# Treatment Response Appraisal in Non-Small Cell Lung Cancer Using $^{18}$F-FDG PET-CT Imaging: Insights from Initial Application of PERCIST 1.0 and RECIST 1.1 Criteria

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## ABSTRACT

***Introduction:*** An $^{18}$F-FDG PET-CT scan is increasingly used in the evaluation of treatment response for patients with non-small cell lung cancer (NSCLC) in a conventional way using SUVmax and a total body survey. The aim of this study was to evaluate responses in NSCLC patients by using PERCIST 1.0 and RECIST 1.1.

***Patients and methods:*** Retrospective data analysis of five patients with NSCLC over a 1.5-year period was done. The assessment included baseline and therapeutic response measurements using $^{18}$F-FDG PET-CTimaging at National Institute of Nuclear Medicine & Allied Sciences (NINMAS) after treatment completion, independent of the type of medication administered.

***Results:*** Three patients were male and two were female, with the mean age being 57 yrs ± 14.76 yrs (mean ± SD). All of them were diagnosed at advanced stages of NSCLC. The mean duration of response evaluation after finishing therapy was 76.6 days. Four out of five patients showed stable disease (SD) after RECIST 1.1, and one showed a complete response (CR). PERCIST 1.0 evaluation showed progressive metabolic disease (PMD) in two patients and partial metabolic response (PMR) in two patients. The patient with CR on RECIST was also found to have a complete metabolic response (CMR) on PERCIST.

***Conclusion:*** Utilizing PERCIST 1.0 and RECIST 1.1 with hybrid imaging allows for a non-invasive assessment of metabolic and morphologic responses, providing clinicians with enhanced information for managing advanced NSCLC patients.

***Keywords:*** PERCIST 1.0, RECIST 1.1, NSCLC, $^{18}$F-FDG PET-CT

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## INTRODUCTION

Based on cell morphology, growth, and spread, lung cancer is mainly divided into two types: small cell lung cancer (SCLC, ~15% of cases) and non-small cell lung cancer (NSCLC, ~85% of cases) (1). It continues to be the primary cause of cancer-related deaths in 2025, accounting for 20.2% of all cancer-related deaths in the USA (2). In Bangladesh, the most recent report shows that lung cancer is the deadliest cancer, with 35000 new diagnoses per year and 5000 deaths annually owing to the additional burden of high treatment costs and late diagnosis (3). The five-year relative survival rate of lung cancer is 28.1%. It depends mostly on the histology and disease's stage at diagnosis, being highest for localized cancer (64.7%) and lowest for distant metastatic spread (9.7%) (1).This emphasizes how crucial are early diagnosis, precise staging with timely therapy commencement, early treatment response evaluation, and prognosis determination for improving patient outcomes and survival (4). Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are major types in NSCLC, where the former two account for the majority of NSCLC (1).

Depending on the stage of the disease, chemotherapy, radiation, surgery, targeted therapy, or different combinations of these modalities are used to treat NSCLC. Both the diagnosis and treatment of NSCLC have advanced significantly in recent years. One of the most significant developments is the routine use of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose positron emission tomography/computed tomography ($^{18}$F-FDG PET-CT) imaging instead of conventional imaging for staging and treatment response evaluation in NSCLC (5,6).

$^{18}$F-FDG PET-CT is also used to assess the effectiveness of treatment (chemotherapy, radiation, or immunotherapy), distinguish between scar tissue/fibrosis and active tumor tissue, and facilitate the early detection of tumor progression or recurrence. The most updated metabolic response criteria for use by PET is PET

response criteria in solid tumors (PERCIST 1.0) based on models of metabolic alterations seen following cytotoxic therapy and/or chemotherapy (6).

By emphasizing the evaluation of tumor metabolic activity, as determined by the uptake of the radiotracer $^{18}$F-FDG, the PERCIST 1.0 response offers functional information (7). The main parameters of PERCIST 1.0 include the following:

- SUV (Standardized Uptake Value): An indicator of the lesion's metabolic intensity.
- SUL (Standardized Uptake Value normalized for lean body mass): A modified SUV that is adjusted for lean body mass.
- Metabolic dimension: The tumor's bulk with strong metabolic activity (7).

