PET/CT evaluation of response to chemotherapy in non-small cell lung cancer: PET response criteria in solid tumors (PERCIST) versus response evaluation criteria in solid tumors (RECIST)

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Background: ¹⁸F-FDG PET/CT is increasingly used in evaluation of treatment response for patients with non-small cell lung cancer (NSCLC). There is a need for an accurate criterion to evaluate the effect and predict the prognosis. The aim of this study is to evaluate therapeutic response in NSCLC with comparing PET response criteria in solid tumors (PERCIST) to response evaluation criteria in solid tumors (RECIST) criteria on PET/CT.

Methods: Forty-four NSCLC patients who received chemotherapy but no surgery were studied. Chemotherapeutic responses were evaluated using ¹⁸F-FDG PET and CT according to the RECIST and PERCIST methodologies. PET/CT scans were obtained before chemotherapy and after 2 or 4-6 cycles' chemotherapy. The percentage changes of tumor longest diameters and standardized uptake value (SUV) (corrected for lean body mass, SUL) before and after treatment were compared using paired t-test. The response was categorized into 4 levels according to RECIST and PERCIST: CR (CMR) =1, PR (PMR) =2, SD (SMD) =3, PD (PMD) =4. Pearson chi-square test was used to compare the proportion of four levels in RECIST and PERCIST. Finally the relationship between progression-free survival (PFS) and clinicopathologic parameters (such as TNM staging, percentage changes in diameters and SUL, RECIST and PERCIST results etc.) were evaluated using univariate and multivariate Cox proportional hazards regression method.

Results: The difference of percentage changes between diameters and SUL was not significant using paired t-test (t=1.69, P=0.098). However the difference was statistically significant in the 40 cases without increasing SUL (t=3.31, P=0.002). The difference of evaluation results between RECIST and PERCIST was not significant by chi-square test (χ²=5.008, P=0.171). If RECIST evaluation excluded the new lesions which could not be found or identified on CT images the difference between RECIST and PERCIST was significant (χ²=11.759, P=0.007). Reduction rate of SULpeak (%), RECIST and PERCIST results were significant factors in univariate Cox analysis. But Multivariate Cox proportional hazards regression analysis demonstrated that only PERCIST was a significant factor for predicting DFS [hazard ratio (HR), 3.20; 95% (CI), 1.85-5.54; P<0.001].

Conclusions: PERCIST and RECIST criteria have good consistency and PERCIST (or PET) is more sensitive in detecting complete remission (CR) and progression. PERCIST might be the significant predictor of outcomes. The combination of PERCIST and RECIST would provide clinicians more accurate information of therapeutic response in earlier stage of treatment.

Keywords: Non-small cell lung cancer (NSCLC); treatment response; response evaluation criteria in solid tumors (RECIST); PET response criteria in solid tumors (PERCIST); ¹⁸F-FDG PET/CT

Submitted Mar 18, 2014. Accepted for publication May 21, 2014.
doi: 10.3978/j.issn.2072-1439.2014.05.10
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.05.10
Introduction

Morphological analysis based on CT is primary method in evaluation of treatment response for non-small cell lung cancer (NSCLC) and other solid tumors. Response evaluation criteria in solid tumors (RECIST) is the “gold” criteria in CT evaluation which was established in 2000 and revised in 2009 (RECIST 1.1) (1). With the popularity of PET/CT many researchers have studied the changes of standardized uptake value (SUV) before and after treatment, but there are no uniform criteria for evaluation of treatment response. In 2009 Wahl et al. proposed the PET response criteria in solid tumors (PERCIST) as a new method in which the treatment response was evaluated by metabolic changes (2). The present study was designed to evaluate the therapeutic response of forty-four NSCLC patients according to PERCIST protocol and to compare with the RECIST 1.1 criteria. Further to access PERCIST criteria and discuss the advantage of it relative to RECIST.

