3, 18.8, 3.8 months, respectively. The Kaplan–Meier method with the log rank test showed a significant difference in PFS on intracomparison within both criteria; however, it was not significant on intercomparison. On univariate analysis, the percentage change in SoD, SoMTV, SoTLG was significant. However, on multivariate analysis, only percentage change in SoD was a significant predictor.

Conclusions We concluded that imPERCIST was equally effective as currently recommended criteria iRECIST for response evaluation of nivolumab in lung cancer patients.

Keywords
- immune checkpoint inhibitors
- nivolumab
- lung carcinoma
- iRECIST
- imPERCIST
- progression-free survival

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Introduction

A proper and accurate response assessment is the essential criteria in cancer management. It is imperative to identify nonresponders early during treatment to ensure adequate control and also to reduce treatment-related side effects from a nonresponding regime. Traditionally, change in tumor size is the key to define response by the use of response evaluation criterion in solid tumors (RECIST 1.1).[1] This mode of response evaluation has been in service with reasonable success with cytotoxic drugs. However, RECIST 1.1 has a few known limitations with targeted cytostatic therapy. Therefore, better criteria for targeted drugs like a Choi criterion for response assessment to imatinib in gastrointestinal stromal tumors (GIST) have been useful.[2] Similarly, response assessment in immune checkpoint inhibitors (ICIs) by RECIST1.1 has also been found to be challenging. ICIs reactivate the adaptive immune system, and these activated T cells aggregate around the cancer cells and eventually destroy them. This unique combat may lead to different response outcomes.[3] Therefore, immune adaptive morphological response criteria like immune-related response criteria (irRC, 2009), immune-related response evaluation criteria in solid tumors (irRECIST, 2013), immune response evaluation criteria in solid tumors (iRECIST, 2017), and immune-modified response evaluation criteria in solid tumors (imRECIST, 2018) have been introduced.[4–7] However, none of these criteria have been validated so far.

Wahl et al proposed positron emission tomography response criteria in solid tumors (PERCIST) in 2009.[8,9] After that, many studies have claimed a better assessment of disease and prognostic impact of PERCIST and other molecular imaging-based parameters.[10–12] However, this criterion has also not been validated for routine clinical use. In similar corollary to immune adapted RECIST, few immune adapted PERCIST response criteria have been evaluated with limited success.[13] Herewith, we compared immune adaptive PERCIST (imPERCIST) to iRECIST in patients of lung carcinoma treated with nivolumab.

Subjects and Methods

We evaluated 97 patients of various malignancies on ICIs who were referred for ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) scan during July 2017 to November 2019. On the initial screening, 57 patients of nonprimary lung malignancy were excluded. In the remaining 40 patients, 21 patients of lung cancer who had PET/CT at baseline (PET-0), post four cycles (PET-1) and six to eight cycles (PET-2) of nivolumab, a programmed cell death 1 (PD-1) blocker human IgG4 monoclonal antibody, were taken up for further analysis. Out of these 21, 20 patients with at least one target lesion on baseline PET/CT were included in the final analysis (►**Fig. 1**). This study was approved by hospital institutional review board (RGCIRC/IRB-BHR/30/2020, 30/05/2020).

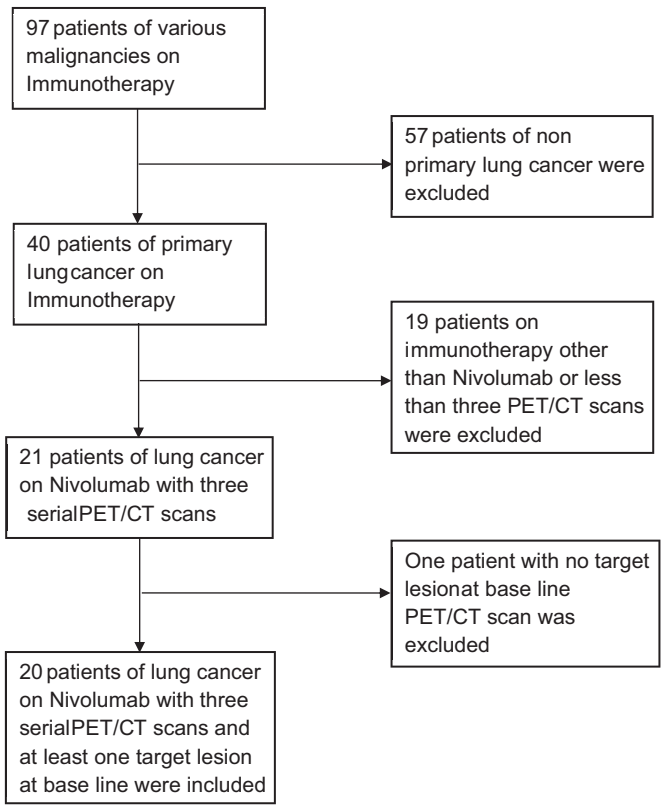

Fig. 1 Flowchart showing patients inclusion process for the study. PET/CT, positron emission tomography/computed tomography.

