

The importance of harmonizing interim positron emission tomography in non-Hodgkin lymphoma: focus on the Deauville criteria

We would like to draw the attention of the hematology and nuclear medicine communities to the importance of standardized uptake value (SUV) harmonization in response evaluation in non-Hodgkin lymphoma (NHL) patients.

In NHL patients, the response evaluation during treatment (interim positron emission tomography (PET)) is currently assessed by comparing the residual metabolic activity in the most active tumor lesion to the liver uptake. These PET-based response criteria are described in the Deauville 5-point scale, in which the tumor-to-liver ratio is the discriminator between positive and negative test results.¹ However, differing degrees in uptake in the tumor and reference background for different PET systems can mislead the reader in both the visual and quantitative analysis.² This situation could be encountered in PET centers running several PET systems or during a system upgrade.

Therefore, visual and quantitative analysis of PET data in the setting of multicenter trials can only be performed reliably if the PET procedure is standardized. Currently, initiatives such as the European Association of Nuclear Medicine (EANM) Research Ltd. (EARL) accreditation for PET/CT systems (<http://earl.eanm.org/cms/website.php>) and the North American Quantitative Imaging Biomarker Alliance (QIBA) (http://qibawiki.rsna.org/index.php?title=Main_Page) aim to ensure comparable performance of PET/CT systems, in addition to the procedure guidelines for tumor PET imaging published by the EANM and the Society of Nuclear Medicine (SNM).³⁻⁵

New generation PET systems generally outperform older PET systems in terms of spatial resolution and activity recovery, thereby increasing SUVs substantially.⁶⁻⁸ We studied the impact of SUV reconstruction dependency on the tumor-to-liver ratio in 23 NHL patients (13 diffuse large B-cell lymphoma (DLBCL), 6 follicular lymphoma and 4 other subtypes) with a total of 388 lesions. The local Ethics Committee (ref. A12-D24-VOL13, Comité de protection

des personnes Nord Ouest III) waived signed informed consent for this type of study.

To mimic a situation in which a patient would undergo a PET exam on different generation PET systems, we reconstructed the PET raw data of these patients with a former generation ordered subset expectation maximization (OSEM) algorithm known to meet the EANM guidelines, the recently commercially available point-spread function (PSF) reconstruction without filter for optimal tumor detection (PSF_{allpass}) and a PSF reconstruction with a Gaussian filter optimized to fulfill EANM requirements (PSF_{EANM}). A detailed description of the PSF_{EANM} strategy is provided elsewhere.⁹

The PET procedure was performed according to the EANM guidelines. All PET studies were performed on a Biograph TrueV (Siemens Medical Solutions) PET/CT system equipped with PSF reconstruction. Regions of interest (ROIs) were drawn on the axial slice on which lesions displayed the highest FDG uptake by means of a 50% isocontour method and the SUVmax for each lesion was measured. A fixed size ROI of 3 cm diameter was used to measure the SUVmax of the physiological liver uptake in the middle of the right liver lobe. For each lesion and reconstruction type, the tumor-to-liver ratio was calculated by dividing the tumor SUVmax by the liver SUVmax. We chose the liver as the reference background, as this background seems preferable in early response assessment¹⁰ and it being the most frequently used cut off for a positive or negative PET exam in the Deauville criteria. Although the liver SUVmean would theoretically be preferable over the liver SUVmax as the reference background, as this parameter is less noise dependent, the liver SUVmax is the parameter currently used in clinical practice and in multicenter trials. The tumor-to-liver ratios for OSEM, PSF_{allpass} and PSF_{EANM} were compared using Bland-Altman plots.

