Editorial

Are the metabolic evaluation criteria sufficient for FDG PET/CT after chemo-radiotherapy in non-small cell lung cancer?

Cetin Ordu

Department of Medical Oncology, Gayrettepe Florence Nightingale Hospital, Istanbul, Turkey

Correspondence to: Cetin Ordu. Department of Medical Oncology, Gayrettepe FNG Hospital, Cemil Aslan Guder St. No: 8 Gayrettepe/Besiktas 34349 Istanbul, Turkey. Email: cetinordu@hotmail.com.

Provenance: This is an invited Editorial commissioned by the Section Editor Jun Zhou (Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Comment on: Turgeon GA, Iravani A, Akhurst T, *et al.* What ^{18}F-FDG PET Response-Assessment Method Best Predicts Survival After Curative-Intent Chemoradiation in Non-Small Cell Lung Cancer: EORTC, PERCIST, Peter Mac Criteria, or Deauville Criteria? J Nucl Med 2019;60:328-34.

Submitted Jan 12, 2019. Accepted for publication Feb 11, 2019.
doi: 10.21037/jtd.2019.02.49
View this article at: http://dx.doi.org/10.21037/jtd.2019.02.49

Although the predictive and prognostic value of metabolic imaging by positron emission tomography (PET) in diagnosis, staging, recurrence determination and early response assessment in non-small cell lung cancer (NSCLC) is known, the standard in the evaluation of response to treatment in locally advanced NSCLC is unclear (1). One of the challenges of post treatment assessment is imaging during and after radiotherapy (RT) (2). Lung injury caused by radiation usually develops in two periods regarding time interval after the end of treatment. An early period of temporary radiation pneumonitis, which occurs, within the first six months typically, and a later period of chronic radiation fibrosis which usually occurs at 6–12 months after completion RT (2,3). In the evaluation of early response, the patient's treatment may be adversely affected due to false positivity with performing fluoro deoxi glucose PET computed tomography (FDG PET/CT) at least 3 months after completion of RT despite the 3-month period considered optimal (2). However, persistent fluorodeoxyglucose (FDG) uptake associated with radiation induced fibrotic or inflammatory change occasionally lasts for 15 months after the end of treatment. This emphasizes the importance of evaluating imaging follow up changes by an expert team and the need for histopathologic confirmation when recurrent disease identified (2). The rate of false positive results is higher in the first 6 months after RT with PET imaging, due to more frequent inflammation (e.g., radiation pneumonia) and respiratory artifacts of the lung. Currently there is no agreement on the optimal imaging modality for posttreatment assessment in lung cancer. Approximately one third of patients with lung cancer have tumor progression during first-line chemotherapy. This high frequency of progression emphasizes the need for monitoring treatment response with advanced imaging modalities, to adopt new treatment regimens and predict outcomes (4,5).

Today, European Organization for Research and Treatment of Cancer (EORTC) and PET Response Criteria in Solid Tumors (PERCIST) criteria are the more frequently used semi-quantative criteria in PET evaluation. Peter Mac and Deauville criteria are visual criteria very little (Peter Mac) is used in NSCLC or none (Deauville) are used. Hopkins criteria can be as an example for visual criteria used in NSCLC (6).

In this article, 87 patients were found eligible and some of them were evaluated with semi-quantative (EORTC, PERCIST) and visual (Peter Mac, Deauville) criteria and the compliance of the observers (<5 years with >10 years experienced of radiology) was investigated.

When we examined the results, the number of stable metabolic disease (SMD) was significantly lower than the semi-quantative criteria according to visual criteria. The number of complete metabolic response (CMR) was significantly higher than the semi-quantative criteria according to visual criteria. Visual response assessment criteria have less false positivity result due to flexibility.

In addition, the compliance between the radiologists used visual assessment criteria were found to be higher than the radiologists who performed the semi-quantitative evaluation.

One of the most important reasons for the higher rate of compliance is the fact that the radiology specialists who make the visual assessment perform the first 19 patients together.

Deauville criteria should be considered for the first time as a NSCLC evaluation criterion outside lymphoma. Again, according to visual criteria CMR *vs.* non CMR between the 2-year overall survival (OS) difference was higher than the semi-quantitative evaluation criteria. However, it has been found that the four criteria for OS make good predictions of OS.