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Imaging Protocol

A standard FDG PET/CT protocol was used.[14] All patients were instructed to fast for 4 to 6 hours after an early light meal and to maintain an adequate hydration. Blood sugar was checked before FDG injection for all patients, and a cutoff value below 200 mg/dL, preferably below 150 mg/dL, was used. 3–4 MBq/kg body weight of FDG was injected intravenously, and patients were rested for 1 hour (±10 minutes) in an isolation room. One liter of plain water was allowed during the uptake period. The scan was performed on a dedicated full ring hybrid PET-CT system (Biograph mCT 20 Siemens Healthcare with LSO crystal, Erlangen, Germany) with 2 minutes per bed position starting from the skull base to mid-thigh. A noncontrast-enhanced CT scan (100 mAs and 120 kVp) was used for attenuation correction and anatomical interpretation. Each scan was reconstructed using iterative reconstruction (two iterations and 12 subsets).

Image Interpretation

All PET/CT studies were reinterpreted independently by two experienced nuclear medicine physicians and a radiologist. Increased FDG uptake in comparison to the background, not in areas of normal bio-distribution, was taken as positive for the disease on PET scan. No size criterion was used for PET interpretation. The highest single voxel maximum standard uptake value normalized to body weight (SUVmax) of any lesion per study was recorded. For CT, more than 1 cm (cm) size in the longest axis for soft tissue lesion was considered measurable, while for lymph node, it was greater than or equal to 1.0 cm in the shortest axis.

Response Criteria

iRECIST criterion was used for the morphological response assessment.[6] A well-defined 1 cm soft tissue lesion in the longest axis was defined as a target lesion, while it was greater than or equal to 1.5 cm in the shortest axis for a lymph node. The largest sum of diameter (SoD) of five target lesions with a maximum of two lesions per organ was measured. Bone lesion with soft tissue component was considered measurable, while sclerotic or lytic/sclerotic (mixed type) bone metastasis was considered nonmeasurable lesions. More than or equal to 30% decrease in SoD was considered a partial response (PR). More than or equal to 20% increase in SoD was considered as immune unconfirmed progressive disease (iUPD) for the first time in clinically stable patients, while immune confirmed progressive disease (iCPD or PD) for the second time. Change in-between PR and PD ($< -30\%$ and $< +20\%$) was considered as stable disease (SD). A new lesion was considered as iUPD for the first time in clinically stable patients, while a subsequent new lesion or greater than or equal to 5 mm increase in SoD of new lesions in the next scan was considered as iCPD or PD.

PERCIST 1.0 with modifications to adapt immunotherapy response outcomes was used for PET response evaluation. The highest SUVmax was recorded for all PET studies irrespective of the number of lesions. It might be two different lesions in a comparison. A drop of greater than or equal to 30% in the highest SUVmax was considered a partial metabolic response (PMR). More than or equal to 30% increase in the highest SUVmax was considered as immune unconfirmed progressive metabolic disease (iUPMD) for the first time, while immune confirmed progressive metabolic disease (iCPMD or PMD/PD) for the second time. Change in-between PMR and PMD ($< -30\%$ and $< +30\%$) was considered as stable metabolic disease (SMD) or SD. A new FDG-avid lesion, likely disease-related, was considered as iUPMD for the first time, while a subsequent new lesion or greater than or equal to 30% increase in SUVmax of previous new lesion was considered as iCPMD or PD.

Metabolic Tumor Volume and Total Lesion Glycolysis

Metabolic Tumor Volume (MTV) and Total Lesion Glycolysis (TLG) are the novel metabolic markers and have been reported to be of diagnostic and prognostic value in various cancers.[15,16] MTV and TLG were measured from attenuation-corrected FDG PET/CT images using an volume of interest (VOI max)-based automated contouring program with a 40% threshold (Syngo.via VB30 Workstation, Siemens). We have calculated MTV and TLG of all target lesions used in iRECIST evaluation and added to calculate the sum of MTV (SoMTV) and the sum of TLG (SoTLG).

Progression-Free Survival

Progression-free survival (PFS) was defined as the time after starting the nivolumab till disease progression or death from any cause. In the case of iUPD was followed by iCPD, time to iCPD was used for calculating PFS. If iUPD was followed by SD/PR/CR, then time to next iUPD followed by iCPD was used for PFS calculation.

Statistical Analysis

Mean, median, range (minimum to maximum), and 95% confidence interval (CI) were evaluated for quantitative data, and absolute frequencies with percentages for categorical data. Spearman's rank correlation was derived for variables like SoD, SUVmax, SoMTV, and SoTLG to measure the strength of association between initial disease burden (PET-0) and PFS. For statistical calculation, iUPD and iUPMD at PET-1 were reclassified as PD or PR or SD based on the overall response in PET-2. Cohen's Kappa coefficient (k) was derived to see the level of agreement between the response outcome of iRECIST and imPERCIST at PET-1. Cohen's Kappa coefficient was also derived to see the level of agreement at PET-2. Univariate and multivariate cox proportional hazard model for percentage change in SoD, SUVmax, SoMTV, and SoTLG at PET-1 in comparison to PET-0 was done to find the best predictor of PFS. Patients were divided into two groups based on PET-1 response outcome. Group 1 (responder) includes PR and SD patients, while group 2 (nonresponder) includes PD

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patients. Univariate PFS curves were computed according to the Kaplan–Meier method and compared with the log rank test. Harell's C-index (concordance index) was used to determine the predictive power of the cox-regression model for the prediction of PFS. Statistical analysis was conducted with MedCalc Statistical Software version 19.1.5 (MedCalc Software bv, Ostend, Belgium). Intercomparison was done with GraphPad Prism4 software (GraphPad Software, La Jolla, California). All tests were two-sided. Harell's C-index was calculated using R studio version 1.3.1056. A *p*-value greater than 0.05 was considered statistically significant.

