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LETTER TO THE EDITOR

FDG PET/CT methodology for evaluation of treatment response in lymphoma: from "graded visual analysis" and "semiquantitative SUVmax" to global disease burden assessment

Sandip Basu · Habib Zaidi · Ali Salavati · Søren Hess · Poul Flemming Høilund Carlsen · Abass Alavi

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Dear Sir,

In recent years, there have been multiple endeavours by various investigators [1–4] seeking to show the importance of semiquantitative analysis of PET data using conventional metrics (e.g. ΔSUVmax) and its superiority over the international prognosis score for prediction of overall outcome and progression-free survival. We agree with these investigators that molecular imaging using FDG PET plays a pivotal role in risk stratification in treatment individualization. While these endeavours are important steps in PET/CT imaging for disease assessment and prognostication, we would like to share our views on the relevance of emerging PET metrics that have the potential to replace existing ones in the near future for optimal patient management [5].

Its use in the interim assessment of chemotherapeutic response has been one of the major strengths of FDG PET/CT, and it has been widely used for this purpose in the management of lymphoma to tailor the treatment regimen as well as to predict disease prognosis and overall outcome. This is now the standard of care in most centres where FDG PET/CT is available. While the utility of FDG PET/CT imaging in lymphoma has been generally recognized, there has been continuing debate on the appropriate PET methodology and the most reliable parameter to interpret the therapeutic response, particularly in mid-cycle. Beyond doubt, visual analysis remains an integral component of the assessment, but there has been persistent endeavour by both oncologists and physicians interpreting PET to define an objective set of parameters, the most common ones being the Deauville criteria for interim response assessment [6]. It has recently been proposed that these criteria be extended to the end of treatment remission assessment, although still based entirely on visual and not quantitative interpretation [7].

In complete metabolic response, visual interpretation is relatively straightforward, whereas in partial response of lesser grade or even in progressive metabolic disease assessment needs more objectivity. In the recommendation of the Imaging Subcommittee of the International Harmonization Project in Lymphoma, mediastinal blood pool activity is considered as reference background activity for interpreting PET positivity for a residual mass equal to or more than 2 cm in greatest transverse diameter. For smaller lesions or for normal sized lymph nodes, uptake more than surrounding background is considered positive [8]. While these criteria have been used in different centres for response assessment, it has been increasingly felt by physicians interpreting PET that visual grading or single point SUVmax measurement is inadequate for appropriate assessment, particularly in malignancies such as lymphoma. There has been some work demonstrating that introducing quantification by measuring SUVmax leads to improvement [1], since changes in this value (ΔSUVmax) were

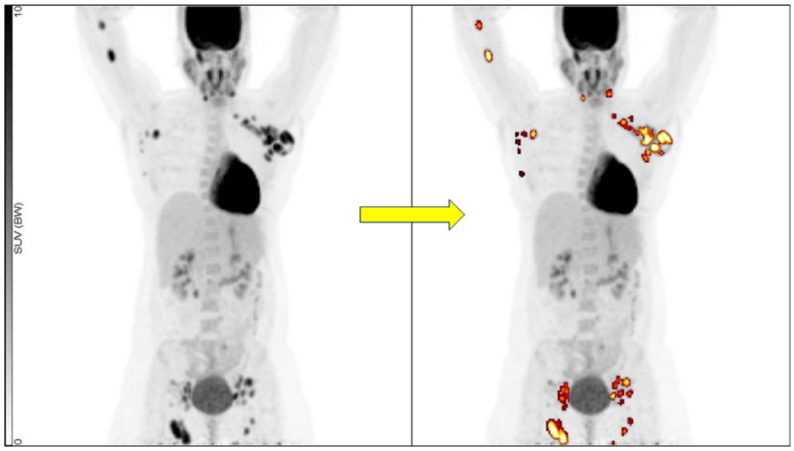
S. Basu
Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Jerbai Wadia Road, Parel, Mumbai 400 012, India

H. Zaidi
Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospital, 1211 Geneva, Switzerland

H. Zaidi
Geneva Neuroscience Centre, Geneva University, 1205 Geneva, Switzerland

A. Salavati · A. Alavi (✉)
Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA
e-mail: Abass.Alavi@uphs.upenn.edu

S. Hess · P. F. H. Carlsen
Department of Nuclear Medicine, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense, Denmark



