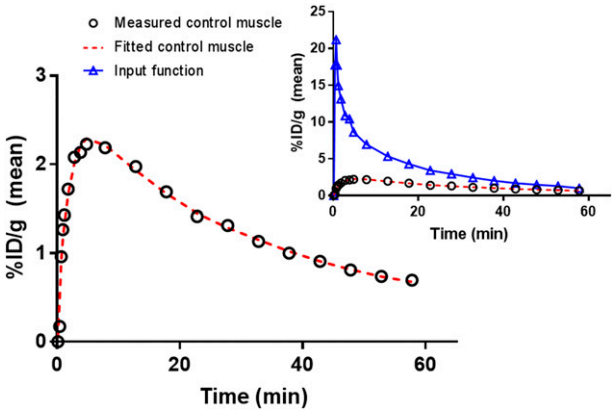

FIGURE 1. Plots of the image-derived IF, the average measured control muscle time–activity curve, and the compartmental model fitted curve. The influx rate constant Ki for the control muscle was estimated to be 0.001084 ± 4.475E−5 mL/min/g (very low as expected for noninfected muscle). If there was tissue uptake saturation, one would not likely be able to fit the control muscle time–activity curve with a linear tracer kinetic model.

To better explain the different shapes of the 2 curves, we believe the issue is more related to the time–activity curve of the active bacteria muscle site. For example, what was the state of the bacteria in tissue 24 h after injection? Was the vascular supply or perfusion to the infected tissue changed? Was the first-pass extraction fraction of the tracer in the infected tissue close to 100%? There are many different but more plausible reasons that could explain the different shapes of the 2 time–activity curves, and would certainly need to be investigated further.

Nevertheless, we and Laffon et al. all agree that 6″-^{18}F-fluoromaltotriose is an exciting new PET tracer that could potentially play an important role in the diagnosis of infectious diseases of bacterial origin as well as in the assessment of antibiotic therapy. Indeed, this new molecular imaging tracer will help us to better understand bacterial biology in living subjects.

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Published online Apr. 13, 2018.
DOI: 10.2967/jnumed.118.208736

Does PET Reconstruction Method Affect Deauville Scoring in Lymphoma Patients?

TO THE EDITOR: Advances in PET/CT technology, such as the development of digital PET detectors, extended axial fields of view (total-body PET), and the use of resolution modeling during reconstruction, improve image quality, for example, 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 multicenter 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 1-to-1 with data generated using the latest systems.

Recently, a shift toward more positive reads for ^{18}F-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 modeling during reconstruction (also called point-spread function [PSF] reconstructions). Such reconstructions are associated with increased SUV in (small) lesions, but not in large uniform organs such as the liver and blood pool (*4*). This nonuniform change in apparent ^{18}F-FDG uptake may affect reads when based on comparing lesion ^{18}F-FDG uptake with that of liver and mediastinal blood pool, as is the case when using the DS. 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 1.0–1.5 cm in diameter (i.e., the upward bias seems to be largest for this particular size). PSF reconstructions also introduce image artifacts, as illustrated in Figure 1 showing reduced uptake at the center of a

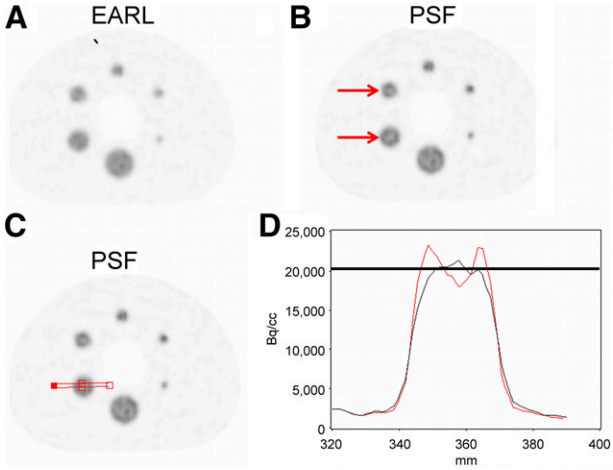

FIGURE 1. PET images (axial slice) of NEMA Image Quality phantom filled conforming with EARL instructions. (A) PET image reconstructed with EARL-compliant settings. (B) PET image reconstructed using resolution modeling (PSF). Red arrows point to typical PSF artifact showing increased uptake at edge of a sphere and reduced uptake at center 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. Red line in D indicates activity profile seen in PSF-reconstructed PET image, and black line indicates that of EARL-compliant reconstruction.

uniformly filled sphere and increased uptake near the edge of this sphere. Clearly, in a sphere filled with a homogeneous ^{18}F-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 ^{18}F-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 is 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 ^{18}F-FDG SUV seen in other studies and for other tumor types (*4,5*). When the data presented by Enilorac et al. (*6*) are considered more closely, a large fraction of the patient scans was evaluated as either DS1 or DS2, at interim (37%) and at the end of treatment (53%), using PSF reconstruction. This result is in line with the high response rate anticipated to treatment in most patients with DLBCL. As European Association of Nuclear Medicine (EANM) Research Ltd. (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, when patient scans with a DS of 4 using PSF reconstruction were considered, 4 of 31 (13%; 95% confidence interval = 5%–29%) at interim and 3 of 17 subjects (18%; 95% confidence interval = 6%–41%) at the end of treatment were scored as DS3 when EARL-compliant reconstructions were used. Or looking at the data in another way, 4 of 22 (18%) patients with interim scans were evaluated as DS3 using EARL but DS4 using PSF. Three of 18 (17%) patients had end-of-treatment scans evaluated as DS3 using EARL but interpreted instead as DS4 using PSF, simply by changing the reconstruction. This is of clinical importance because the cutoff between DS3 and DS4 is generally used to distinguish responders from nonresponders. Hence, whereas 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 nonresponders 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. (*6*) 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 due to 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 multicenter trials without further evaluation.