As illustrated in Figure 1, the PSF_{allpass} image is optimal for visual analysis, with improved detection of small lesions and improved tumor delineation. Regarding the quantitative analysis, the tumor SUVmax was found to be 54% higher for PSF_{allpass} compared to OSEM (ratio 1.54, 95%CI: 0.95-2.14), whereas for PSF_{EANM} versus OSEM no significant difference was found (ratio 1.04, 95%CI: 0.93-1.14). Moreover, as shown in Figure 2, PSF_{allpass} increased the

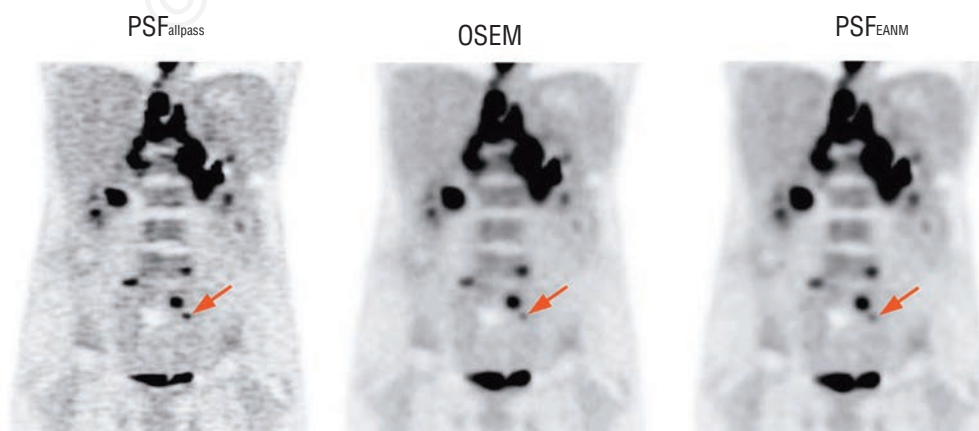


Figure 1. Improved visual analysis with a new generation PET system. Representative coronal slices for PSF_{allpass}, OSEM, and PSF_{EANM} reconstructions in a patient with multiple NHL locations below the diaphragm. Note the improvement in activity recovery visible in a small lymph node on the PSF_{allpass} image (arrow) as well as the liver background that appears more intense on the PSF_{allpass} images. All images have been scaled on the same maximum value.

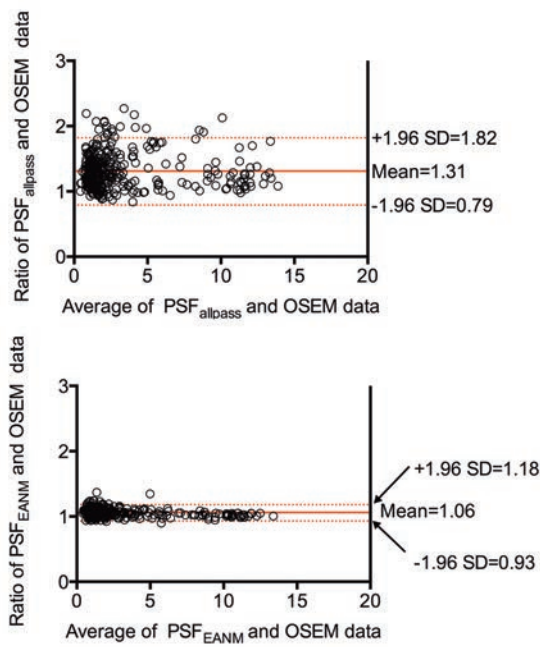


Figure 2. Harmonization of the tumor-to-liver ratio. Relationship between quantitative values for the tumor-to-liver ratio (tumor SUVmax divided by liver SUVmax for 388 lesions) for PSF_{alfpass}, OSEM and PSF_{EANM}, assessed by Bland-Altman plots.

tumor-to-liver ratio by 31% (ratio 1.31, 95%CI: 0.79-1.82) compared to OSEM. The ratio of the tumor-to-liver ratio for PSF_{EANM} and OSEM was found to be 1.06 (95%CI: 0.93-1.18), with a narrow 95% confidence interval.