Results

Seventeen males and three females of lung carcinoma (9 adenocarcinomas, 4 squamous cell carcinomas, 6 nonsmall cell lung cancer [NSCLC]–not otherwise specified, and 1 small cell lung cancer) were treated with average 18.7 cycles (median: 13.5, range: 4–56) of nivolumab. The patient characteristics are summarized in ►**Table 1**. In our study, 65% of the patients received nivolumab after the first line of chemotherapy. In contrast, 20 and 15% of the patients received second line and third line of chemotherapy, respectively, before nivolumab. The semiquantitative analysis and overall response outcome by iRECIST and imPERCIST have been described in ►**Supplementary Table S1**. At PET-0, mean SoD was 7.6 cm (median: 6.6, range: 1.5–16.7), while at PET-1 mean SoD was 7.8 cm (median: 5.7, range: 2.6–26.6). At PET-0, mean SUVmax was 13.5 (median: 12.7, range: 5.7–29.7) while at PET-1, mean SUVmax was 10.6 (median: 10.6, range: 2.1–24.4). At PET-0, mean SoMTV was 45.7 (median: 27.4, range: 1.6–185), while at PET-1, mean SoMTV was 50.8 (median: 21.0, range: 3.6–353). At PET-0, mean SoTLG was 278.3 (median: 219.1, range: 6.3–736.1), while at PET-1, mean SoTLG was 314.2 (median: 107.2, range: 5.1–1990.6). Response assessment by iRECIST on PET-1 showed 8/20 (40%) of the patients had iUPD, 5/20 (25%) of the patients had SD, and 7/20 (35%) of the patients had PR. Response assessment by imPERCIST on PET-1 showed 8/20 (40%) of the patients had iUMPD, while 4/20 (20%) of the patients had SD and 8/20 (40%) of the patients had PR. At PET-1, 16/20 (80%) of the patients had concordance in response outcome by iRECIST and imPERCIST (►**Fig. 2**). At PET-2 response assessment by iRECIST, 6/8 (75%) of the iUPD patients showed iCPD; hence, these were the true progression cases. However, 2/8 (25%) of iUPD patients showed SD in one and PR in other cases; hence, these were the pseudoprogression cases. On PET-2 response assessment by imPERCIST, ⅝ (62.5%) of iUPMD patients showed iCPMD; hence, these were the true progression cases. While ⅜ (37.5%) of iUPMD patients showed SD in one and PR in two patients; hence, these were the pseudoprogression cases (►**Fig. 3**). As mentioned before, to take care pseudo or true progression, PET-1 response of iUPD and iUPMD was reclassified based on PET-2 response as PD or PR or SD. Cohen's Kappa coefficient showed a substantial level of agreement (k 0.769) between iRECIST and imPERCIST response outcomes at PET-1 (►**Table 2**). A substantial level of agreement (k 0.767) was also noticed between two criteria at PET-2 as well.

Table 1 Patients characteristics (*n*-20)

Age (y)	
Median	62
Mean	60.43
Range	32–73
Gender	
Male	17
Female	3
Smoking status	
Smoker	17
Nonsmoker	3
Histology	
Adenocarcinoma	9
Squamous	4
NSCLC-NOS	6
SCLC	1
Prior lines of chemotherapy	
1	13
2	4
3	3

Abbreviations: NSCLC-NOS, nonsmall cell lung cancer-not otherwise specified.

Progression-Free Survival Analysis

In our study, 9/20 (45%) of the patients were still on nivolumab therapy till the last follow-up, while the change of treatment protocol was advocated in 11/20 (55%) of the patients (►**Fig. 4**). Mean PFS was 13.6 months (median: 11, range: 3–31). On the Kaplan–Meier analysis, PFS at 1 year and 2 years was 53.6 and 35.2%, respectively (►**Supplementary Fig. S1**). Mean PFS in PR, SD, and PD groups of iRECIST at PET-1 was 27.3 months (95% CI: 26.3–28.4), 17.7 months (95% CI: 9.8–25.6), and 4.2 months (95% CI: 3.4–5.0), respectively. Mean PFS in PR, SD, and PD groups of imPERCIST at PET-1 was 23.3 months (95% CI: 18.2–28.3), 18.8 months (95% CI: 9.5–28.0), and 3.8 months (95% CI: 3.4–4.2), respectively. A statistically significant difference (p-value < 0.05) was found on intracomparison with the Kaplan–Meier method and the log rank test for three response groups (PR, SD, and PD) within each response criteria (►**Fig. 5**). However, on intercomparison in iRECIST and imPERCIST, no significant difference was found (p-value > 0.05), though findings are in little favor of iRECIST. Group 1 (responder) and 2 (nonresponder) on iRECIST at PET-1 had mean PFS of 23.7 months (95% CI: 18.6–28.9) and 4.2 months (95% CI: 3.8–5.0), respectively. One year and 2 years, PFS for iRECIST group 1 (responder) was 76.9 and 67.3%, respectively. Group 1 (responder) and 2 (nonresponder) on imPERCIST at PET-1 had mean PFS of 22.6 months (95% CI: 17.3–27.8) and 3.8 months (95% CI: 3.4–4.2), respectively.

