

## Original Article

# Impact of expectation-maximization reconstruction iterations on the diagnosis of temporal lobe epilepsy with PET

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**Abstract:** There is a well known tradeoff between image noise and image sharpness that is dependent on the number of iterations performed in ordered subset expectation maximization (OSEM) reconstruction of PET data. We aim to evaluate the impact of this tradeoff on the sensitivity and specificity of <sup>18</sup>F-FDG PET for the diagnosis of temporal lobe epilepsy. A retrospective blinded reader study was performed on two OSEM reconstructions, using either 2 or 5 iterations, of 32 <sup>18</sup>F-FDG PET studies acquired at our institution for the diagnosis of temporal lobe epilepsy. The sensitivity and specificity of each reconstruction for identifying patients who were ultimately determined to be surgical candidates was assessed using an ROC analysis. The sensitivity of each reconstruction for identifying patients who showed clinical improvement following surgery was also assessed. Our results showed no significant difference between the two reconstructions studied for either the sensitivity and specificity of <sup>18</sup>F-FDG PET for predicting surgical candidacy, or its sensitivity for predicting positive surgical outcomes. This implies that the number of iterations performed during OSEM reconstruction will have little impact on a reader based interpretation of <sup>18</sup>F-FDG PET scans acquired for the diagnosis of temporal lobe epilepsy, and can be determined by physician and institutional preference.

**Keywords:** <sup>18</sup>F-FDG PET, temporal lobe epilepsy, OSEM reconstruction, ROC analysis

## Introduction

Positron emission tomography with 2-deoxy-2-(<sup>18</sup>F)fluoro-D-glucose (<sup>18</sup>F-FDG PET) has become an integral part in the diagnosis and pre-surgical evaluation of temporal lobe epilepsy (TLE), and its diagnostic efficacy and ability to predict surgical outcomes have been demonstrated in numerous studies [1-4]. TLE is diagnosed on <sup>18</sup>F-FDG PET by identifying hypometabolic regions with decreased <sup>18</sup>F-FDG uptake in a diseased temporal lobe relative to a healthy contralateral one. The diagnosis may be difficult to make if the degree of hypometabolism is subtle, and <sup>18</sup>F-FDG uptake in small regions may be obscured if resolution is poor or noise variance is high. A number of approaches have been developed to improve diagnosis by reducing partial volume effects, for example by using anatomical information from MRI scans, to make small hypometabolic regions more detectable [5-7]. However, such correction methods are not read-

ily available at most clinical centers and their use is only beginning to be validated.

A more clinically accessible approach to reduce partial volume effects is simply increasing the number of iterations performed during expectation-maximization (EM) reconstruction. EM reconstructions, particularly with ordered subsets (OSEM) [8, 9], are now widely used for diagnostic PET. There is a well-known tradeoff between increased image sharpness and increased noise variance as the number of EM iterations is increased during reconstruction [10, 11]. In the context of <sup>18</sup>F-FDG PET for TLE, a greater number of iterations may increase image sharpness and thus improve the detectability of small regions of hypometabolism, but this may be offset by the associated increase in image noise. The impact of the number of iterations performed during reconstruction on diagnostic accuracy has been studied in the context of several imaging tasks [12-16], and unsurprisingly the opti-

mal implementation of EM reconstruction is dependent on the task. However, to our knowledge such a study has not been undertaken for  $^{18}\text{F}$ -FDG PET acquired to diagnose TLE, and the specific reconstruction algorithm used is typically determined by physician preference. Our aim here is to evaluate the impact of the number of EM reconstruction iterations, and hence the tradeoff between image sharpness and noise, on the diagnostic accuracy of clinical  $^{18}\text{F}$ -FDG PET scans acquired for TLE diagnosis. We do this for two OSEM reconstructions with a blinded reader study using a receiver operating characteristic (ROC) analysis of the predictive power of  $^{18}\text{F}$ -FDG PET for identifying surgical candidates, and a comparison of the sensitivity of the two different reconstructions for identifying patients who improved with surgery.