Methods

Patients information

With the approval of Ethics Review Board in our hospital the records of NSCLC patients on PACS (Picture Archiving and Communication Systems) were retrospectively reviewed who underwent $^{18}$F-FDG PET/CT examination twice or more without operation between Jan 2010 and Jun 2013. The patients were histologically confirmed NSCLC and received chemotherapy which consisted of cisplatin and another drug (such as pemetrexed and so on). After the chemotherapy targeted drugs might be used. The first time of PET/CT examination was before the start of treatment and the second was in 15-30 days after 2 or 4-6 cycles’ chemotherapy. The images met the criterion of RECIST and PERCIST and at least one target lesion could be confirmed. The SUL$_{\text{peak}}$ (SUV normalized to body weight and lean body mass) of target lesions at baseline (pretreatment) must not less than $1.5 \times$ mean liver SUL + 2SDs of mean SUL. According to the above requirements 44 patients were collected (33 men and 11 women; median age, 67 years; range, 41-83 years; mean weight, 66.3±12.9 kg, range, 43-98 kg).

PET/CT protocol

PET/CT examination was performed with an integrated scanner (Siemens biograph 16). $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) was produced by CTI RDS III cyclotron (GE) and the radiochemical purity was more than 95%. Each patient had to fast for 6 hours at least and the blood glucose level must be less than 200 mg/dL before intravenous injection of $^{18}$F-FDG at the dose of 3.7-5.5 MBq/kg body weight and been suggested to drink about 1,000 mL water after injection. PET/CT scan was begun about 60 min after injection and the range was from the skull base to the middle of the femur. CT acquisition parameters were as follows: 120 kV and 200 reference mAs; dynamic dose control mode (Caredose 4D); 1.5-mm detector collimation and 5.0-mm slice thickness. PET parameters: 3D emission scan, 1.5-2 min per bed position; 6-7 beds, ordered-subset expectation maximization (OSEM) reconstruction. CT scan data was used for attenuation correction of PET image. Breath-holding CT images including lung lesions were obtained after PET/CT program and thin-section images were reconstructed.

Target lesions and measurement

The target lesions of patients on PET/CT images were determined by two experienced radiologists. Only one target lesion was chosen in the present study because there is one target lesion in PERCIST protocol, and this might be more comparable for PERCIST and RECIST. The target lesion size (length x width) was measured on breath-holding CT mediastinal window images and recorded as CT baseline data. The peak SUL of hottest single tumor lesion with maximal 1.2-cm diameter volume ROI (SUL$_{\text{peak}}$) was required to measure in PERCIST. The software on Siemens PET/CT wizard workstation had limitations in obtaining the peak SUV directly. In this study we used layer by layer accumulated region of interest (ROI) measurement method by reference to the related literatures (3,4). At the center layer of lesion (including the maximal SUV) the ROI with 1.2-cm diameter was made and the mean SUV of three continuous layers (layer thickness was about 4 mm) adjoin to the centre layer were measured. The average of three mean SUVs was approximately taken as the peak SUV (SUV$_{\text{peak}}$) of volumetric ROI. Then the SUV$_{\text{peak}}$ was normalized for the lean body mass and generated SUL$_{\text{peak}}$ According to the formula as follows (5): SUV = A/(ID/LBM), LBM (male) = 1.10x BW − 120 (BW/H)$^2$, LBM (female) = 1.07x BW − 148 (BW/H)$^2$. Where A is the decay-corrected tissue activity concentration (measured in megabecquerels per milliliter), ID is the net injected dose (in megabecquerels), BW is the patient’s body weight (in grams), and LBM is the patient’s

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lean body mass. The longest diameters and SUL\textsubscript{peak} of target lesions on the PET/CT images before and after treatment were measured and recorded as D1, D2 and SUL1, SUL2.

