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Letter to the editor.

Does PET reconstruction method affect Deauville scoring in lymphoma patients?

Ronald Boellaard^{1,2}, Carsten Kobe³, Josée M. Zijlstra⁴, N George Mikhaeel⁵, Peter W.M. Johnson⁶, Stefan Müller⁷, Ulrich Dührsen⁸, Otto S. Hoekstra¹, Sally Barrington⁹.

Affiliations

1. Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands.
2. Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, The Netherlands
3. Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany.
4. Department of Hematology, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands.
5. Guy's Cancer Centre, Guy's and St Thomas' NHS Hospital and Cancer Division, School of Life Sciences and Medicine, King's College London, London, UK
6. Cancer Research UK Centre, University of Southampton, Southampton, UK
7. Department of Nuclear Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
8. Department of Hematology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany.
9. King's College London and Guy's and St Thomas' PET Centre, School of Biomedical Engineering and Imaging Sciences, King's College London, King's Health Partners, London, UK.

To the editor:

Advances in PET/CT technology, such as the development of digital PET detectors, extended axial field of views (total body PET) and the use of resolution modelling during reconstruction, improves image quality e.g. by affecting sensitivity and spatial resolution. This results in enhanced lesion detectability and changes both visual and quantitative reads. These developments however pose challenges for multicentre studies and the application of previously validated interpretation criteria, such as the Deauville score (DS) in the clinical management of patients with lymphoma (1,2). These criteria are derived from studies performed on previous generations of PET/CT systems and do not necessarily translate one-to-one with data generated using the latest systems.

Recently, a shift towards more 'positive' reads for FDG PET/CT studies in patients with Hodgkin lymphoma with clinical consequences was reported by Barrington *et al.* (3) This shift was found to coincide with the introduction of a new generation of PET/CT systems that incorporate resolution modelling during reconstruction (also called 'PSF reconstructions'). Such reconstructions are associated with increased standardised uptake values (SUV) in (small) lesions, but not in large uniform organs such as liver and blood pool (4). This non-uniform change in apparent FDG uptake may affect reads when based on comparing lesion FDG uptake with that of liver and mediastinal blood pool, as is the case when using the Deauville score. PSF reconstructions have also been found to overestimate SUV in lung cancer patients (4,5). This upward bias seems also to depend on the size of the lesion or sphere, being the largest (sometimes up to 60%) for spheres and lesion of about 1.0 to 1.5 cm in diameter (i.e. the upward bias seems to be largest for this particular size). PSF reconstructions also introduce image artefacts, as illustrated in Figure 1 showing reduced uptake at the centre of a uniformly filled sphere and increased uptake near the edge of this sphere. Clearly, in a sphere filled with a homogeneous FDG solution, reduced core uptake surrounded by increased uptake near the edges above the actual value (similar to the distribution observed in truly necrotic lesions *in vivo*) does not represent the real FDG distribution.

Enilorac *et al.* (6) recently reported on the effects of using PSF reconstruction on Deauville scoring in lymphoma patients. The authors conclude that *neither the DS nor risk-stratification of diffuse large B-cell lymphoma (DLBCL) patients are affected by the choice of PET reconstruction. Specifically, the use of PSF is not an issue in routine clinical processes or in multicenter trials.* Yet, the authors admit that their findings need to be confirmed. Their conclusions are in contrast with the observations of Barrington *et al.* (3) and with the large changes in FDG SUV seen in other studies and for other tumor types (4,5). Having a closer look at the data presented by Enilorac *et al.* (6), a large fraction of the patient scans were evaluated as either DS1 or DS2, at interim (37%) and at end of treatment (53%) with PSF reconstruction. This result is in line with the high response rate anticipated to treatment in the majority of patients with DLBCL. As EARL compliant reconstructions typically result in lower lesion SUV, it is to be expected that moving from EARL compliant to PSF reconstruction would not affect risk stratification for these patients. However, considering patient scans with a DS of 4 using PSF reconstruction, 4/31 (13%, CI=5-29%) at interim and 3/17 subjects (18%, CI=6-41%) at end of treatment were scored as DS3 when using EARL compliant reconstructions. Or looking at the data in another way, 4/22 (18%) patients with interim scans were evaluated as DS3 using EARL but DS4 using PSF. 3/18 (17%) of patients had end of treatment scans evaluated as DS3 using EARL but interpreted instead as DS 4 using PSF, simply by changing the reconstruction. This is of clinical importance as the cut-off between DS3 and DS4 is generally used to distinguish responders from non-responders. Hence, whilst PSF may not have a major impact on PET interpretation for the overall study population, it could have potential consequences for approximately 1 in 6 patients who would be deemed 'responders' using the standard EARL reconstruction but 'non responders' using PSF. Additionally, changes in reconstruction would not be expected to alter the progression and overall survival of the whole population. The study by Enilorac *et al.* (2) was not powered to show such a difference, but even in large studies in aggressive non-Hodgkin lymphomas, such as the PETAL study (862 patients) (7), the risk stratification provided by PET did not alter patient outcomes. This is because of the ineffectiveness of current salvage treatment options for patients at high risk of relapse. This situation may change with more promising agents, which are currently being tested in relapsed/refractory patients with DLBCL. We believe this is a strong argument against altering the status quo in multicentre trials without further evaluation.