According to these evaluation criteria, it is possible to say that the visual assessment criteria are more compatible and better predictive of OS. However, it should be accepted that the semi-quantitative evaluation criteria, which should be more objective, have lower inter-observer coefficients and the radiologists who make the visual assessment have a common evaluation in 19 patients and they are bias. On the other hand, inconsistencies in objective evaluations due to false positives may also affect this result.

Although it is frequently used in patients with NSCLC who received concurrent chemo-radiotherapy, the limitations of metabolic evaluation with PET are evident and yet the gold standard is not clear. The most important limitation is the false positive results caused by radiation induced by inflammation and movement artifacts due to the lung and is not clear in the ideal time between treatment and imaging. According to the results of this study, it is not possible to say which metabolic evaluation criteria are superior.

As in many studies, it was not taken into consideration that different cell subtypes could have different results in the evaluation of response to treatment with RT and chemotherapy. Inflammatory reactions due to treatments are variable with respect to different cell subtypes and there is not enough study. Because in some patients with NSCLC there is no anatomical response, but metabolic response (necrosis) continues for a long time, whereas in others, although there is an anatomical response, aggressive clones cause rapid progression (7).

From this point of view, we can think that metabolic imaging with PET provides additional information according to the anatomical response criteria with CT, but it does not meet the ideal response evaluation criteria. When we consider different cell subtypes and different clones that provide resistance to treatments, it should be considered that imaging with a single radiotracer may be insufficient to evaluate the response of different cell clones. Considering the response evaluation of RT in local advanced NSCLC, it is possible to say that FDG imaging performed with PET in the response evaluation after chemo-radiotherapy did not meet the expectations.

In addition, it has been shown that PET imaging predicts the response and is prognostic in patients with driver mutation treated with tyrosine kinase inhibitors. However, only 12–15% of patients have a driver mutation (8). Apart from this, the uncertainty of metabolic response criteria may make the current practice more difficult in the evaluation of the response with the addition of immunotherapy (Durvalumab-Pacific) after chemo-radiotherapy in the local treatment of NSCLC. IRECIST developed in the evaluation of the response of immunosuppressed solid tumors has included the moderate progression with immunotherapy. However, it is not clear how hyperprogression due to immunotherapy will be interpreted in response evaluation. There is ongoing study which immunotherapeutic agent (Durvalumab) started with chemo-radiotherapy in locally advanced NSCLC. So, it's not known if these criteria will be enough in response assessment after chemo-radiotherapy and immunotherapy combinations (9,10).

It should be noted that the Deauville criteria apply only to lymphoma, but it should be noted that there is no prospective evidence in the NSCLC response evaluation. Peter Mac criteria is not be applied in clinical practice for NSCLC. Although the criteria for metabolic evaluation with PERCIST and EORTC are more commonly used in NSCLC, I think they are less used in clinical practice. Despite the retrospective and limited number of patients, this study can be considered as a well-designed study. The results of the study show that the metabolic response criteria made by PET are insufficient in locally advanced NSCLC and the objective evaluation criteria are needed in this area. Development of different therapeutic agents in NSCLC due to multislice results with next generation sequencing (NGS) may suggest that different evaluation criteria should be used in the future

Today, restaging after induction therapy remains a controversial topic. Although some studies showed the usefulness of FDG PET/CT in predicting response induction therapy in lung cancer (11). Sometimes, it is not possible to make final therapeutic decision for mediastinal involvement. An invasive technique providing histologic

confirmation is still recommended (12,13). Recent trials suggested that more sophisticated assessments, such as percentage change in metabolic parameters in FDG PET/CT combined with EBUS or endoscopic ultrasound can better verify the mediastinal lymph node clearance (14). Besides, data are limited and further prospective trials are needed to confirm the utility of EBUS or endoscopic ultrasound together with FDG PET/CT in restaging of locally advanced NSCLC.

Furthermore, targeting treatment response assessment with novel PET radiotracer could be more specific. The concept of using tumor genomic characteristics has revolutionized the landscape of personalized treatment with the ability to assess response targeted therapy in patients with lung cancer. Recent studies have shown that imaging features of lung cancers closely related to tumor genomic profiling and prognosis. FDG PET has been shown to be useful for early response assessment in patients treated with tyrosine kinase inhibitors (e.g., erlotinib, or gefitinib) (15,16).