### Materials and methods

#### *Subject selection*

This study was carried out as a retrospective analysis of clinical  $^{18}\text{F}$ -FDG PET studies previously acquired at our institution for the diagnosis of medically intractable TLE. The medical and imaging records of all patients ( $n=184$ ) who received  $^{18}\text{F}$ -FDG PET scans for the diagnosis of TLE between 2000-2010 were investigated for inclusion and exclusion criteria as follows. Inclusion criteria included diagnosis or suspicion of TLE; consideration for surgical treatment of epilepsy; age  $\geq 18$  years; clinical documentation of age, gender, seizure onset, and seizure frequency, antiepileptic drug (AED) trials, EEG report, PET report, MRI report, and in patients ultimately receiving surgery: postoperative follow-up, seizure frequency, and seizure character. Exclusion criteria included a history of cerebral vascular accident (CVA), brain tumor, head trauma, tuberous sclerosis, prior cranial surgery, and hemispheric congenital malformations (e.g., porencephaly, lissencephaly, perisylvian polymicrogyria, hemimegalencephaly).

Medical records were then reviewed to determine the documented findings of  $^{18}\text{F}$ -FDG PET, MRI, EEG exams, and postoperative outcomes.  $^{18}\text{F}$ -FDG PET was deemed positive if unilateral temporal lobe hypometabolism was noted in the medical record. MRI was deemed positive if mesiotemporal sclerosis, hippocampal atrophy, unilateral temporal atrophy, or temporal gliosis were noted. EEG was deemed localizing if re-

ports indicated that seizures originated from one temporal lobe. Surgical outcome data were evaluated in patients who had at least one assessment of their postoperative seizure course in the electronic medical record. Surgical outcomes were graded according to the International League Against Epilepsy (ILAE) scale [17]. For the purposes of this study, surgical outcomes were further categorized as positive for ILAE scores of 1-4 (1 = absence of seizures, 4 = 4 seizures per year up to a 50% seizure reduction from baseline), and negative for scores of 5 or 6 (less than a 50% reduction in seizures from baseline). Of the patients receiving surgery, only one had a negative outcome (ILAE score of 5). Following the compilation of these data, subjects were anonymized. The general characteristics of this population of subjects and an analysis of their outcomes has previously been published [18].

A subset of 32 subjects were then selected to be used in the blinded reader study. This subset of subjects was selected to maximize the number of patients whose scans were initially read as negative with positive surgical outcomes (i.e. false negatives), as the interpretation of these scans is plausibly the most likely to change. The other scans included in the reader study were selected such that the population of patients used in the reader study maintained the general diagnostic characteristics of the overall population of patients who received  $^{18}\text{F}$ -FDG PET for TLE. In particular, the percentage of scans initially read as positive and negative was kept approximately the same between the subset of subjects used in the reader study and the overall number of  $^{18}\text{F}$ -FDG PET studies for TLE, as was the proportion of scans with findings concordant and discordant with MRI and/or EEG.

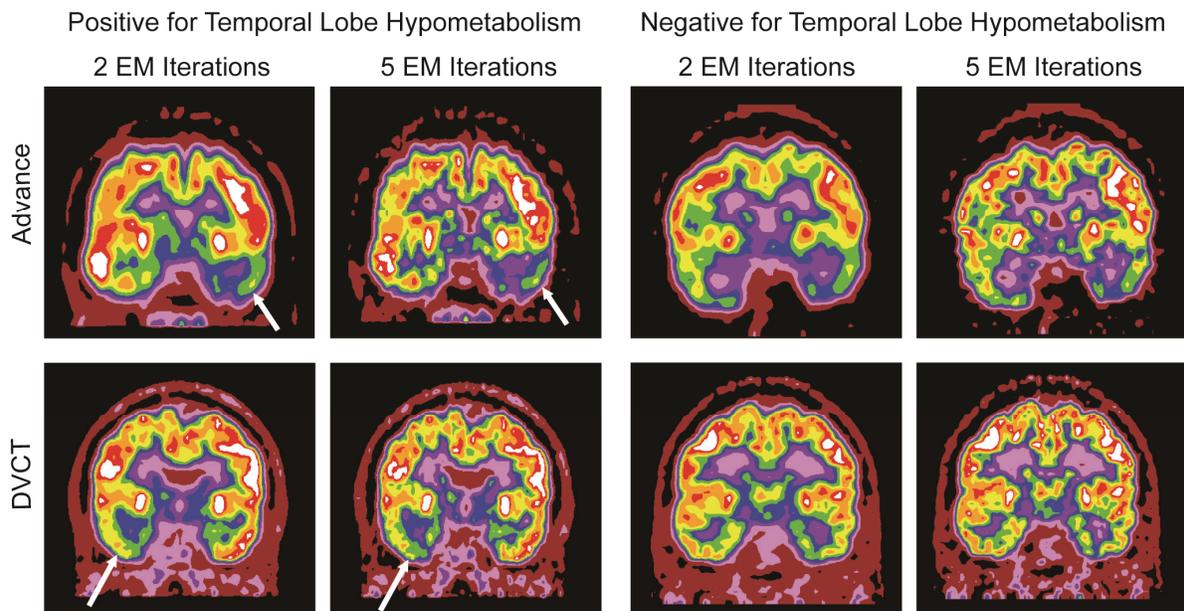
#### *PET image acquisition and reconstruction protocols*