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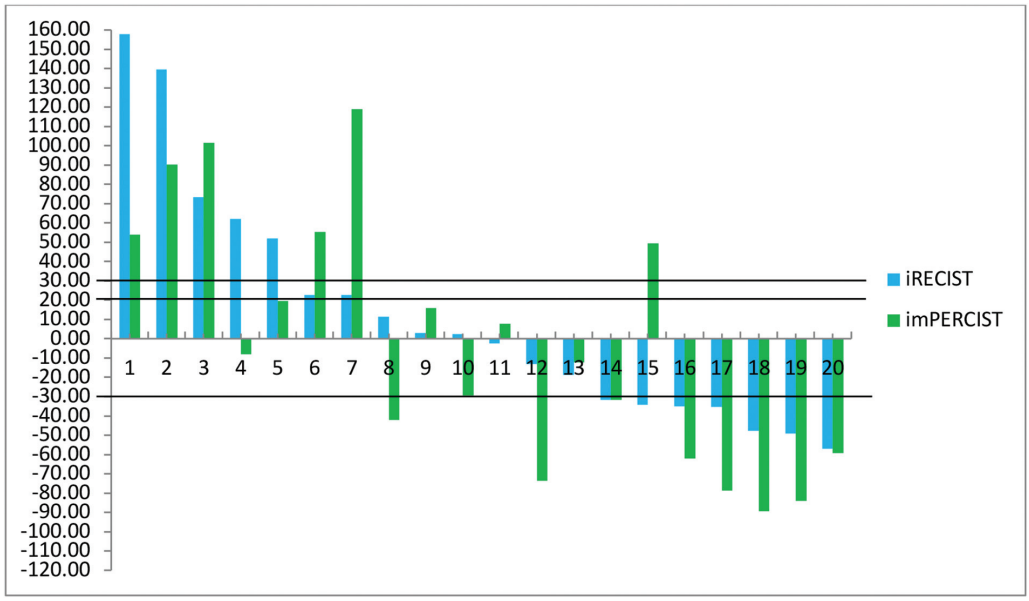

Fig. 2 Waterfall plot showing percentage change in SoD and SUVmax at PET-1 by iRECIST and imPERCIST response criteria in 20 patients. imPERCIST, immune adaptive positron emission tomography response criteria in solid tumors; iRECIST, immune response evaluation criteria in solid tumors; PET, positron emission tomography; SoD, sum of diameters; SUVmax, standard uptake value maximum.

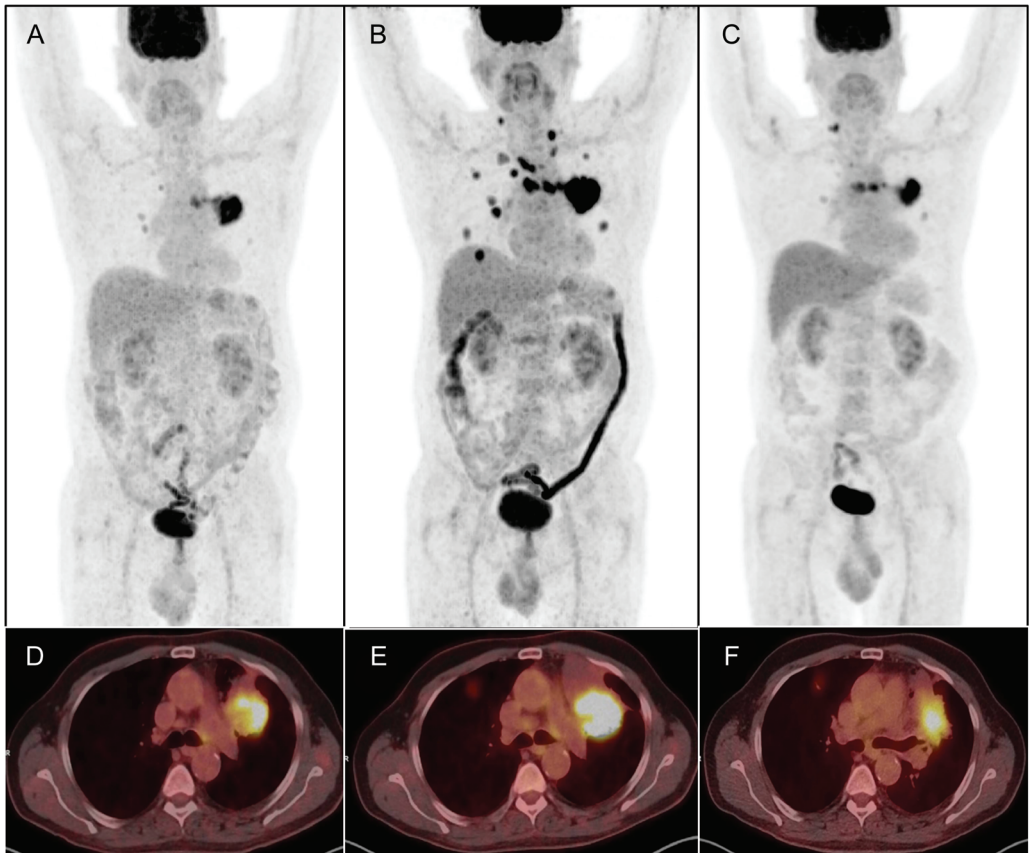

Fig. 3 FDG PET/CT maximum intensity projection (**A–C**) and fused axial (**D–F**) images. A 58 years old man with metastatic adenocarcinoma left lung showed FDG avid left lung mass with mediastinal lymph-nodes and bilateral lung nodules at baseline PET scan (**A, D**). Post four cycles of nivolumab PET scan (**B, E**) showed progression by both iRECIST and imPERCIST criteria; however, considered as iUPD/iUPMD because of immunotherapy and clinically stable patient. Post six cycles of nivolumab PET scan (**C, F**) showed partial response by both criteria. Hence, this case highlighted pseudoprogression. FDG PET/CT, fluoro-2-deoxyglucose positron emission tomography/computed tomography; imPERCIST, immune adaptive positron emission tomography response criteria in solid tumors; iRECIST, immune response evaluation criteria in solid tumors; iUPD, immune unconfirmed progressive disease; iUPMD, immune unconfirmed progressive metabolic disease.