In clinical practice we also consider that reads should be performed with caution using resolution modelling, in particular when patient scans are evaluated near the decision threshold between clinically negative and positive findings, i.e. in lymphoma between DS3 and DS4, as using newer reconstructions tends to shift findings to produce more 'positive' reads (3). This is also demonstrated by Elinorac *et al.*(6). The conclusion drawn by Elinorac *et al.* (6) is only correct when considering all patients in their study, dominated by the large fraction of DS1, 2 and 3 subjects seen with PSF reconstructions. However, the paper also demonstrates that the choice of reconstruction method (EARL versus PSF) does affect Deauville scores, in particular for patients being evaluated around the clinically relevant cut-off as DS3 with EARL or DS4 with PSF. An illustrative example was also shown in that paper in Figure 1. We believe that the use of PSF reconstruction is not detrimental but beneficial for lesion detectability (8,9) and should be further pursued. Yet, resolution modelling should be used with caution, in particular in small lesions (1.0-1.5 cm diameter) having a DS of 3 or 4 and if treatment change is planned, until a revisit or update of the Deauville scoring system has been made to accommodate these new reconstruction approaches. Moreover, PSF reconstructions are not necessarily the same nor behave the same on each (type of) PET/CT system. Results obtained with one system can therefore not be generalized to all other systems. The different PSF implementations will therefore result in performance variabilities across systems. For multicentre studies use of PSF reconstruction mandate an update of harmonizing performance standards. Recently, a first feasibility study for harmonizing performance of state of the art PET/CT systems was published by Kaalep *et al.*(10) Once these new standards have been implemented, the impact of PSF reconstructions in multicentre studies on image interpretation, e.g. Deauville scoring, can be performed in

a standardized manner and may imply that interpretation criteria will need to be adapted, in particular for patients with scans evaluated as DS3 or DS4.

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Conflicts of interest

Professor Boellaard is member of the EARL scientific advisory board (unpaid) and has collaborative research programs with Philips and Siemens Healthcare. Professor Barrington receives research funding from Siemens Healthcare.

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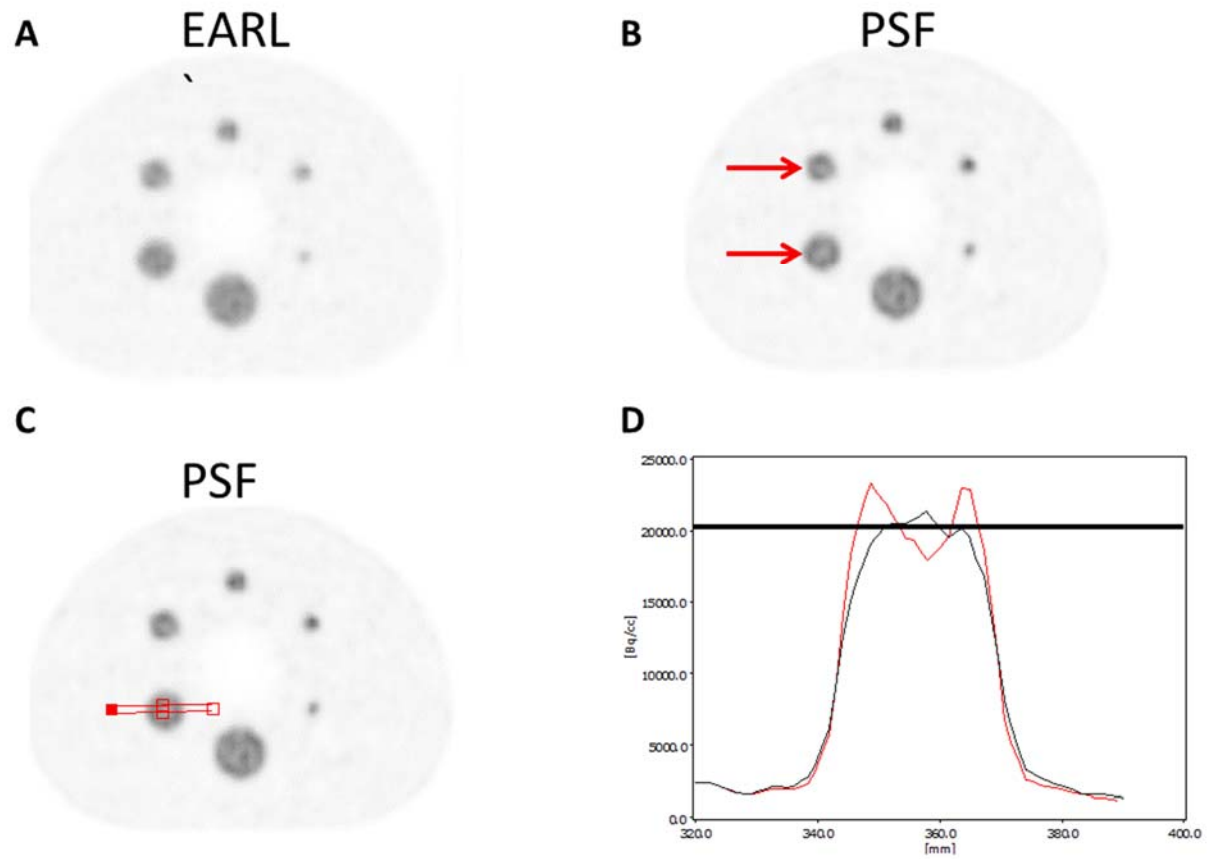


Figure 1: PET images (axial slice) of the NEMA Image Quality phantom filled conforming with EARL instructions. (a) PET image reconstructed with EARL compliant settings. (b) PET image reconstructed using resolution modelling (PSF). The red arrows point to a typical PSF artefact showing increased uptake at the edge of a sphere and reduced uptake at the centre of the sphere, which appear most strongly for 1 to 1.5 cm diameter spheres. (c) Image illustrating location of activity profile (red line) as plotted in (d). In subfigure (d) the red line indicates the activity profile seen in the PSF reconstructed PET image and the black line indicates that of the EARL compliant reconstruction.



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