Patients fasted for 6 hours prior to injection of  $^{18}\text{F}$ -FDG. Diabetic patients were instructed to withhold diabetic medications for 6 hours and blood glucose measurements were required to be  $< 200$  mg/dL at the time of tracer injection. Patients were injected intravenously with 0.14 mCi/kg (minimum of 10 mCi)  $^{18}\text{F}$ -FDG, and were then instructed to relax quietly for 45 minutes in a dimly lit room. Patients were imaged at 60 minutes after injection with one of two scanners: the Advance and the Discovery VCT (GE

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**Table 1.** Reconstruction parameters for each scanner used in the study. The number of iterations was the only parameter varied between the two OSEM reconstructions for each patient exam.

Scanner	GE Advance	GE Discovery VCT
Reconstruction	2D OSEM	3D OSEM
Matrix Size	128x128x35	128x128x47
Voxel Size	2.3x2.3x4.25 mm <sup>3</sup>	2.3x2.3x3.27 mm <sup>3</sup>
Number of Subsets	28	35
Number of Iterations: Smooth	2	2
Number of Iterations: Sharp	5	5
Post-Smoothing Filter (Gaussian FWHM)	3.27 mm	2.57 mm



**Figure 1.** Example images of the reconstructions studied. Example slices are shown of the 2 different reconstructions that were compared for both the GE Advance and GE Discovery VCT scanners used in the study. Examples from each scanner for patients with <sup>18</sup>F-FDG PET scans initially read as positive and with positive surgical outcomes, and for patients with <sup>18</sup>F-FDG PET scans initially read as negative who did not receive surgery are both shown. Hypometabolic regions are indicated with arrows.

Healthcare).

Two OSEM reconstructions were performed on each <sup>18</sup>F-FDG PET exam. The first used reconstruction parameters typical of our institution for the type of scanner used. These reconstructions were considered the smooth, relatively low-resolution, and low-noise standards. The second reconstruction increased the number of iterations used during reconstruction, while keeping all other parameters constant. The specific number of iterations to be used for the second set of reconstructions was determined by a

nuclear medicine physician using a test set of subjects by qualitatively determining the number of iterations at which possible increased confidence in the diagnosis would be offset by increased noise. These reconstructions served as the sharper, higher noise comparisons. Pertinent reconstruction parameters are summarized in **Table 1**, and example reconstructions from each scanner for <sup>18</sup>F-FDG PET scans initially read as both positive and negative are shown in **Figure 1**. Note that 3D OSEM reconstructions of shorter acquisitions with more subsets (35 versus 28) were used for the Discovery

VCT, which is standard practice at our institution. Corrections for normalization, deadtime, and scatter radiation were applied using system software. Attenuation correction was applied to the scans acquired on the GE Advance using a transmission scan acquired with two Ge-68 rod sources, and to the scans acquired on the GE Discovery VCT using a co-registered CT scan.

### *Reader study design and analysis*

Each individual reconstruction was assigned a random number and all associated patient, exam, and reconstruction information were removed. All reconstructions were then presented to the blinded readers interspersed randomly. Two readers, reader 1 and reader 2, assigned a diagnostic score of 1-5 to each reconstructed image (1 = unequivocal hypometabolic focus, 2 = strong confidence of hypometabolic focus, 3 = moderate confidence of hypometabolic focus, 4 = equivocal for hypometabolic focus, 5 = no hypometabolic focus). Readers were also blinded to MRI, EEG, and other clinical findings.

ROC curves for surgical candidacy were then generated for each reconstruction, and analyzed for each reader separately and with their results combined. The area under the curve (AUC) was calculated for each ROC curve, and curves for smooth reconstructions (2 EM iterations) were compared with curves for sharp reconstructions (5 EM iterations) using the non-parametric comparison approach of DeLong et al. [19].