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Table 2 Cohen's Kappa coefficient (k) derived to see the level of agreement between iRECIST and imPERCIST response outcome at PET-1 after considering results of iUPD or iUPMD in subsequent PET-2

		imPERCIST			Total	Kappa	*p*-Value
		PD	PR	SD			
iRECIST	PD	5	0	1	6	0.769	0.000
	PR	0	8	0	8		
	SD	0	2	4	6		
Total		5	10	5	20		

Abbreviations: imPERCIST, immune adaptive positron emission tomography response criteria in solid tumors; iRECIST, immune response evaluation criteria in solid tumors; iUPD, immune unconfirmed progressive disease; iUPMD, immune unconfirmed progressive metabolic disease; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

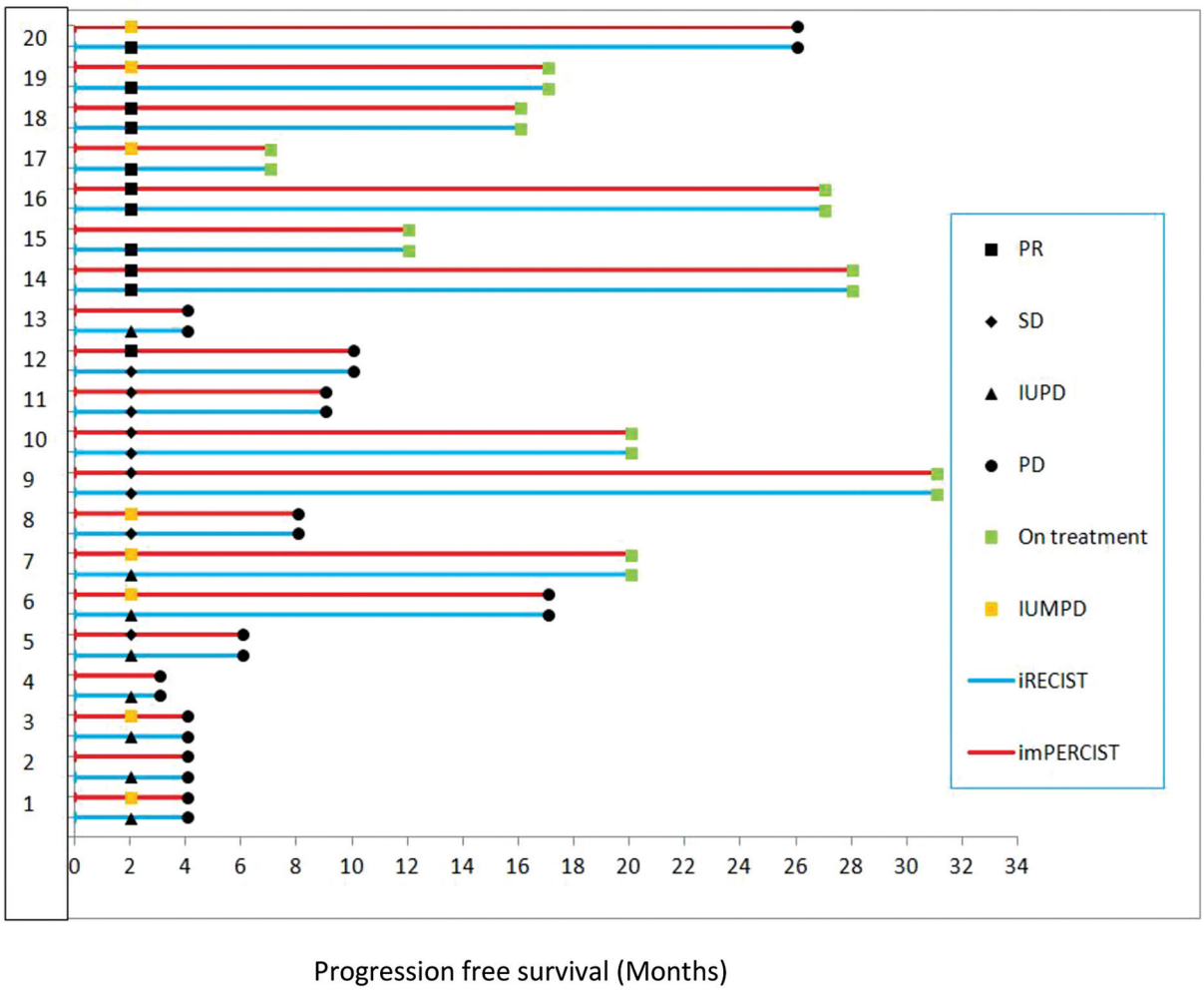

Fig. 4 Swimmers plot showing the response outcome of 20 patients on PET-1 by both iRECIST and imPERCIST criteria and their follow-up outcome. imPERCIST, immune adaptive positron emission tomography response criteria in solid tumors; iUPD, immune unconfirmed progressive disease; iUPMD, immune unconfirmed progressive metabolic disease; iRECIST, immune response evaluation criteria in solid tumors; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