A published set of guidelines called Response Evaluation Criteria in Solid Tumors (RECIST) is used to quantify tumor burden objectively to determine response to traditional systemic therapy, which mainly relies on anatomical measurements by conventional imaging methods, e.g., CT scan or magnetic resonance imaging (MRI) (6). They were first released in 2000 (RECIST 1.0), and the most recent version was released in 2009 (RECIST 1.1). In RECIST 1.1, a PET scan can be used to identify disease progression if a metabolically active new lesion is seen that is also measurable in corresponding CT images, e.g., bone metastasis (8). It is termed as the PET-adapted version of morphologic response evaluation criteria in solid tumors (6).

This narrative article aims to critically appraise the current role of $^{18}$F-FDG PET-CT imaging in assessing therapy response in NSCLC, with a focus on the use of updated imaging response criteria evaluation and potential avenues for future research in the context of Bangladesh. PERCIST 1.0 and RECIST 1.1: both responses have been evaluated and recorded for the first time in the Bangladeshi population of NSCLC.

## PATIENTS AND METHODS

Patient data from January 2023 was retrospectively reviewed for five NSCLC patients who underwent both baseline and post-treatment $^{18}$F-FDG PET-CT imaging at NINMAS between January 2021 and June 2022. The study adhered to PERCIST evaluation criteria (9), with all scans performed on the same Philips Dual Modality Ingenuity TF PET-CT machine. After fasting, $^{18}$F-FDG was administered, allowing radiation uptake in a controlled environment. The PET-CT scans, including fusion images, took about 20 to 25 minutes to complete. Responses were evaluated using PERCIST 1.0 and RECIST 1.1 guidelines, focusing on the hottest lesions and multiple target lesions respectively. Conventional SUVmax-based responses were also recorded, with all evaluations conducted by experienced nuclear medicine physicians and SPSS was used for statistical analysis.

### *PERCIST 1.0 overview*

Metabolic tumor response has the following four categories as per PERCIST 1.0 criteria:

**(i) Complete metabolic response (CMR):** Complete resolution of $^{18}$F-FDG uptake or reduction of FDG avidity below background in all lesions.

**(ii) Partial metabolic response (PMR):** A minimum of 30% reduction of the SULpeak and an absolute drop of 0.8 SULpeak units of target lesion and no new FDG-avid lesion(s);

**(iii) Progressive metabolic disease (PMD):** >30% increase in the SULpeak value of the FDG uptake and an absolute increase of 0.8 SULpeak units or appearance of FDG-avid new lesion(s);

**(iv) Stable metabolic disease (SMD):** Not CMR, PMR, or PMD (10).

### *RECIST 1.1 overview*

For RECIST 1.1, target lesions are chosen (a maximum total of five in number and not more than two in a single organ) at baseline and always remain as target lesions for follow-up. Small lesions (<10 mm), leptomeningeal disease, ascites, pleural effusions, pericardial effusion, inflammatory breast disease, lymphangitis cutis or pulmonis, abdominal masses that are not confirmed and followed up with imaging techniques, bone lesions that are only PET detectable, cystic lesions, etc. are listed as non-target lesions for RECIST 1.1 (8). The four objective responses include the following:

**(i) Complete response (CR):** Disappearance of all target and non-target lesions; any pathological lymph nodes must have a reduction in short axis to <10 mm.

**(ii) Partial response (PR):** At least a 30% decrease in the sum of diameters (SOD) of target lesions from baseline SOD and no new lesion(s) or non-PD of non-target lesions defined as the persistence of one or more non-target lesions above normal limits but without unequivocal progression.

**(iii) Progressive disease (PD):** At least a 20% increase in the SOD of target lesions (and also an absolute increase of at least 5 mm) or the appearance of new lesions (both target and non-target) on CT or PET scan or unequivocal progression of non-target lesions (> 75% increase in the volume) or a new "positive PET" scan of non-target lesions with confirmed anatomic progression.