As only one patient out of all the patients meeting the inclusion and exclusion criteria for the study had a negative surgical outcome as we have defined (ILAE score of 5 or 6), the specificity of  $^{18}\text{F}$ -FDG-PET for predicting surgical outcomes cannot be assessed. We therefore compared only the sensitivities of the two OSEM reconstructions for identifying patients who improved with surgery at each level of reader confidence. Ninety-five percent confidence intervals (CIs) were found for the sensitivities at each level of diagnostic confidence using the Clopper-Pearson interval, and McNemar's test was used to test for significance.

Access to imaging and medical records of all patients for the purpose of this study, and permission to reprocess and reinterpret imaging studies, was approved by the local institutional review board.

## Results

### *Patient selection*

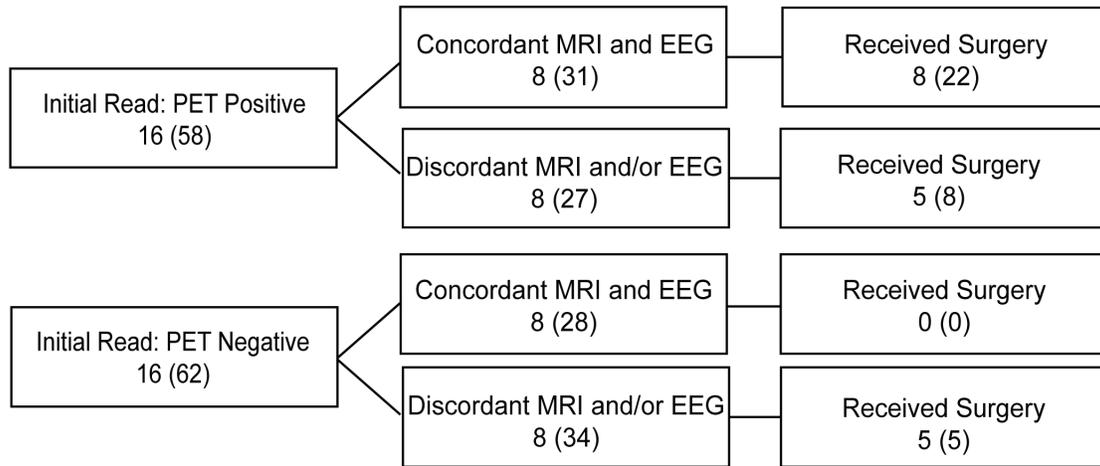
A total of 120 patients met the initial inclusion and exclusion criteria and 32 were included in the reader study. As outlined above, the subset of 32 scans used for the reader study were selected to maximize the number of scans whose initial interpretations were false negative while keeping the percentage of scans initially read as  $^{18}\text{F}$ -FDG PET positive and negative for hypometabolism, and with concordant and discordant MRI and/or EEG findings, approximately the same as in the 120 patients meeting the inclusion and exclusion criteria. Of the 32 patients included in the reader study, 26 were scanned on the GE Advance and 6 were scanned on the GE Discovery VCT. The diagnostic characteristics of the scans selected for the reconstruction study and for the overall population of patients undergoing  $^{18}\text{F}$ -FDG PET for TLE are summarized in **Figure 2**. Of the patients receiving surgery who were included in the reader study ( $n=18$ ), 9 had an ILAE outcome of 1 (seizure free), 4 had an ILAE outcome of 2 (auras, but no seizures), 4 had ILAE outcomes of 3 (1-3 seizures per year), and 1 had an outcome of 5 (<50% reduction from baseline). The representation of these outcomes in the reader study population is likewise similar to their representation in the overall population of patients receiving surgery. Two patients were identified as surgical candidates but had not received surgery at the time of data collection. One patient was awaiting surgery at the time the study was conducted, and one did not proceed with surgical treatment. Both of these patients were scanned on the GE Discovery VCT.

