# The age of reason for FDG PET image-derived indices.

Dimitris Visvikis, Mathieu Hatt, Florent Tixier, Catherine Cheze Le Rest

# The age of reason for FDG PET image derived indices

Dimitris Visvikis[1], Mathieu Hatt[1], Florent Tixier[1], Catherine Cheze-le Rest[2]

[1]INSERM, UMR1101LaTIM, Brest, France

[2]Department of Nuclear Medicine, CHU Milétrie, Poitiers, France

Keywords: image derived parameters, 18F-FDG-PET, prediction, prognosis, therapy response

Corresponding author:

Dimitris VISVIKIS, PhD, FIPEM

LaTIM, INSERM UMR1101

CHRU MORVAN

5 avenue Foch

29609 Brest

France

Tel.:+33298018111

Wordcount: 2374

The clinical use of Positron Emission Tomography (PET) imaging using the 2-deoxy-2-(18F)fluoro-D-glucose (18F-FDG) is currently predominantly focused on diagnostic purposes within the field of oncology. Within this context, image analysis is largely based on visual interpretation and the use of simple image derived indices, such as the maximum standardised uptake value ($SUV_{max}$), which corresponds to the voxel with the maximum activity concentration within the tumourscaled by the administered activity, patient weight andblood glucose concentration.On the other hand, during the last few years there has been increasing interest in the use of 18F-FDG PET imagingfor the prediction and monitoring of therapy response. Within this context the $SUV_{max}$ has been also predominantly used, where differences between a pre-treatment and post-treatment scan have been shown to closely correlate with clinical response to treatment for a number of different cancer models [1,2].

The clear advantage of such a simplistic image derived index is the easiness of use which has significantly contributedto its widespread application in clinical practice. $SUV_{max}$is also in principle less dependent to partial volume effects (PVE), resulting from the limited spatial resolution of PET imaging [3]. On the other hand, there are a number of issues associated with its use,such as lack of robustnessin terms of image noise, as well as in terms of the reconstruction algorithm and the associated corrections used during the reconstruction process.Clearly the impact of these issues can be minimised by standardisation of the injection, acquisition,and finally image reconstruction and analysis protocols. In addition, the use of peak SUV ($SUV_{peak}$), measured by averaging the voxel values inside a small region of interest centered on the tumor maximum activity concentration voxel, can reduce the $SUV_{max}$ sensitivity to noise, although results may be sensitive to the actual definition of the ROI used to compute $SUV_{peak}$ [4].However and most importantly, $SUV_{max}$ represents only very limitedinformation considering the radiotracer accumulation and no information on the associated tumour uptake distribution as well as on the overall tumour functional volume. This is true even within the context of static acquisitions associated with routine whole body 18F-FDG PET imaging, where one does not consider dynamic acquisitions whichoffer the possibility, through kinetic modelling, to derive quantitative glucose metabolic rates on a voxel by voxel basis.

Remaining within the context of static PET imaging, overall tumour activity accumulation can be alternatively characterised using the mean standardised uptake value ($SUV_{mean}$). $SUV_{mean}$ corresponds to the mean activity concentration within a

delineated three dimensional functional tumour volume. The most significant issues associated with the accuracy of $SUV_{mean}$determination include the precision and robustness in the delineation of the tumour functional volume used [5,6], as well as an important influence of PVE which is closely related to the overall tumour size. The impact of PVE becomes more significant in the case of response to therapy studies where the metabolically active tumour volume (MATV) may change during treatment, consequently introducing a variable PVE influence on the calculated difference in $SUV_{mean}$ between the baseline and the post-treatment image. All these dependence issues combined with the lack of robust tools for tumour volume segmentation and PVE correction in PET oncology imaging has previously limited the widespread use of $SUV_{mean}$.

A combination of the metabolically active tumour volume (MATV) and the $SUV_{mean}$, defined as the total lesion glycolysis (TLG)or total glycolytic volume originally proposed by Larson et al [7],would allow in principle a more comprehensive functional tumour characterisation. The advantage of such an index is that it includes the average level of uptake within the tumour in addition to the spatial extent of the tumour uptake distribution, which facilitates the discriminationbetween lesions with similar size, but different uptake levels andvice-versa.The potential clinical impact of using such a parameter, reflecting overall tumour metabolic information rather than a single or few voxel measures based on $SUV_{max}$or $SUV_{peak}$ respectively, has been recently demonstrated. TLG levels derived from a baseline PET image were able to predict, in contrast to $SUV_{max}$, response to therapy in different cancer models, including mesothelioma [8], lymphoma [9] and oesophageal carcinoma[10].