**(iv) Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD (8, 11).

## RESULT

Sociodemographic and clinical characteristics of the studied subjects is shown in Table 1. The study included five (M = 3, F = 2) NSCLC patients with a mean age of 57 ± 14.8 (mean ±SD) years. Histopathology revealed adenocarcinoma in 3 patients (60%), large cell carcinoma in one (20%), and EGFR-positive NSCLC in one (20%). Right lung involvement was detected in 3 patients (60%) and left in 2 (40%). Calculated staging was IIIB in 2 (40%) patients and stage IV in 3 (60%). Treatment modalities included chemotherapy alone in 2 (40%) patients, chemoradiotherapy in 2 (40%), and targeted therapy in one (20%), with a therapy duration of mean ± SD: 10.2 ± 8.5 months (vs. 6.8 ± 4.0 months excluding targeted therapy). The mean interval between therapy completion and PET-CT response evaluation was 76.6 days. Table 2 shows $^{18}$F-FDG PET-CT findings in studied subjects emphasizing on FDG avidity of lesions pre and post treatment in advanced NSCLC with changes in respective SUVmax values (mean ± SD where applicable). Primary tumors involved the left upper and lower lobes as well as the right apical and lower lobes. Metastatic sites included lymph nodes (cervical, hilar, supraclavicular, and peritoneal); skeleton (scapula, vertebrae, ribs, and sternum); brain; and choroid. SUVmax values generally decreased post-therapy (SUVmax reduction from mean ± SD: 8.45 ± 3.18 at baseline to 2.7 post-therapy for lymphnodes), except for skeletal lesions (SUVmax increasing from mean ± SD:6.13 ± 2.62 to mean ± SD: 8.17 ± 6.93). The SUVmax value of a single brain lesion and choroidal mass was recorded, and they disappeared on the post-therapy scan, while pleural infiltration showed minimal change after treatment.

**Table 1. Sociodemographic and clinical characteristics of study subjects (N=5) with NSCLC**

| | Parameters | Frequency (%) |
|---|---|---|
| 1. | Sex | Male: 03 (60%)<br>Female: 02 (40%) |
| 2. | Age at diagnosis | 57yrs±14.76yrs (Mean ± SD)<br>Male: 56±21.7yrs (Mean ± SD)<br>Female: 58.5±12.0yrs (Mean ± SD) |
| 3. | Histopathological diagnosis: | Adenocarcinoma: 03 (60%)<br>Large cell carcinoma: 01 (20%)<br>NSCLC (EGFR positive): 01 (20%) |
| 4. | Side of lung involvement: | Right lung: 03 (60%)<br>Left lung: 02 (40%) |
| 5. | Stage at diagnosis: | Stage IIIB: 02 (40%)<br>Stage IV: 03 (60%) |
| 6. | Type of treatment received: | Only CT: 02 (40%)<br>CT+RT: 02 (40%)<br>Targeted therapy: 01 (10%) |
| 7. | Mean duration of therapy: | 10.2±8.47months (Mean ± SD) (incl. targeted therapy)<br>6.75±4.03months (Mean ± SD) (excl.targeted therapy) |
| | Duration between therapy completion and response evaluation: 76.6days (Mean) | |

**Table 2: Distribution of FDG avid lesions in NSCLC among study subjects (N=5)**

| FDG avid Lesions | - | Frequency | Mean of SUV max (±SD) | |
|---|---|---|---|---|
| **1. Primary sites** | | | **At Baseline** | **After therapy** |
| Left upper lobe | - | 1 | | |
| Left lower lobe | - | 1 | **5.69± 3.98** | **2.83±1.68** |
| Apical lobe of right lung | - | 1 | | |
| Lower lobe of right lung | - | 2 | | |
| **2. Metastatic sites** | | | | |
| **Lymphnodes** | | | **8.45±3.18** | **2.7±0** |
| Cervical | - | 1 | | |
| Hilar | - | 2 | | |
| Supraclavicular | - | 2 | | |
| Peritoneal | - | 1 | | |
| **Skeletal lesions** | | | **6.13±2.62** | **8.17±6.93** |
| Scapula | - | 2 | | |
| Vertebrae | - | 6 | | |
| Ribs | - | 5 | | |
| Sternum | - | 2 | | |
| **Brain** | - | 1 | **7.81** | **0** |
| **Choroidal mass** | - | 1 | **3.5** | **0** |
| **Pleural effusion** | - | 2 | | |
| **Pleural infiltration** | - | 1 | **12.7** | **12.6** |

*SUVmax value is given as '0' (zero) where lesion disappeared post-treatment.