In clinical practice, we also consider that reads should be performed with caution using resolution modeling, in particular when patient scans are evaluated near the decision threshold between clinically negative and positive findings, that is, 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 Enilorac et al. (*6*). The conclusion drawn by Enilorac et al. (*6*) is only correct when considering all patients in their study, dominated by the large fraction of DS1, DS2, and DS3 subjects seen with PSF reconstructions. However, the paper also demonstrates that the choice of reconstruction method (EARL vs. PSF) does affect DSs, in particular for patients being evaluated around the clinically relevant cutoff 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 modeling should be used with caution, in particular in small lesions (1.0–1.5 cm in 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 multicenter studies, use of PSF reconstruction mandates 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 multicenter studies on image interpretation, for example, Deauville scoring, can be determined 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.

DISCLOSURE

Professor Barrington acknowledges support from the National Institute of Health Research (NIHR; RP-2-16-07-001). King's College London and UCL Comprehensive Cancer Imaging Centre is funded by the CRUK and EPSRC in association with the MRC and Department of Health (England). Professor Boellaard is a 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. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. No other potential conflict of interest relevant to this article was reported.

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Published online Apr. 6, 2018.
DOI: 10.2967/jnumed.118.211607

Embrace Progress

TO THE EDITOR: We would like to comment on the letters by Boellaard et al. in this issue of *The Journal of Nuclear Medicine* and Barrington et al. (*1*). The authors urge reporters not to use PET reconstruction algorithms, which exploit point-spread function (PSF) modeling or Bayesian penalized likelihood (BPL) techniques for response assessment in lymphoma. This call to ignore a more sensitive reconstruction technique, demonstrated to yield image data closer to phantom truth (*2*), and with the ability to detect smaller volume disease, is of concern. The Deauville criteria (DC) were designed to simplify and standardize how we interpret an ^{18}F-FDG PET/CT scan for the presence or absence of active lymphoma and to guide clinicians in the management and prognosis of their patients. The comment that there is "a shift toward more positive reads" is unfortunate as it references a letter by Barrington et al. that has only anecdotal evidence from 3 patients and is not a peer-reviewed paper or a large-cohort series. We believe there is insufficient evidence to support the recommendation to not use these more sensitive PET/CT reconstruction methods.

Recent publications have emphasized that BPL PET reconstruction is particularly advantageous in patients with high body mass index (*3*), that is, in patients with the greatest background noise in whom the detection of small abnormalities is most problematic. This improvement in signal-to-noise ratio may improve inter- and intraobserver variation in assessing DC. With older reconstruction techniques, even among experts, interobserver agreement using the DC is only moderate (*4*), and it has been suggested that this may be because of difficulty comparing the signal in a lesion with noisy background signal in the liver or mediastinal blood (*5*). PSF and BPL still underestimate true activity in small foci, however, they are a step forward and nearer to phantom truth. This truth can make reporting more challenging, requiring careful consideration of the clinical significance of the detection of small-volume and subtle abnormalities.

The recent publication by Enilorac et al. (*6*) compared a PSF reconstruction with European Association of Nuclear Medicine (EANM) Research Ltd. (EARL)–compliant reconstruction in 126 diffuse large B-cell lymphoma patients. They concluded that neither DC score nor risk stratification of diffuse large B-cell lymphoma patients was significantly affected by the choice of PET reconstruction and that specifically the use of PSF is not an issue in routine clinical processes or in multicenter trials. In practice, there are probably few patients with discordant DC on ordered-subset expectation maximization versus more advanced reconstructions, with potential to alter management. It will be of immense value to study these patients, which may require collaboration between centers, so that going forward lessons can be learned. Nonetheless, it is also important to remember that the interpretation of interim scans and the decisions related to them are not binary. They should ideally be made in the clinical context, in relation to lymphoma type, stage, and risk factors, such as bulk or B symptoms and the intensity of treatment given before and after the PET scan (*5*).

Alongside the use of interim PET, it is important to remember that PET is used to more accurately stage lymphoma at presentation, with significant value in detecting extranodal disease, and this is likely to be further improved using more sensitive imaging techniques. The use of new reconstruction methods at baseline staging then effectively mandates its use for follow-up scans, as the detection of new or progressive disease remains important.

We would argue that early disease detection often leads to better treatment and clinical outcomes. We need to embrace technologic advances and innovation even if these lie outside our comfort zone. The current situation is very similar to any major advance in imaging, such as the transition from 2-dimensional to 3-dimensional PET reconstruction. However, this learning curve does not mean these advanced methods should be avoided; we would suggest that patients with malignancies should be staged and followed up as accurately as possible using the most sensitive technique available. This may require alteration to the DC as previously occurred with changes to the International Harmonization Project in 2014 after the increased use of more modern PET/CT scanners.

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Published online Apr. 26, 2018.
DOI: 10.2967/jnumed.118.212761