In conclusion, visual criteria were better in terms of survival and inter-observer compliance than semi-quantative criteria. This difference can be achieved by the fact that flexibility of visual criteria reduce the rate of false positivity due to inflammation after chemo-radiotherapy. In addition, the more flexible visual criteria than the semi-quantitative criteria, resulted better in metabolic evaluation after chemo-radiotherapy suggest that the criteria are not enough. Because, different cell clones' different responses to treatments and the lack of objective criteria in the evaluation of inflammation and fibrosis response after treatment. General metabolic assessment with a single radiotracer can be considered to be insufficient for the evaluation of targeted therapies and immunotherapies against driver mutations. Such as Ga-68 PSMA PET in prostate cancer, and radioiodine-131 uptake in thyroid cancer may be one of the solutions to organ and disease-specific radiotracers. Although the metabolic response assessment in targeted therapies with tyrosine kinase inhibitors seems to be both early and more effective, the number of studies on this issue is not sufficient. When we consider moderate progression and even hyperprogression, it can be said that the criteria for evaluating metabolic response in response to immunotherapy are insufficient. There is a need for more recent evaluation criteria in this area. As a result, a well-designed study and its results indicate the need for different response evaluation criteria.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Kitajima K, Doi H, Kanda T, et al. Present and future roles of FDG-PET/CT imaging in the management of lung cancer. Jpn J Radiol 2016;34:387-99.
2. Larici AR, del Ciello A, Maggi F, et al. Lung abnormalities at multimodality imaging after radiation therapy for non-small cell lung cancer. Radiographics 2011;31:771-89.
3. Huang W, Fan M, Liu B, et al. Value of metabolic tumor volume on repeated 18F-FDG PET/CT for early prediction of survival in locally advanced non-small cell lung cancer treated with concurrent chemoradiotherapy. J Nucl Med 2014;55:1584-90.
4. Crabtree TD, Puri V, Chen SB, et al. Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? J Thorac Cardiovasc Surg 2015;149:45-52.
5. Nishino M, Hatabu H, Johnson BE, et al. State of the art: Response assessment in lung cancer in the era of genomic medicine. Radiology 2014;271:6-27.
6. Sheikhbahaei S, Mena E, Marcus C, et al. 18F-FDG PET/CT: therapy response assessment interpretation (hopkins criteria) and survival outcomes in lung cancer patients. J Nucl Med 2016;57:855-60.
7. Tsuchida T, Demura Y, Sasaki M, et al. Differentiation of histological subtypes in lung cancer with 18F-FDG-PET 3-point imaging and kinetic analysis. Hell J Nucl Med 2011;14:224-7.
8. Fledelius J, Winther-Larsen A, Khalil AA, et al. 18F-FDG-PET/CT for very early response evaluation predicts CT response in Erlotinib treated NSCLC patients–A comparison of assessment methods. J Nucl Med 2017;58:1931-7.
9. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N Engl J Med 2017;377:1919-29.
10. ClinicalTrials.gov Identifier: NCT03694236. Available online: https://clinicaltrials.gov/ct2/show/NCT03694236

11. Kremer R, Peysakhovich Y, Dan LF, et al. FDG PET/CT for assessing the resectability of NSCLC patients with N2 disease after neoadjuvant therapy. Ann Nucl Med 2016;30:114-21.
12. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy- proven stage IIIA-N2 non-small-cell lung cancer: a Leuven Lung Cancer Group Study. J Clin Oncol 2006;24:3333-9.
13. Stamatis G. Staging of lung cancer: the role of noninvasive, minimally invasive and invasive techniques. Eur Respir J 2015;46:521-31.
14. Genestreti G, Burgio MA, Matteucci F, et al. Endobronchial/endoesophageal ultrasound (EBUS/EUS) guided fine needle aspiration (FNA) and 18F-FDG PET/CT scanning in restaging of locally advanced non-small cell lung cancer (NSCLC) treated with chemo-radiotherapy: a mono-institutional pilot experience. Technol Cancer Res Treat 2015;14:721-7.
15. Wang J, Wong KK, Piert M, et al. Metabolic response assessment with 18F-FDG PET/CT: inter-method comparison and prognostic significance for patients with non-small cell lung cancer. J Radiat Oncol 2015;4:249-56.
16. Van Gool MH, Aukema TS, Hartemink KJ, et al. FDG-PET/CT response evaluation during EGFR-TKI treatment in patients with NSCLC. World J Radiol 2014;6:392-8.

Cite this article as: Ordu C. Are the metabolic evaluation criteria sufficient for FDG PET/CT after chemo-radiotherapy in non-small cell lung cancer? J Thorac Dis 2019;11(Suppl 9):S1263-S1266. doi: 10.21037/jtd.2019.02.49