Our data confirm that technological advances in PET reconstruction can lead to an important increase in not only the tumor SUVmax but also the tumor-to-liver ratio. The tumor-to-liver ratio as used in the Deauville criteria was increased by 31% for the PSF_{alfpass} reconstruction. This finding is of major importance because it shows that the discriminator between a positive and negative exam in NHL patients is PET system-dependent. Moreover, our data show that it is possible to get rid of reconstruction-dependent variations in SUV by applying an additional filtering step to the PSF_{alfpass} data. This strategy can be readily applied on any PET system. As advanced reconstruction algorithms such as PSF reconstruction are expected to gradually replace OSEM reconstructions, the choice of using a filtered PSF instead of OSEM reconstruction for the harmonized quantitative analysis might be preferable. This is also the technique proposed in the SUVref methodology,¹¹ which has the advantage of obviating the need to reconstruct two datasets. This methodology is not yet commercially available, and ideally should be vendor independent.

Of course, reconstruction parameters are not the only source of variation in SUV and tumor-to-liver ratios, and imaging protocols (including scanner calibration), patient preparation (fasting period, uptake time between injection and scan) and data analysis (ROI definition) should be stan-

dardized and closely matched for serial PET scans.

In conclusion, when interpreting interim PET scans from different generation PET systems, we recommend the reconstruction of two image sets, one for optimal visual analysis and one for standardized quantification, whilst awaiting future developments that might allow for both analyses to be carried out on the same dataset.

Elske Quak,¹ Narinée Hovhannisyan,¹ Charline Lasnon,^{1,2} Christophe Fruchart,³ Jean-Pierre Vilque,³ Dada Musafiri,³ and Nicolas Aide^{1,2}

¹Department of Nuclear Medicine, François Baclesse Cancer Centre, Caen; ²Normandie Université, Caen; and ³Department of Haematology, François Baclesse Cancer Centre, Caen, France

Correspondence: e.quak@baclesse.unicancer.fr
doi:10.3324/haematol.2014.104125

Key words: interim PET, FDG-PET/CT, non-Hodgkin lymphoma, Deauville criteria, SUV, PSF reconstruction.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

- Meignan M, Gallamini A, Itti E, Barrington S, Haioun C, Polliack A. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. *Leuk Lymphoma*. 2012;53(10):1876-81.
- Meignan M, Barrington S, Itti E, Gallamini A, Haioun C, Polliack A. Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3-5 October 2012. *Leuk Lymphoma*. 2014;55(1):31-7.
- Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging*. 2010;37(1):181-200.
- Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *J Nucl Med*. 2006;47(5):885-95.
- Makris NE, Huisman MC, Kinahan PE, Lammertsma AA, Boellaard R. Evaluation of strategies towards harmonization of FDG PET/CT studies in multicentre trials: comparison of scanner validation phantoms and data analysis procedures. *Eur J Nucl Med Mol Imaging*. 2013;40(10):1507-15.
- Lasnon C, Hicks RJ, Beaugard JM, Milner A, Paciencia M, Guizard AV, et al. Impact of Point Spread Function Reconstruction on Thoracic Lymph Node Staging With 18F-FDG PET/CT in Non-Small Cell Lung Cancer. *Clin Nucl Med*. 2012;37(10):971-6.
- Andersen FL, Klausen TL, Loft A, Beyer T, Holm S. Clinical evaluation of PET image reconstruction using a spatial resolution model. *Eur J Radiol*. 2013;82(5):862-9.
- Akamatsu G, Mitsumoto K, Taniguchi T, Tsutsui Y, Baba S, Sasaki M. Influences of point-spread function and time-of-flight reconstructions on standardized uptake value of lymph node metastases in FDG-PET. *Eur J Radiol*. 2014;83(1):226-30.
- Lasnon C, Desmots C, Quak E, Gervais R, Do P, Dubos-Arvis C, et al. Harmonizing SUVs in multicentre trials when using different generation PET systems: prospective validation in non-small cell lung cancer patients. *Eur J Nucl Med Mol Imaging*. 2013;40(7):985-96.
- Itti E, Juweid ME, Haioun C, Yeddes I, Hamza-Maaloul F, El Bez I, et al. Improvement of early 18F-FDG PET interpretation in diffuse large B-cell lymphoma: importance of the reference background. *J Nucl Med*. 2010;51(12):1857-62.
- Kelly MD, Declerck JM. SUVref: reducing reconstruction-dependent variation in PET SUV. *EJNMMI Res*. 2011;1(1):16.