One year and 2 years, PFS for imPERCIST group 1 (responder) was 71.8 and 62.8%, respectively. A statistically significant difference (p-value < 0.05) was found on intracomparison in the Kaplan–Meier method with the log rank test for group 1 and 2 within each response criteria (►**Fig. 6**). However, it was not significant in intercomparison (p-value > 0.05). Patients with pseudoprogression on PET-1 by iRECIST (n-2) and imPERCIST (n-3) had a mean PFS of 18.5 and 16.3 months, respectively. On PET-1, 5/20 (25%) of the patients developed a new lesion, and all of these patients showed true progression on subsequent analysis (PET-2) with a mean PFS of 3.8 months.

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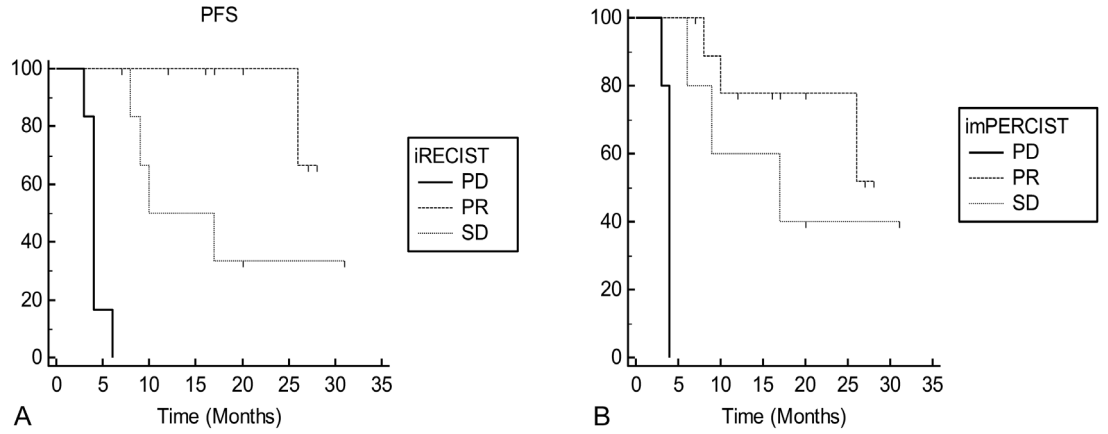

Fig. 5 Kaplan–Meier PFS curve for three response groups (PR, SD, and PD) for iRECIST (**A**) and imPERCIST (**B**). imPERCIST, immune adaptive positron emission tomography response criteria in solid tumors; iRECIST, immune response evaluation criteria in solid tumors; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

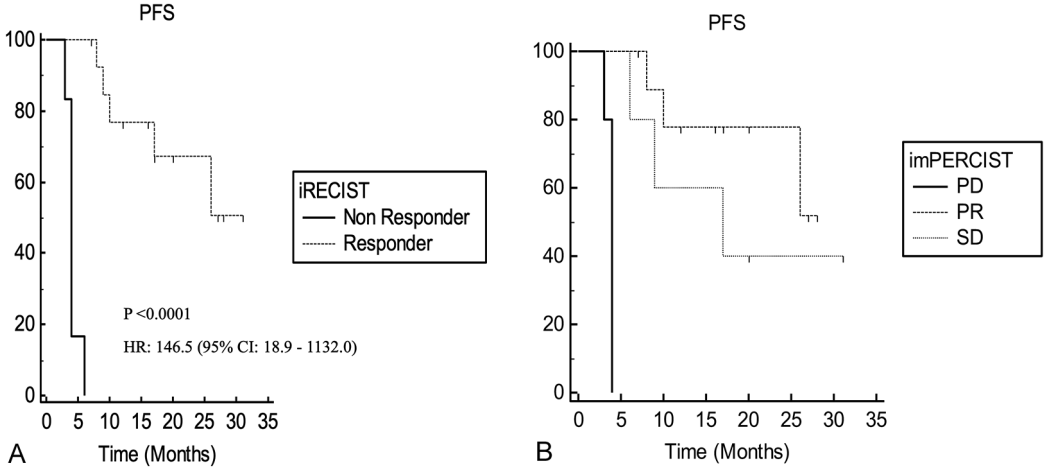

Fig. 6 Kaplan-Meier PFS curve for group 1 (responder) and group 2 (nonresponder) for iRECIST (**A**) and imPERCIST (**B**). Immune unconfirmed progressive metabolic disease. HR, hazard ratio; imPERCIST, immune adaptive positron emission tomography response criteria in solid tumors; iRECIST, immune response evaluation criteria in solid tumors; PFS, progression-free survival.

No significant correlation (p-value > 0.05) was seen on Spearman's rank test for SoD, SUVmax, SoMTV, and SoTLG with PFS, indicating no significant association between initial disease burden (PET-0) and PFS in our study (►**Table 3**). On univariate regression analysis, percentage change in SoD, SoMTV, and SoTLG at PET-1 as compared with PET-0 was found to be significant variables (p-value < 0.05) for the prediction of PFS. In contrast, the percentage change in SUVmax was not significant (►**Table 4**). On multivariate regression analysis, the percentage change in SoD was the only significant predictor, although the hazard ratio was not high (1.015). Harell's C-index was 0.8162, which indicates a robust cox-regression model for prediction of PFS in our study. Receiver operating characteristic curve analysis for the percentage change in SoD for prediction of PFA at 2 years showed a sensitivity of 90.9% and specificity of 66.7% for a 27.5% decrease in SoD with the area under the curve of 0.808 (►**Fig. 7**).

