Commentary

Developments in oncological positron emission tomography/computed tomography assessment

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Submitted Nov 15, 2015. Accepted for publication Nov 23, 2015.
doi: 10.3978/j.issn.2072-1439.2015.12.45
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.12.45

Positron emission tomography (PET)/computed tomography (CT) using ^{18}F-fluorodeoxyglucose (FDG) has become a standard tool for staging and therapy monitoring in oncology. Qualitative assessment of tracer uptake has become the basis for important therapy decisions such as whether to continue or abandon radiotherapy after effective chemotherapy in advanced Hodgkin lymphoma (1,2). The tools for this PET interpretation have to be reproducible and standardized, to ensure adequate treatment for all patients (2,3). In contrast to some lymphatic malignancies, cure rates are generally lower in most advanced solid tumors. If responses to a specific treatment occur, they can easily be detected by quantitative analyses, which are more sensitive than visual criteria. Therefore, quantitative PET analyses have been introduced in solid tumor PET studies and several PET parameters have been proposed as a supplement to visual analyses to measure the patient's response to a specific treatment (4).

Although overall survival has improved little over the past decades, in advanced non-small cell lung cancer patients modern treatment methods with molecularly targeted agents have shown promising results with improved overall survival, independent of genetic profile, when patients are treated with the epidermal growth factor receptor inhibitor erlotinib (5). Here, response assessment through quantitative PET/CT analyses has brought promising results in terms of predictive value, as documented by several, independent research groups (6,7). The most commonly used metric applied in this context is the percentage change of the maximal standardized uptake value (SUVmax). This value reflects changes in the tumor's metabolism under treatment. One might argue that an FDG-PET/CT image contains more information on tumor FDG uptake than the single hottest voxel, which is measured by the SUVmax. Recently, it has been proposed that so-called textural features characterize tumor heterogeneity and these have thus become a focus of research (8). Here textural features derived from PET/CT are categorized as first, second or high-order metrics. First-order features are based on intensity histograms and include the SUVmax, but offer various additional values such as standard deviation, skewness and kurtosis. Second-order features may be calculated from the gray-level co-occurrence matrix (9). High-order features can be calculated from various matrices including the gray-level size zone and the neighbor gray tone difference matrix (10,11).

In this context, Cook and co-workers (12) analyzed first-order and high-order textural features derived by FDG-PET/CT and the ability to predict response and survival in 47 non-small lung cancer patients treated with erlotinib. After 6 weeks of treatment they found that changes in standard deviation, first-order entropy, uniformity and SUVmax were associated with survival, as defined by RECIST after 12 weeks. In contrast, neither the baseline parameters nor any of the percentage change parameters tested was strongly associated with overall survival.

Statistically significant association with survival was reached for high-order contrast at 6 weeks. Multivariate analysis revealed an association between high-order contrast at 6 weeks and percentage change in first-order entropy. This leads the authors to conclude that a PET/CT provides parameters supplementary to the SUVmax that reflect heterogeneity and warrant further testing in a prospective trial to determine their predictive and prognostic value.

What can we learn from this trial? On the one hand, we see once again that changes in SUVmax, the measure predominantly used in routine clinical practice, demonstrate the ability of this parameter to predict response to treatment. On the other hand, we learn that a number of other quantitative measures can be derived from PET/CT, some of which may have more clinical impact than the de facto standard currently in use.

When considering further quantitative uptake parameters on which to base clinical decisions, it should be kept in mind that even fairly simple quantitative measures such as the SUVmax are highly dependent on reconstruction methods and settings, which cannot easily be resolved by normalizing to the liver (13). It is to be expected that more complicated measures will be prone to even more variability so that a rigid standardization of image quality and characteristics is a prerequisite to exploration of the clinical utility for these parameters (14). A potential textural feature for use as a new imaging biomarker should possess at least similar if not better repeatability and reproducibility, compared to the clinical standard SUVmax. Some new features that meet these criteria have been identified by Yan and colleagues (15). Texture analysis of tracer uptake is a promising tool that could achieve results superior to those reached so far. We would agree with Buvat and co-workers (16) that careful introduction with both technical and clinical validation is warranted for these new imaging biomarkers.

But what needs improvement? The SUVmax and measurement of its percentage change in the respective single lesion is the best tool available to reflect response to treatment, even in patients with advanced oncological disease involving metastases displaying marked heterogeneity, and furthermore, it helps to select the optimal treatment for the individual patient (17). SUVmax is a quantitative, widely available measure, which unlike many other quantitative measures of uptake, is independent of delineation strategy and observer variability. Moreover, when functional imaging is used to identify patients who might profit from a certain therapy, regardless of their genetic profile, the assessment should be made at the earliest stage possible to avoid futile therapy. For this reason, we favor imaging with FDG PET/CT as promptly as possible e.g., after 2 weeks of treatment when the SUVmax has previously been shown to display its high predictive value (7). Interestingly, prolonged survival in non-small lung cancer patients was observed not only in the total group of patients with epidermal growth factor receptor mutations but also in patients without detected mutation (7).

Selecting the best time and method of analysis for FDG PET/CT is not the only way in which to develop and facilitate individualized cancer treatments. Although the glucose analog FDG has proved useful in various oncological diseases it has been of little help in prostate cancer. Here, the development of new prostate-specific membrane antigen (PSMA) linking tracers has presented a powerful tool, providing highly specific and sensitive diagnostics and enabling individual targeted therapies (18). More specific markers are on the way to being introduced into routine clinical practice, which will provide more specific information than that reflected in glucose metabolism, e.g., the imaging of the CXCR4 expression by 68Ga-Pentixafor (19).

It would be worthwhile exploring whether and how new image analysis methods and tracer developments could be used to improve prognostic and predictive differentiation and whether these might be of potential benefit to patients. PET is already being used to monitor and to demonstrate the effectiveness of a specific treatment in routine clinical practice. In Hodgkin lymphoma visual analysis of FDG-PET/CT in combination with well-defined criteria has been shown to provide a valid basis for treatment decisions (1). Care should be taken to plan and perform well-conducted trials in solid tumors to validate new quantitative PET measures, not only for treatment response monitoring but also as a tool to guide treatment decisions in order to improve patient outcome.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by the Guest-Editor Lihua Chen [Department of Radiology, Taihu Hospital (PLA 101 Hospital), Wuxi, Jiangsu, China].
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Kobe C, Boellaard R, Wolf J, Kuhnert G, Dietlein M, Neumaier B, Drzezga A, Kahraman D. Developments in oncological positron emission tomography/computed tomography assessment. J Thorac Dis 2015;7(12):E637-E639. doi: 10.3978/j.issn.2072-1439.2015.12.45