**Response evaluation methods**

Objective therapeutic responses according to RECIST 1.1 are as follows (1): complete remission (CR) is disappearance of target lesion for at least 4 wk; partial remission (PR) is a decline of at least 30% in tumor diameter; stable disease (SD) is neither PR nor progressive disease (PD); and PD is at least a 20% increase in tumor diameter and 5-mm absolute increase was required. Objective therapeutic responses according to PERCIST 1.0 are as follows (2): complete metabolic response (CMR) is complete resolution of \(^{18}\text{F}\)-FDG uptake within the measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels with no new \(^{18}\text{F}\)-FDG-avid lesions. Partial metabolic response (PMR) is reduction of a minimum of 30% in the target tumor \(^{18}\text{F}\)-FDG SUL\textsubscript{peak}. Stable metabolic disease (SMD) is disease other than CMR, PMR, or progressive metabolic disease (PMD); and PMD is a 30% increase in \(^{18}\text{F}\)-FDG SUL\textsubscript{peak} or advent of new \(^{18}\text{F}\)-FDG-avid lesions that are typical of cancer.

**Statistical and survival analysis**

The percentage changes of longest diameters and SUL\textsubscript{peak} of target lesions in 44 patients before and after treatment were calculated according to the formula as follows: \(\Delta D\% = \frac{(D1 - D2)}{D1} \times 100\%\); \(\Delta SUL\% = \frac{(SUL1 - SUL2)}{SUL1} \times 100\%\). A paired Student’s \(t\)-test method was used to assess the statistical significance of these two changes and the results could evaluate the sensitivity of CT and PET on the response. Then the response was classed into four levels according to RECIST and PERCIST: CR (CMR) = 1, PR (PMR) = 2, SD (SMD) = 3, PD (PMD) = 4. Pearson chi-square test was used to compare the proportion of four levels in RECIST and PERCIST. Because the new lesions noted on PET/CT were used for progress in RECIST 1.1, in order to compare PET/CT and CT in the evaluation of treatment response, the new lesions which could not be found or confirmed on routine CT were eliminated in RECIST and compared with PERCIST once more with chi-square test. A \(P\) value of less than 0.05 was considered to be significant.

The relationship between progression-free survival (PFS) and clinicopathologic results (such as TNM stage, percentage changes, RECIST and PERCIST results etc.) were evaluated using univariate Cox proportional hazards regression analysis. Significant parameters identified by univariate analysis were included in a multivariate Cox proportional hazards regression analysis [stepwise selection (Wald) method; \(P \leq 0.05\) was used for entry into the model, and \(P > 0.1\) was selected for removal]. The statistical software was SPSS17.0.

**Results**

**The relation between the changes of diameter and SUL**

There were 30 adenocarcinoma and 14 squamous cell carcinoma cases in 44 patients. TNM staging were 10 cases in stage II, 7 cases in stage III and 27 cases in stage IV. Twenty-five patients were reviewed at the end of 2 cycles of chemotherapy and 19 patients at the end of 4-6 cycles of chemotherapy. The longest diameters, SUL and percentage changes of target lesions before and after treatment were shown in Table 1 and Figure 1. The difference of percentage changes between diameter and SUL was not significant using paired \(t\)-test (\(t=1.69\), \(P=0.098\)). However if the 40 cases without increasing SUL after treatment were analyzed there was significant difference in the percentage changes between diameter and SUL (\(t=3.31\), \(P=0.002\)).
The response classification for 44 patients according to RECIST and PERCIST criteria was as follows: CR/CMR, 2/7; PR/PMR, 22/22; SD/SMD, 19/8; PD/PMD, 6/7; and 15 patients were not consistent. The difference between RECIST and PERCIST was not significant by chi-square test (Pearson $\chi^2=5.008$, $P=0.171$). If the new lesions which could not be found or identified on CT images were revaluated in RECIST, the evaluation results were CR/CMR, 2/7; PR/PMR, 22/22; SD/SMD, 19/8; PD/PMD, 1/7.

The grading of 20 patients were not consistent and the difference between RECIST and PERCIST was significant by chi-square test (Pearson $\chi^2=11.759$, $P=0.007$). The details of evaluation results were summarized in Tables 2 and 3.