Table 3 Spearman's rank correlation for PET-0 SoD, SUVmax, SoMTV, and SoTLG with PFS

Variables	SoD (cm)	SUVmax	SoMTV	SoTLG
Correlation Coefficient	−0.018	−0.026	−0.085	0.042
p-Value	0.940	0.912	0.721	0.862

Abbreviations: PET, positron emission tomography; PFS, progression-free survival; SoD, sum of diameters; SoMTV, sum of metabolic tumor volumes; SoTLG, sum of total lesion glycolysis; SUVmax, standard uptake value maximum.

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Table 4 Univariate and multivariate cox proportional hazard model for percentage change in SoD, SUVmax, SoMTV, and SoTLG at PET-1 in comparison to PET-0

Variables	Univariate analysis				Multivariate analysis			
	p- Value	HR	95.0% CI		*p*-Value	HR	95.0% CI	
			Lower	Upper			Lower	Upper
Percentage difference in SoD	0.004	1.017	1.005	1.029	0.032	1.015	1.001	1.028
Percentage difference in SUVmax	0.214	1.006	0.997	1.015				
Percentage difference in SoMTV	0.004	1.009	1.003	1.015	0.273	1.009	0.993	1.026
Percentage difference in SoTLG	0.006	1.004	1.001	1.006	0.698	0.999	0.991	1.006

Abbreviations: CI, confidence interval; HR, hazard ratio; PET, positron emission tomography; SoD, sum of diameters; SoMTV, sum of metabolic tumor volumes; SoTLG, sum of total lesion glycolysis; SUVmax, standard uptake value maximum.

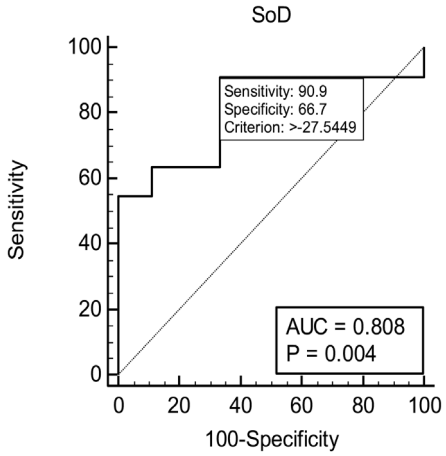

Fig. 7 Receiver operating characteristic curve (ROC) analysis for the percentage change in the sum of diameters (SoD) for 2 years progression-free survival (PFS) prediction.

Discussion

The ICIs have changed the outcome of many cancer patients, and the indications of using these are increasing day by day. The complexity of the novel mechanism of action and combinations makes it difficult to assess response in the clinical setting. Many imaging biomarkers have been explored and proposed for this, but due to the limited and heterogeneity of the data, concrete guidelines are still missing. Therefore, it has become of utmost importance to reassess the criteria for the evaluation of treatment response. iRECIST is one of the steps in this direction. Many questions like pseudoprogression, hyperprogression, early response assessment, and prediction of outcome still need to be answered.

"Molecular changes precede morphological changes" is a well-known fact in oncology.[17] Therefore, both tissue and imaging biomarkers are used for response assessment. FDG PET/CT is a better modality in cancers like lymphomas, GIST, and many others. So far, there is limited data regarding its role in response assessment of ICIs available. Goldfarb et al introduced iPERCIST in a recent retrospective analysis of 28 patients of NSCLC treated with nivolumab.[18] During the assessment of the first response with PET/CT, 13/28 (46.4%) of the patients were found to be unconfirmed progressive metabolic disease (UPMD) in their study. Out of these 13 UPMD patients, 3 were responders in subsequent assessment; hence, pseudoprogression was seen in 3/28 (10.7%) of the patients. The remaining 10 patients were considered as actual progression due to clinical degradation, and no further imaging was performed. We had 8/20 (40%) iUPMD patients during the first response assessment, and 3 of these were responders on subsequent examination; hence, pseudoprogression cases were 3/20 (15%) in our study. Since we have included only those patients with three sequential PET/CT studies available, this may be the reason for the higher pseudoprogression rate in our study. Goldfarb et al also reported 11/28 (39%) discordance between iRECIST and iPERCIST results. More number of patients were classified as PR by iPERCIST. We found a discordance in 4/20 (20%) of the patients in our analysis at PET-1. Two patients with SD with iRECIST were classified as PR by iPERCIST. Subsequent response analysis of both these two patients showed disease progression with PFS of 8 and 10 months. The mean PFS (9 months) of these two patients was significantly lower than the mean PFS of the overall SD group (17.7 months) of iRECIST. One patient of iUPD with iRECIST was classified as SD with iPERCIST; however, this patient showed progression on subsequent analysis with PFS of only 6 months. One patient showing PR with iRECIST was classified as iUPMD with iPERCIST, which showed PR on the next assessment and was still on nivolumab treatment with 12 months follow-up. Therefore, we found that iPERCIST was unable to identify a better subgroup of patients in our study.