However, despite their potential value, image derived indices such as 3D MATV and TLG have found only limited useup to date, including within the context of recent recommendations for response to therapy assessment using 18F-FDG PET imaging [11]. Thiscan be mostly explained by the limited accuracy, robustness and reproducibility of the clinically available tumour delineation tools. The shortcomings of standard threshold based approaches for MATV, which are currently the only widely available in clinical practice, have been previously highlighted in the literature [6,12]. They include a strong dependence on overall tumour volume and contrast. On the other hand, manual MATV delineation is a time consuming process prone to high inter- and intra-operator variability [13]. This renders manual tumor delineation a non-viable tool for allowing the introduction of MATV as an image derived index in routine

clinical practice.Different automatic segmentation approaches have been recently proposed, motivated by the interest of using 18F-FDG PET for the MATV delineation within the field of radiotherapy treatment planning [14]. Some of these approaches have shown high robustness and reproducibility to variable quality PET images (depending on factors such as scanner sensitivity and image reconstruction parameters) and tumour activity distribution characteristics, allowing similar to $SUV_{max}$ physiological reproducibility limits [15]. In addition, the use of these approaches has shown promising results for employing MATV measures in the prediction and prognosis of response to therapy based on 18F-FDG PET imaging [6,10]. However, being able to accurately determine a 3D functional tumour volume does not obviate the need for partial volume effects correction in order to ensure the calculation of an accurate tumour$SUV_{mean}$. This extra step clearly further complicates the process of accurately determining TLG values.

For all these reasons a novel parameter entitled SAM or “standardized added metabolic” activity parameter, recently proposed by Mertens J and colleagues [16] in the European Journal of Nuclear Medicine and Molecular Imaging,may be of particular interest. The attractiveness of this parameter is its potential independence to an accurate MATV determination as well as partial volume effects. Its derivation is based on considering the product of the concentration of activity and corresponding volume within two manually defined concentric volumes of interest (VOIs). These VOIs are placed around the tumour in sufficient distance from the MATV border to avoid partial volume effects. The concentration of activity in the difference VOI is used to determine the background activity which is subtracted by the $SUV_{mean}$derived using the VOI closer to the tumour. Although this parameter contains information related to both MATV and $SUV_{mean}$ it does not provide precise 3D tumour volume measurements and as such does not require an accurate MATV segmentation algorithm or manual tumour delineation. At the same time the mean tumour activity concentration calculated within the context of SAM is in principle not influenced by partial volume effects. In this same study it was also shown that SAM was less influenced by noise compared to the $SUV_{max}$.Finally, a potential dependence on the scanner calibration and activity injection parameters can beexcluded using a“normalized SAM”version by dividing the calculated tumourSAM value with the mean background SAM, assuming that the background and the tumour will be equally influenced by the different acquisition factors.

A preliminary clinical evaluation of this new PET image derived parameter was performed as part of the same study [16] considering 19 colorectal carcinoma patients undergoing baseline and treatment follow-up PET scans (after 3-6 chemotherapy cycles). In this patient population,consisting of only responders and non-responders, no statistically significant differences were found between $SUV_{max}$or SAM for assessing response to therapy based on PET imaging. This was the case considering either the baseline PET image values or differences between the baseline and the follow-up scans. More studies are now necessary considering different cancer models and larger and more variable patient populations in order to demonstrate the value of SAM not only compared to $SUV_{max}$ but also in comparison to other 18F-FDG PET image derived parameters such as 3D MATV and TLG values in terms of both prediction and assessment of response to therapy.

One can imagine going even further in exploiting tumor activity distribution features extracted from static PET images. These include assessing different levels of tumour uptake distribution heterogeneity which can eventually correlate with the underlying physiological processes governing tumor function. Since some of these physiological processes are potential mediators or targets of different therapeutic regimes, such image derived indices can be also proposed within the context of therapy response prediction and prognosis. Some recent studies have shown the interest of such indices for predicting response to therapy in head and neck [17], cervical [17] and esophageal cancer [18].

Finally it may be appropriate to combine multiple PET image derived indices and even multimodality and/or multi-tracer image derived parameters for a more complete tumor characterization. Complex correlations will have to be considered given the complexity of underlying tumour biology.Molecular profiling of biological specimens allows today to reveal the expression level of multiple genes and proteins. Obtaining biological specimens requires invasive procedures and may depend on the locationof the biopsy within a tumour.Would it be ever possible to imagine as an alternative the use of multimodality imaging, combining different image derived indices that will be identified as gene expression specific “signatures” and as such allow a non-invasive molecular profiling of individual patient cancers? This is still a dream but based on a few existing studies we may consider this idea as a future target for becoming reality [19]. Only future will tell…..