**Table 3. Response evaluation Parameters and Recorded Responses (N=5)**

| SUL peak of target at baseline | SUL peak of target after therapy | Sum of Target longest dimension at baseline | Sum of Target longest dimension after therapy | PERCIST 1.0 | RECIST 1.1 | Reported response (based on SUVmax and total body survey) |
|---|---|---|---|---|---|---|
| 10.91 | 15.11 | 26.8mm +Pleural effusion | 23.3mm +pleural effusion | PMD | SD | Stable disease |
| 3.86 | Disappeared | 31.5mm | disappeared | CMR | CR | Therapy response |
| 5.66 | 2.35 | 96.7 mm | 68mm | PMR | SD | Disease progression |
| 9.24 | 3.75, new metabolically active lesion in bone | 99mm | 80mm;. No measurable new lesion; but PET detected new bone lesion. | PMD | SD | Disease progression |
| 4.1 | 1.32 | 21mm | 15mm | PMR | SD | Therapy response |
| Mean ± SD | 6.75±3.17 | 5.63±6.40 | 34.38±28.17 | 31.05±25 | | |

Parameters used for PERCIST 1.0 and RECIST 1.1 evaluations along with responses derived are demonstrated in Table 3. Baseline SULpeak of target lesions ranged from 3.86 to 10.91 (mean ± SD: 6.75 ± 3.17), ranging in post-therapy between 1.32 and 15.11 (mean ± SD: 5.63 ± 6.40). The SOD of target lesions ranged from 21 mm to 99 mm at baseline (mean ± SD: 34.38 ± 28.17) and 15 mm to 80 mm post-therapy (mean ± SD: 31.05 ± 25). By PERCIST 1.0, one patient achieved CMR, two showed PMR, and two patients demonstrated PMD. In contrast, RECIST 1.1 classified one patient as CR and the remaining patients as SD. Notably, $^{18}$F-FDG PET detected new metabolically active lesions in one patient that was not measurable by RECIST criteria, illustrating the higher sensitivity of PERCIST in identifying early disease progression.

Figure 1 and Figure 2 are presented for demonstration and academic purposes to illustrate the methodology of both anatomic and metabolic treatment response assessment from $^{18}$F-FDG PET-CT hybrid imaging technique. Figure 1 demonstrates metabolic response evaluation using PERCIST 1.0, while Figure 2 demonstrates anatomical response evaluation using RECIST. The images represent two different patients of NSCLC who underwent $^{18}$F-FDG PET-CT scan in Philips Dual Modality Ingenuity TF PET-CT machine of NINMAS both in baseline and post-treatment time points. These representative images are included solely to demonstrate the principles of response assessment followed in this study according to the respective criteria