Survival analysis and prognosis

The PFS of 44 patients was 2-49 months and the average was 14.8 months. Associations between PFS and clinicopathologic results, changes of imaging parameters and chemotherapeutic responses [such as TNM stage, reduction rate of tumor diameter (%), chemotherapy cycles (2 or 4-6), reduction rate of SUL$_{\text{peak}}$ (%), RECIST (CR/PR/SD/PD) and PERCIST (CMR/PMR/SMD/PMD)] were assessed using univariate and multivariate Cox proportional hazards regression analysis (Table 4). Reduction rate of SUL$_{\text{peak}}$ (%), RECIST and PERCIST were significant factors in univariate Cox analysis. But Multivariate Cox proportional hazards regression analysis demonstrated that only PERCIST was a significant factor for predicting DFS [hazard ratio (HR), 3.20; 95% CI: 1.85-5.54; $P<0.001$]. The survival curve of RECIST and PERCIST produced by SPSS was shown in Figures 2 and 3.

Discussion

RECIST criteria is widely applied to evaluate the treatment response for solid tumors, but is known to have limitations because it depends on the morphologic changes (2,6). Now with increasing use of the targeted therapy, such as
antiangiogenic therapy in clinic, a new evaluation method is necessary to effectively monitor the response of this therapy (6). 18F-FDG PET or PET/CT is considered to overcome such limitations and more suitable for assessment of therapeutic effect because it can better reflect the intrinsic nature of malignant tumor (7). The present study demonstrated that the percentage changes of SUL after treatment for NSCLC monitored by PET were higher than the percentage changes of diameter by CT and the evaluation results by PERCIST were more sensitive and prognostic than the evaluation results by RECIST.

Many studies have confirmed that 18F-FDG PET can monitor the metabolic changes of tumors after treatment when the morphologic changes on CT images can not been detected (8,9). The data of most patients in this study also support this viewpoint in which the reduction percentages of diameter were significantly lower than that of SUL on PET/CT images. But no statistically significant result was obtained in 44 patients' data with paired t-test or nonparametric test methods (Wilcoxon signed-rank test). The selection bias should be responsible for this inconformity because of the negative data of progression patients. If the increasing SUL cases and decreasing SUL cases were respectively analyzed, the percentage reduction of SUL in 40 patients was significantly higher than that of diameter. To our knowledge there is no research that proposed the similar problem although a considerable proportion of assessment result was progression in clinic. The reason may be that the similar comparison of percentage changes was not studied by the other research. However the classification according to RECIST or PERCIST or others is established by the researchers rather than tumors itself and it may be a problem when the reduction of 29% is compared with the

| Table 4 Univariate cox proportional hazards regression analysis for prediction of DFS |
|-----------------------------------|---|---|---|---|
| Univariate analysis               | n  | HR  | 95% CI     | P    |
| TNM (II, III, IV)                 | 10/7/27 | 1.23 | 0.84-1.80 | 0.280 |
| Reduction rate of tumor diameter (%) | 44  | 0.38 | 0.10-1.43 | 0.162 |
| Reduction rate of SUL_peak (%)    | 44  | 0.22 | 0.08-0.65 | 0.006 |
| RECIST (CR/PR/SD/PD)              | 2/21/15/6 | 2.55 | 1.42-4.59 | 0.002 |
| PERCIST (CMR/PMR/SMD/PMD)         | 7/22/15/6 | 3.20 | 1.85-5.54 | <0.001 |
| Chemotherapy cycles: 2 or [4-6]   | 25/19 | 0.68 | 0.32-1.45 | 0.345 |

Note: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease; RECIST, response evaluation criteria in solid tumors; PERCIST, PET response criteria in solid tumors.

Figure 2 The survival of RECIST evaluation results (CR =1, PR =2, SD =3, PD =4) in 44 patients. RECIST, response evaluation criteria in solid tumors; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Figure 3 The survival of PERCIST evaluation results (CMR =1, PMR =2, SMD =3, PMD =4) in 44 patients. PERCIST, PET response criteria in solid tumors; CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease.
reduction of 31%. Further research should pay attention to the details of information in the response assessment.