Early prediction of outcome is vital to avoid futile treatment, drug, and financial toxicities. Response criteria are commonly challenged for this purpose in the clinical setting. FDG PET-CT has been used successfully for early prediction in lymphomas and advanced melanomas.[19,20] Kaira et al recently reported a favorable predictive role of metabolic response in a prospective study of 24 NSCLC patients treated with nivolumab.[21] A statistically significant difference in PFS was reported in responder (PD) and nonresponder (no PD) according to PET biomarkers (SUVmax, MTV, and TLG). At the same time, it was not-significant for CT post one month of treatment. On multivariate analysis, change in TLG in 1 month FDG PET/CT following nivolumab had significant

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prognostic value. We found that percentage change in MTV, TLG, and SoD were the predictive biomarkers for PFS outcome on univariate analysis while it was only SoD in multivariate analysis. On critical analysis, we realized that Kaira et al have used PERCIST criteria for metabolic response and RECIST 1.1 for morphological assessment. For TLG and MTV calculation, they have used the SUV threshold of 2.5 for defining tumor volume, while we have used a 40% threshold method. They have calculated MTV and TLG of all measurable lesions with a maximum of five lesions per organ. In comparison, we used five measurable lesions as per RECIST 1.1 with a maximum of two lesions per organ. Despite these fundamental differences in study design, we found both criteria (iRECIST and imPERCIST) were able to predict the outcome with no significant difference in our study.

Rossi et al recently reported low concordance between CT (RECIST 1.1 and irRC) and PET-based criteria (PERCIST and imPERCIST) and limited prognostic value for overall survival at first response assessment in 48 NSCLC patients treated with nivolumab.[22] Patients classified as PD by all criteria had a uniformly poor prognosis. Unexpectedly, patients classified as SD by both CT criteria had a better outcome than PR patients. Patients classified as SMD by both PET criteria had a similar result as a PMD. On posthoc analysis, the authors demonstrate some prognostic significance of PET responder (PMR) versus PET nonresponders (PMD + SMD) within the irRC PD group. Conversely, we showed that both criteria (iRECIST and imPERCIST) response groups (PR, SD, and PD) had prognostic significance. However, imPERCIST was unable to identify a better response subgroup within iRECIST group.

Another critical issue is the new lesion during response evaluation of ICIs, which may be either due to inflammatory response or disease progression. Anwar et al proposed PET response evaluation criteria for immunotherapy (PERCIMT) and reported four new FDG avid lesions on posttherapy PET/CT have a sensitivity of 84% and specificity of 100% for actual progression in metastatic melanoma patients (n-41) under ipilimumab treatment in a retrospective analysis.[23] The authors also reported sensitivity and specificity for three new (> 1.0 cm) and two new (> 1.5 cm) FDG avid lesions on posttherapy scan as 90%, 90% and 94%, 90%, respectively, for accurate progression prediction. In our study, we also found that all patients with a new lesion (n-5) on the first follow-up scan developed disease progression on subsequent analysis. A large prospective study to evaluate the role of a new lesion in the prediction of actual progression is urgently required to clarify this issue further.

We have come across a few limitations in our study. Major limitations of the work are the modest study population and the retrospective design of the study. We have included lung cancer patients on nivolumab with three sequential PET-CT scans, which limited the sample size but led to more accurate assessment following unconfirmed progression. For imPERCIST criteria, we used only the highest SUVmax per study. However, for iRECIST, MTV, and TLG analysis, we have analyzed five target lesions per patient. That may be a reason why the percentage change in SUVmax was not a significant predictor for PFS. Hence, further research to find out the appropriate number of lesions for SUVmax measurement needs to be looked in.

MTV and TLG were the novel molecular imaging biomarkers. However, there was heterogeneity in their methods of calculation exists. There may be instances that a target lesion for RECIST may not be the target lesion for PERCIST or vice versa. A subcentimeter lesion may have the highest SUVmax, while a large lesion may not. Another critical issue was the tumor margin for MTV calculation. In our experience, a percentage thresholds method (for example, 40% of SUVmax) may underestimate tumor volume in high SUVmax lesion. However, a fixed threshold method (e.g., SUVmax 2.5) may overestimate in low SUVmax lesion. For response assessment where we assumed low SUVmax in the follow-up scan, a percentage thresholds method was found to be more appropriate for us. Therefore, we proposed that to find out the predictive value of MTV at a baseline, a fixed threshold method. However, for response assessment, a percentage threshold method should be the topic of further research. Overall survival may have been a better indicator to determine the impact of the response outcome of two criteria. However, survival data was not available for these patients. It may be analyzed in future studies. We used PERCIST criteria with modifications, like SUVmax rather than SULpeak, for PET interpretation. We found that SUVmax was preferred in practice and for communication with the medical oncologist despite its known limitations. We follow a standard PET protocol in all patients, which will reduce the impact of noise on SUVmax. Moreover, it is reasonably easy to determine the SUVmax, while SULpeak is more challenging to measure. This difference in methodology may compromise the interstudies comparison during meta-analysis of the two criteria.

Studies using SULpeak are warranted in the future and may have different results. Another issue of this study was a noncontrast CT scan for iRECIST interpretation; however, despite this limitation, we found that iRECIST is slightly better than iPERCIST.

Conclusion

We concluded that imPERCIST was not better than the currently recommended morphological criteria iRECIST for response evaluation in lung cancer patients on nivolumab treatment. Further prospective studies are warranted for imPERCIST to find out its advantages in clinical practice in this setting.

Conflicts of Interest
None.

Acknowledgment
None.

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