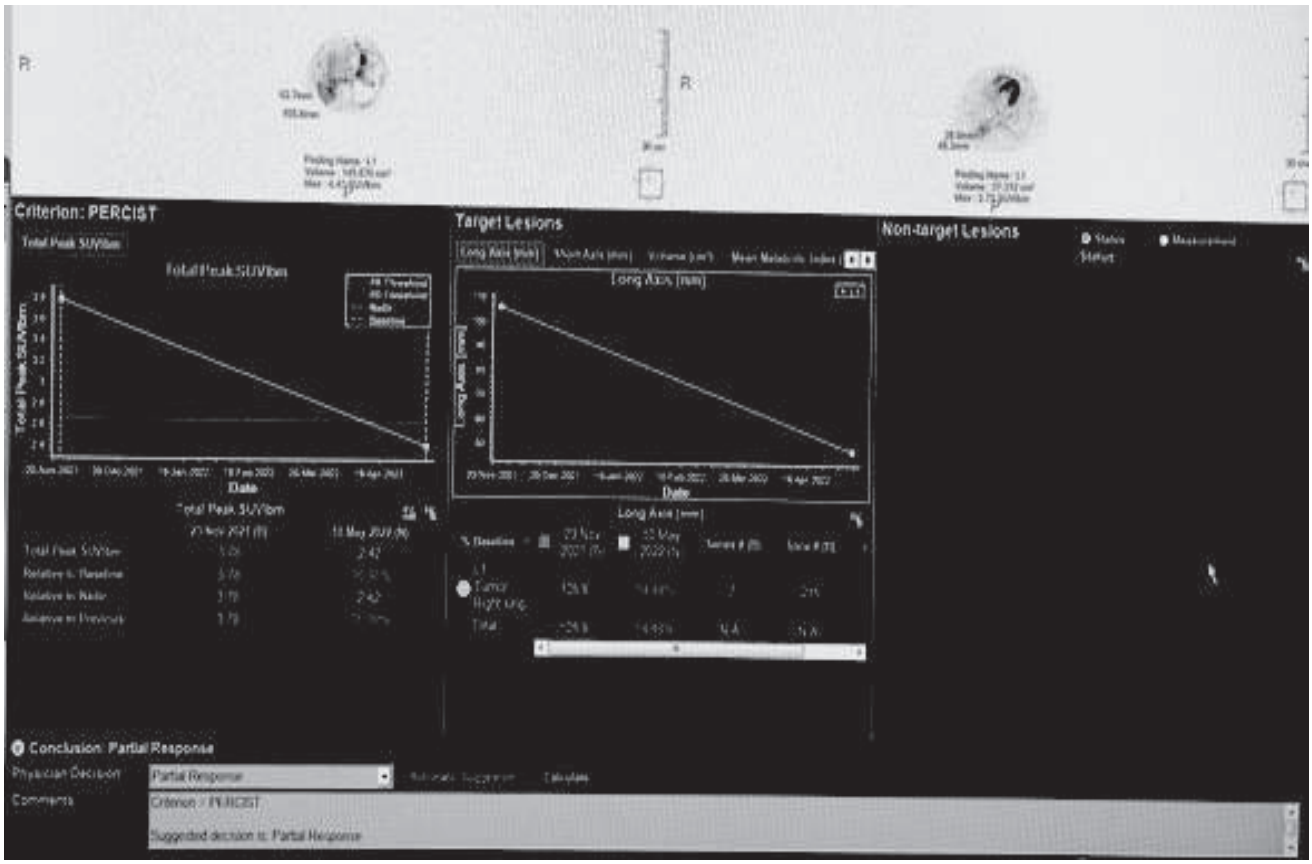


**Figure 1: Sample picture demonstrating metabolic treatment response assessment of a case of NSCLC (right lung) using PERCIST 1.0 methodology on PET scan portion of 18F-FDG PET-CT scan. The SULpeak of target lesion decreased from 3.78 at baseline to 2.42 post-treatment representing a 35.98% reduction in metabolic activity. Concurrently, the long-axis diameter of the target lesion decreased by 54.44% from baseline. Based on PERCIST 1.0 criteria, these findings are consistent with a partial metabolic response (PMR).**

