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EDITORIAL COMMENTARY

Quantification: there is more to worry about than good scanner hardware and reliable calibration

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Positron emission tomography (PET) is "an analytical imaging technology developed to use compounds labelled with positron-emitting radioisotopes as molecular probes to image and measure biochemical processes of mammalian biology in vivo" [1]. One outstanding feature of the PET technology is the ability to perform absolute quantification of regional perfusion, metabolism, and function [2]. There are clinical demands for quantification regarding description of biodistribution, dosimetry, intra- and inter-individual comparisons, and setup of age- and gender-specific (normal) databases. Notably, FDG PET allows diagnosis, differential diagnosis, assessment of prognosis, and patient stratification in malignant disease. Moreover, image guided therapy has been proven to improve tumour delineation and irradiation field definition regarding protection of normal tissue and dose escalation on tumour tissue [3]. After initial assessment, follow-up investigations describe the effect of therapy and influence therapeutic management regarding continuation or change of modality and intensification or de-escalation of therapy. In addition to qualitative description and quantification of tracer uptake or uptake changes during follow-up, more sophisticated kinetic modelling and analysis may be applied. However,

This Editorial Commentary refers to the article http://dx.doi.org/10.1007/s00259-017-3779-0

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reliability and significance of all derived numbers is influenced by technical factors and biological processes.

Methodological aspects of quantification

Formally, the principal goal in quantitative oncological FDG PET is to measure a surrogate of the tumour's metabolic rate of glucose consumption. Ideally, the surrogate parameter should be proportional to the latter quantity but, of course, a more general (linear or nonlinear) monotonic relation between surrogate and target parameter would suffice, too. But in any case, the respective relation has to be universally valid (i.e., invariant) across different scans, scanners, and patients. Otherwise, comparisons between different investigations are affected by spurious variability of the measured surrogate that is unrelated to actual changes in tumour metabolism.

Currently, the standardized uptake value (SUV) is accepted as a suitable surrogate parameter derivable from static investigations, although it is widely recognized that its properties are far from ideal. Consequently, much effort has been invested to improve the reliability of SUV measurements by means of addressing the recognized technical issues, e.g., by focusing on strict calibration procedures and SOPs on how to perform measurement and data evaluation [4].

Despite the unquestionable value of these efforts, test-retest stability of SUV remains rather unsatisfactory: even under highly controlled study conditions with nearly perfectly observed constant uptake times, test-retest variability is of the order of $\pm(30–40)\%$ [5, 6]. Consequently, SUV is not able to reliably detect (or exclude) moderate changes of the tumours' metabolic rate.

In this context it is interesting to observe that there exist assorted reports of superior performance of ratio methods that relate lesion uptake to some reference region. So far, in

oncological PET, especially the tumour to liver ratio (TLR) has been used (one example of this approach is the work of Huang et al. [7]). More recently, we have proposed the image-derived tumour to arterial blood standard uptake ratio (SUR) as a promising alternative [8, 9] and investigated its properties and performance compared to SUV [5, 10, 11]. We also addressed the question to what extent the healthy liver parenchyma might act as a substitute for actual arterial tracer supply [12].

Target/background approaches are usually viewed as only semi-quantitative and inferior to methods addressing absolute quantitation of relevant parameters. This view is frequently justified. For oncological FDG PET, however, it can be argued that SUR and — with some reservations — TLR are truly quantitative approaches yielding approximately proportional measures of the lesion's glucose consumption which outperform the supposedly inherently more quantitative SUV.

On theoretical grounds alone it can be expected that SUR correlates much better with the targeted quantity (the metabolic rate of FDG accumulation in the tumour) than SUV. This theoretical prediction has in fact been verified in patient data [9, 11]. Two causes (beyond the elimination of all calibration related issues that is the principal advantage of any ratio method) are operational here: SUR corrects for the inherent variability of actual arterial tracer supply (present even after SUV normalization of the image data) [9] as well as for the practically unavoidable substantial variability of uptake time prior to scanning [8].

Biological aspects

Regional FDG uptake is influenced by fuel supply, hormones, medication, perfusion, hypoxia, inflammation, malignancy, immune reaction, proliferation, receptor and mutation status, and many more factors which cannot be separated and have to be taken into consideration while analysing PET images. The seed and soil hypothesis explains organ-preference patterns of tumour and metastasis as a consequence of the specificities of interaction between tumour cells and their respective environment, which control to what extent the demands of the malignant cells are satisfied. This, in turn, determines their growth, infiltration, displacement, and metastatic spread. [13]. While one organism is able to outbalance tumour cells and prevent them from growing, another one fails to do so and the cancer prospers. Cancer is always a systemic disease. The surrounding tissue in detail and the condition and comorbidity of the patient in general influence the natural course of the disease as well as the possibilities of treatment. Moreover, every treatment, be it surgery, irradiation treatment, or chemotherapy, not only attacks the tumour itself but also the surrounding tissue as well as the whole body. Therefore, therapy monitoring will not only catch the tumour response to therapy but also the whole

body answer including immune reactions as well as metabolic changes [14]. Nevertheless, we can discriminate tumour viability from the immune reaction that will control the tumour or even destroy it. Actually, the intensity of the immune reaction might be a prognostic marker as suggested by Huang et al. and others [7, 15].

Beyond simple quantification

Standardization is part of quality assurance. It is necessary not only in clinical trials but also in clinical practice regardless of the tailored individualized therapy in an individual patient. However, all clinicians know that in real life medicine many unforeseeable things may occur influencing, delaying, and changing the PET procedure. The diagnostic algorithm encompasses adequate indication, suitable technique, and consideration of biologically related factors and ends (hopefully) with patient related benefit (i.e., prolonged survival or increased quality of life). If all these factors in the process cannot be standardized for reliable quantification in daily practice then the quantitation procedure should be adapted to compensate for this variability (which makes SUR an attractive alternative to SUV). With such an improvement in analysis, further information can be deduced from the image data that could influence therapeutic management and improve patients' outcome. Dedicated software allows for fast analysis of several parameters [16]. While tumour metabolism before and after radio-, chemo-, or immunotherapy was the primary focus for therapy assessment so far, more recently there is increasing evidence that also normal tissue reaction could be an important biomarker of response due to the patient's own immune defence [17]. Elimination of the technical and methodological factors allows us to focus more on biology, on the patient's profile, and the tumour's characteristics.

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