In the present study the evaluation results were not significantly different between PERCIST and RECIST 1.1 (with new lesions determined on PET/CT), but showed significant difference between PERCIST and RECIST 1.0 (without new lesions determined on PET/CT). This result revealed that PERCIST and RECIST 1.1 had good consistency and PERCIST (or PET) was more sensitive in detection the CR and progression patients. In the study of Van Ruychevelt et al. 59 NSCLC patients were evaluated by RECIST and EORTC criteria, and the results showed that PET was more sensitive than CT in early detecting the patients of PD (10). In the research of Yanagawa et al. Fifty-one patients with locally advanced esophageal cancer who received neoadjuvant chemotherapy were studied. Chemotherapeutic lesion responses were evaluated using \(^{18}\)F-FDG PET and CT according to the RECIST and PERCIST methods. There was significant difference between the PERCIST and RECIST evaluation results and the number of CR cases in PERCIST was much more than which in RECIST (4). All these studies indicated that PERCIST is superior to RECIST in the detection of CR and progression. One possible reason is that the metabolic changes after treatment is more sensitive than morphologic changes in the nature of tumors and PET can just monitor the metabolic changes. The other reason may be that the intrinsic properties of this two criteria because the achievement to CR in RECIST is more difficult. In the ordinary PET/CT work we found that some NSCLC lesions didn’t further shrank or disappear when they reduced to a certain degree but no uptake of \(^{18}\)F-FDG. The residual lesions may be the fiber texture or scar tissue and can be confirmed by surgery.

The relationship between the metabolic changes of tumors and prognosis was discussed in many studies. The prognostic value of parameters about SUV and the evaluation results was not in agreement (8-10). In the study of van Ruychevelt et al. only a significant reduced survival was observed in progressive patients and no differences among the else (10). The other study about Esophageal Cancer concluded that PERCIST 1.0 (CMR vs. non-CMR) was the most significant prognostic factor for predicting DFS and OS in the multivariate Cox proportional hazards regression analysis (4). The results of another study showed that an early metabolic response did not translate into better survival outcome (8). The present study draw a conclusion that only PERCIST evaluation result is a significant prognostic factor and the survival curve suggested that the progressive patients had significantly shorter PFS. The conclusions in the above studies have limitations because of the small number of cases and different classification results. In the further study, the factors affecting the survival and evaluation results [including age, TNM stage, pathological type, subsequent treatment, the basal SUV, Total lesion glycolysis (11) and review time et al.] should be taken into account as far as possible in the multivariate Cox proportional hazards regression analysis, thus the conclusion may be more credible.

Limitations in this study included the retrospective nature of patient data collection, the number of target lesion and the different cycles’ interval of PET/CT review. In PERCIST only one target lesion was required to evaluate but in RECIST 1.1 no more than five target lesions were included. In order to precisely compare PERCIST with RECIST we evaluated the longest diameter of just one target lesion that was assessed in PERCIST. The study of Darkeh MH et al. suggested that measuring fewer than four target lesions might cause discrepancies when more than five target lesions are present in RECIST 1.0 (12). So the evaluation results according to RECIST criteria in the present study might not be accurate. Here a new problem will be proposed that how many target lesions should be chosen when the research aim to compare the PERCIST with RECIST. Another limitation is the time of PET/CT review was not consistent in the present study. Although the cycles’ interval (2 or 4-6 cycles) was not significant factor in the univariate Cox proportional hazards regression analyses and the present study is paired analysis, the difference of sensitivity between PERCIST and RECIST will reduce as the time go on. The further research had better separate the different treatment time of patients and analyze respectively.

**Conclusions**

In conclusion, RECIST criteria are still a “gold standard” in the response evaluation of the solid tumor. The present study indicates that PERCIST and RECIST 1.1 have good consistency and PERCIST (or PET) is more sensitive in detection the CR and progression patients. Combining the PERCIST and RECIST the clinician will acquire more response information relatively early. However because of the small number of patients the selection bias could not be avoided. More researchers are expected to join the study of PERCIST and make it serve for tumor patients better.
Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Ding Q, Cheng X, Yang L, Zhang Q, Chen J, Li T, Shi H. PET/CT evaluation of response to chemotherapy in non-small cell lung cancer: PET response criteria in solid tumors (PERCIST) versus response evaluation criteria in solid tumors (RECIST). J Thorac Dis 2014;6(6):677-683. doi: 10.3978/j.issn.2072-1439.2014.05.10