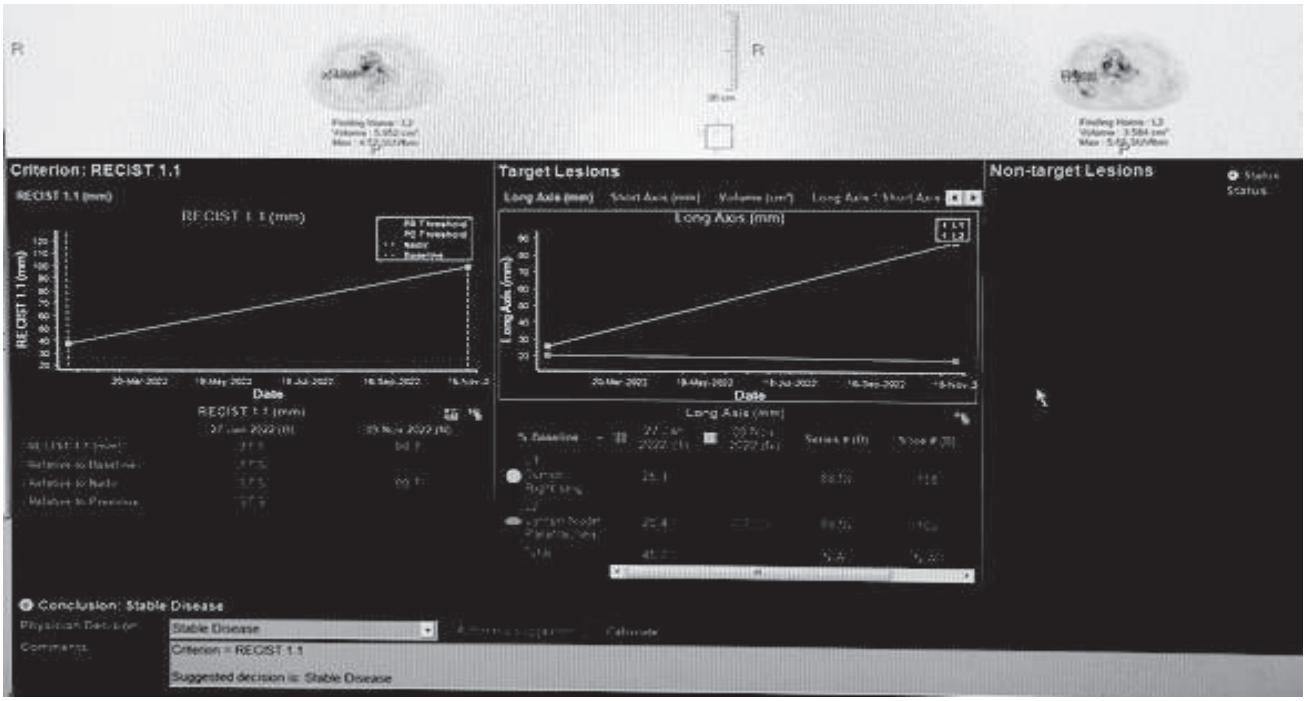


**Figure 2: Sample picture demonstrating anatomic treatment response assessment of a case of NSCLC (right lung) based on RECIST using measurements on CT scan portion of $^{18}$F-FDG PET-CT scan. The sum of the long-axis diameters of target lesions increased from 37.3 mm at baseline to 99.7 mm at follow-up representing a 167.29% increase relative to baseline. The right lung lesion demonstrated a marked increase in size, while the right paratracheal lymph node showed a slight reduction. Despite the increase in the sum of target lesion diameters, the overall assessment according to RECIST 1.1 criteria was stable disease (SD).**

## DISCUSSION

An insight into demographic and clinical variables in current study revealed male predominance as well as an age range at diagnosis between 48 yrs and 70 yrs. Another similar study in a similar population category, including n=53 patients of lung cancer, also demonstrated a similar age range and male predominance. Adenocarcinoma is the predominant histological NSCLC type found among study subjects, which is a similar result to the earlier mentioned study (12). We can observe that study subjects were diagnosed at advanced stages of NSCLC (IIIB and IV), and they were referred for therapy response evaluation by $^{18}$F-FDG PET-CT imaging, indicating that clinicians are more inclined towards PET-CT-based response assessments in these categories of patients.

There are various qualitative and quantitative as well as semiquantitative techniques for evaluating treatment response in patients with NSCLC using $^{18}$F-FDG PET-CT imaging, depending on the kind of therapy. It is ideal to use $^{18}$F-FDG PET-CT to evaluate treatment response 12 weeks following radiation or chemoradiation therapy in advanced stages and as early as four weeks following chemotherapy or surgery. This is due to the fact that post-therapy inflammatory uptake is reduced and disappears quickly, unless there are accompanying wound healing difficulties (13). In studied cohort, the mean interval between treatment completion and response assessment was 76.6 days, which approximately corresponds to a 12-week follow-up period. It is observed that the mean duration of received therapy is reduced when the duration of received targeted therapy in one study subject is excluded, which corresponds to a stated fact that a long median duration applies to anti-EGFR targeted therapy in patients with the EGFR positive variety of NSCLC (19.5 months, including any sequential EGFR-TKI) (14).