Parameter	
SUVmax	12.6
SUVmean	5.8
pvcSUVmean	10.5
SUVpeak	10.6
MTV	80.5 cc
TLG	471.4
pvcTLG	845

Fig. 1 Representative image analysis results in identifying disease sites, and the corresponding quantitative measures provided by this analysis scheme in a patient with Non-Hodgkin Lymphoma. *SUVmax*, *SUVmean*, *SUVpeak*, *MTV* (Metabolic Tumor Volume), *TLG* (Total Lesional Glycolysis=MTV*SUVmean), *pvcSUVmean* (partial volume effect corrected SUVmean), *pvcTLG* (partial volume effect corrected TLG=MTV*pvcSUVmean)

found to be a more accurate predictor of outcome in patients with Hodgkin lymphoma than the five-point scale of the Deauville criteria [6].

However, there is room for further improvement, because even SUVmax is, for a number of reasons, not a valid expression of the degree of malignancy or tumour burden. Particularly not when considering that most malignant tumours are heterogeneous, and thus for this reason alone SUVmax is not a reliable measure of any of these characteristics. Therefore, assessment approaches taking this into account have been proposed, including estimating the "whole-body metabolic burden" or "total lesion glycolysis" [9, 10]. The extent of disease, reflected by its stage, is considered one of the most important predictors of outcome in almost any type of lymphoma, and thus may serve as a guide for therapy. From a clinical point of view, therefore, calculation of a global disease score would be a major step in the right direction, because then the patient's doctor could judge from only a single number how ill the patient is and whether an instituted therapy is likely to be effective. With this approach, a decline in total lymphoma burden with treatment from a score of, say, 640 to one of 320 would indicate that management is on the right track. One should bear in mind only that this kind of response evaluation is not a trivial matter even with a global score available. A change from a baseline value before treatment to a lower score during treatment is often considered a fairly reliable sign of progress, but it may not be, because if one does not know the true trend of the disease course during therapy (that requires repeat measurements), mistakes can occur [11].

PET image segmentation and partial volume correction are two important steps, particularly for heterogeneous and smaller lesions, respectively, for accurate approximation of the estimates. A number of commercial software packages assessing the metabolic–volumetric product, that are integrated in some recent PET/CT systems, are important developments towards this end that could enable accurate quantification for treatment response monitoring during the treatment course. Reliable segmentation is mandatory and often not clear-cut in lymphoma patients with conglomerations of lymph nodes lying close to structures of varying vascularization. It is not surprising, therefore, that SUVmax has become popular since it is relatively independent of activity in neighbouring structures and an immediate read-out is automatically available on all workstations. In addition, it is reproducible as long as it is obtained from acquisitions on the same scanner. Nonetheless, SUVmean is a much more relevant indicator of malignancy as it takes into account tumour heterogeneity by expressing the average increase in tracer uptake in a lesion. As with SUVmax, its major confounder, causing significant underestimation of the derived number, is the partial volume effect caused by improper segmentation. An example of this is shown in Fig. 1 in a patient with Non-Hodgkin lymphoma in whom a 'global disease score' was calculated as the product of the volume of metabolic tumor volume and the SUVmean of this volume, to yield a useful score for diagnosis, grading of the amount (extent and activity) of disease, and response evaluation. In such cases, correction of the partial volume effect typically yields values that are higher by a factor of two or more.

Finally, other factors should also be considered when calculating the correct extent and severity of cancer. For PET studies with FDG, imaging about 1 h after injection of tracer has become the arbitrary rule, but most cancers continue to accumulate FDG for several hours, typically at least for one or two more hours, while at the same time activity in the blood and background tissue continues to decrease, rendering the signal-to-noise ratio increasingly larger. The net effect is not only an increase in SUVmax and SUVmean, but often also in

tumour volume and the number of detectable malignant lesions, as with time more lesions stand out significantly from the background, while the margin of tumours visible at 1 h tends to expand. Thus, we suggest that it is now need of the hour for studies involving quantification of PET scans, taking into account these important factors and newer methodologies in global disease assessment that will significantly improve prediction of outcome in lymphoma and other malignancies.

Conflicts of interest None.

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