In conclusion, we have available today a number of algorithms and approaches that allow the automatic or semi-automatic extraction of accurate quantitative parameters from the tumor activity distribution in static 18F-FDG PET images. We have in this sense reached the age of reason in PET image derived parameters. There is now an urgent need for these tools to become widely available in order to allow the clinical research community to demonstrate their potential interest for therapy assessment, therapy response prediction and patient survival in different cancer models. A first step within this process involves standardization, robustness and reproducibility studies for all these “novel” PET image derived indices in comparison to current “state of the art” in clinical use such as $SUV_{max}$.

**References**


[1]. Weber WA.Assessing tumor response to therapy.J Nucl Med. 2009 May;50Suppl 1:1S-10S

[2]. Michalski MH, Chen X.Molecular imaging in cancer treatment. EurJ Nucl Med Mol Imaging. 2011; 38(2):358-77.

[3]. Tylski P, Stute S, Grotus N, Doyeux K, Hapdey S, Gardin I, et al Comparative Assessment of Methods for Estimating Tumor Volume and Standardized Uptake Value in 18F-FDG PET. J Nucl Med. 2010; 51: 268-276

[4]. Vanderhoek M, Perlman SB, Jeraj R. Impact of the definition of peak standardized uptake value on quantification of treatment response. J Nucl Med. 2012, 53(1):4-11.

[5]. Krak NC, Boellaard R, Hoekstra OS, Twisk JW, Hoekstra CJ, Lammertsma AAEffects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. Eur J Nucl Med Mol Imaging. 2005; 32(3):294-301.

[6].M Hatt, D Visvikis, NM. Albarghach, Tixier F, Pradier O, Cheze-le Rest CPrognostic value of 18F-FDG PET image-based parameters in esophageal cancer and impact of tumor delineation methodology Eur JNucl Med Mol Imaging, 2011, 38(7):1191-1202.

[7]. Larson SM, Erdi Y, Akhurst T, Mazumdar M, Macapinlac HA, Finn RD, et al. Tumor treatment response based on visual and quantitative changes in global tumor

glycolysis using PET-FDG imaging: the visual response score and the change in total lesion glycolysis. Clin Positron Imaging. 1999;2:159–171.

[8].Lee HY, Hyun SH, Lee KS, Kim BT, Kim J, Shim YM, et al. Volume-based parameter of (18)F-FDG PET/CT in malignantpleural mesothelioma: prediction of therapeutic response and prognostic implications. Ann SurgOncol 2010;17(10):2787–94.

[9]. Cazaentre T, Morschhauser F, Vermandel M, Betrouni N, PrangèreT, Steinling M, et al. Pre-therapy 18F-FDG PET quantitative parameters help in predicting the response to radioimmunotherapyin non-Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37(3):494–504.

[10].Hatt M, Visvikis D, Pradier O, Cheze-le Rest C Baseline 18F-FDG PET image-derived parameters for therapy response prediction in oesophageal cancer. Eur J Nucl Med Mol Imaging, 2011; 38:1595–1606.

[11]. Wahl RL,Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50Suppl 1:122S-50S.

[12]. Nestle U, Kremp S, Schaefer-Schuler A, Sebastian-WelschC, Hellwig D, Rübe C, et al Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. J Nucl Med. 2005;46(8):1342-8.

[13]. Hatt M, Cheze Le Rest C, Aboagye EO, Kenny LM, Rosso L, Turkheimer FE, et al. Reproducibility of 18F-FDG and 18F-FLT PET tumour volume measurements. J Nucl Med. 2010; 51(9):1368-1376.

[14]. Zaidi H, El Naqa I. PET-guided delineation of radiation therapy treatment volumes: a survey of image segmentation techniques. EurJ Nucl Med Mol Imaging. 2010;37(11):2165-87.

[15]. Hatt M, Cheze Le Rest C, Albarghach N, Pradier O, Visvikis DPET functional volume delineation: a robustness and repeatability study. Eur J Nucl Med Mol Imaging. 2011; 38(4):663-72.

[16]. Mertens J, Dobbeleir A, Ham H, D'Asseler Y, Goethals I, Van de Wiele C. Standardized added metabolic activity (SAM): a partial volume independent marker of total lesion glycolysis in liver metastases. EurJ Nucl Med Mol Imaging. 2012;39(9):1441-8.

[17]. El Naqa I, Grigsby PW, Aptea A, Kidd E, Donnelly E, Khullar D, et al. Exploring feature-based approaches inPET images for predicting cancer treatment outcomes. Pattern Recognit.2009;42:1162–1171.
[18]. Tixier F, Le Rest CC, Hatt M, Albarghach N, Pradier O, Metges JP, et al Intratumor heterogeneity characterized by textural features on baseline 18F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. J Nucl Med. 2011;52(3):369-78.
[19]. Segal E, Sirlin CB, Ooi C, Adler AS, Gollub J, Chen X et al. Decoding global gene expression programs inliver cancer by noninvasive imaging. Nat Biotechnol. 2007;25:675–680.