The mean SULpeak of primary tumors at baseline is usually high, frequently reported around mean ± SD:9.9 ±4.8 to mean ± SD:14.9 ± 6.7, according to studies using

PERCIST in advanced NSCLC. These readings usually decline considerably after treatment, with one study demonstrating a drop to a mean SULpeak value between 3.2 and 5.6 (15). The mean SULpeak value in present study at baseline (mean ± SD: 6.75±3.17) and at post-therapy (mean ± SD: 5.63±6.40) corresponded with the above result. However, it did not drop to a significant level post-therapy owing to the fact that nearly half of the study subjects had been found with PMD.

The most common metastatic locations for advanced NSCLC include the brain (21–30%), adrenal glands (10–21%), liver (13–17%), distant lungs or mediastinal nodes, and bones (25–39%). The skin, pleura, and pericardium are additional, less frequent locations, making the most frequent distant, non-lymph node locations being the brain and bone (16). A similar observation can be made about the current study regarding skeletal metastases, especially. Due to significantly increased glucose usage in NSCLC, a large amount of the radiolabeled $^{18}$F-FDG is taken up by the tumor. For the detection of lymph node and distant metastases, PET imaging with $^{18}$F-FDG has been proven to be much more sensitive and specific than traditional techniques (17).

In present study cohort, tumor responses have shown considerable differences between the PERCIST 1.0 and RECIST 1.1 in advanced NSCLC. SUVmax based total body survey responses are reported conventionally at NINMAS. Patients with CMR in PERCIST 1.0 and CR in RECIST 1.1 were originally reported as therapy responses in a conventional way also. One patient demonstrated a PMR by PERCIST 1.0, correlating with conventional therapy response, while RECIST 1.1 classified that subject as SD. PMD on PERCIST corresponded to conventional disease progression in two cases, despite RECIST 1.1 showing SD in them. One unique feature of PERCIST 1.0 is, it allows response assessment after selection of the hottest lesion at each time point independently, which reduces the bias of tracking the same lesion at both baseline and post-treatment imaging compared with RECIST 1.1 (9,10). Also it overcomes interobserver variability of size-based morphological response assessments and makes it less time-consuming (8, 10, 11).

Overall, the cohort exhibited a modest decrease in tumor metabolic activity and size, with metabolic criteria detecting changes not captured by anatomical measurements alone. Also, conventional SUVmax-based total body surveys and updated single lesion-based PERCIST 1.0 responses correspond well in this study. This can be highlighted as a very important finding further adding to the strength of metabolic treatment response assessment by PERCIST 1.0 in which result can be derived from a single hottest with highest SULpeak comparable to conventional SUVmax based total body survey method.

Patients who only have osseous metastases cannot have their response assessed using RECIST 1.1, because sclerotic lesions frequently occur and, in some cases, worsen as a result in the presence of a healing bone. However, osseous metastases can be monitored metabolically using PERCIST 1.0 in PET in the same way that soft tissue metastases can (18). In the present study cohort, in one of the study subject, a PET-detectable bony lesion was defined as non-measurable in RECIST evaluation as it was not found in corresponding CT images (8), whereas PERCIST 1.0 classifies that study subject as having PMD.

The limitation of this study was the small sample size owing to meet the specific requirements of PERCIST 1.0 and RECIST 1.1 evaluation and also the lack of overall survival data for comparative analysis to determine which response corresponds more to the patient outcome.

## CONCLUSION

$^{18}$F-FDG PET-CT imaging provides us unique opportunity to convey information about both RECIST 1.1 and PERCIST 1.0 results which can help better clinical decision making in advanced NSCLC patients. Prompt readouts of therapeutic results and elimination of patients from failed treatments is possible by determining change in metabolism by using $^{18}$F-FDG PET-CT as an imaging biomarker of advanced NSCLC. This is a highly appealing potential for customized healthcare called response-adaptive modality if comparative studies by survival analysis can be done.

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