### *Reader study results*

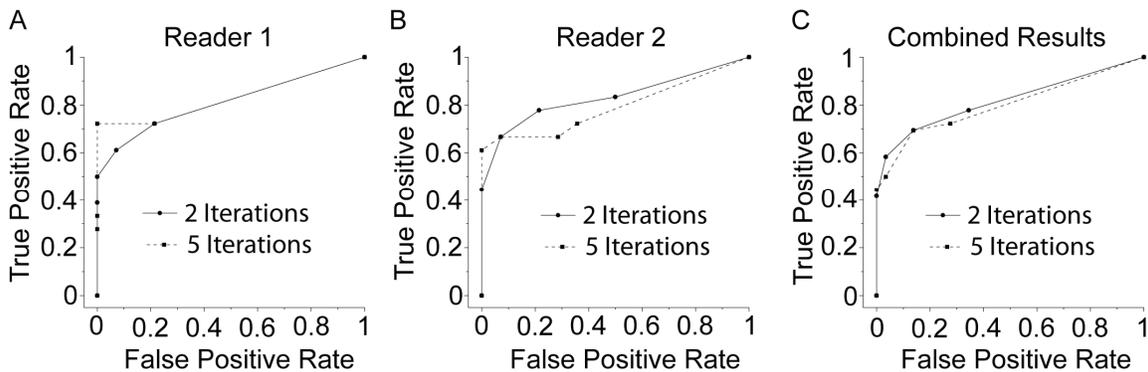
The two readers were very consistent in their interpretations of the  $^{18}\text{F}$ -FDG scans, regardless of the number of iterations used. When the results of the two readers are combined, 48/64 (75%) of the studies were given an identical rating between the two reconstructions, and 13/64 (20.3%) were given ratings that differed by one degree of reader confidence.

The ROC curves for surgical candidacy are shown in **Figure 3**. The ROC curves of the individual readers and their combined results are both included. The area under each curve and the results of the nonparametric statistical com-

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**Figure 2.** Patient population diagnostic characteristics. The diagnostic characteristics of the patient scans included in the study are shown, and the characteristics of all of the  $^{18}\text{F}$ -FDG PET scans acquired for TLE diagnosis that met the initial inclusion and exclusion criteria are also included in parentheses. The proportion of scans initially read as positive and negative, and concordant and discordant with MRI and/or EEG were kept approximately the same between the scans included in the reader study and the overall number of scans meeting the inclusion and exclusion criteria. All but one of the patients who received surgery showed clinical improvement, and the patient who did not improve had an  $^{18}\text{F}$ -FDG PET scan initially read as negative.



**Figure 3.** Surgical candidacy ROC curves. ROC curves for surgical candidacy are shown for both readers individually (A & B), and with their results combined (C). Smooth reconstructions (2 EM iterations) are compared with sharp reconstructions (5 EM iterations) in each case. There was no statistically significant difference between the AUC of the two reconstructions for either reader separately or with their results combined.

parison between them are summarized in **Table 2**. There was no statistically significant difference between the AUCs for the reconstructions with 2 iterations and 5 iterations for either of the readers individually and with their results combined. As the acquisitions and reconstructions from the GE Discovery VCT were 3-dimensional and those from those from the GE Advance were 2-dimensional, the areas under

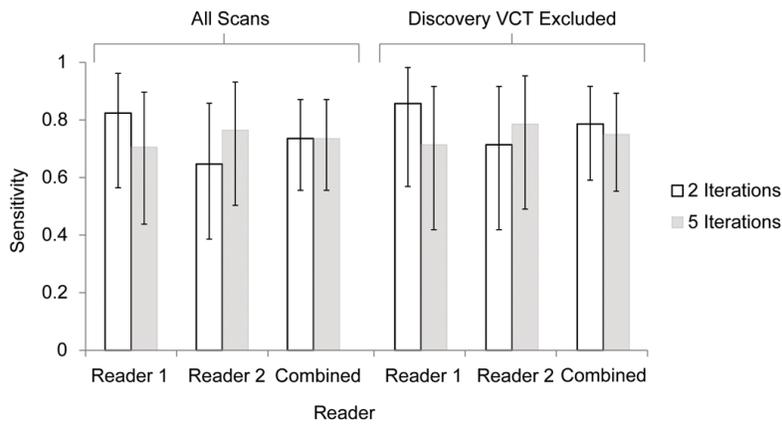
ROC curves excluding the scans acquired on the GE DVCT ( $n=6$ ) were also examined (**Table 2**). Excluding the GE Discovery VCT scans also excludes the two patients identified as surgical candidates but who had not received surgery at the time of data collection. Excluding these scans did not alter the results.

The sensitivities of the 2 iteration and 5 iteration OSEM reconstructions for predicting surgi-

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**Table 2.** The areas under the ROC curves from each reconstruction for the individual readers and with their results combined. The P-values for the difference between the AUCs of each reconstruction are shown. None reached significance. The AUCs and the P-values comparing them after excluding the scans acquired of the GE Discovery VCT are also shown. The exclusion of these scans did not alter the results.

Surgical Candidacy		All Scans			Discovery VCT Excluded		
OSEM Iterations	Reader 1	Reader 2	Combined	Reader 1	Reader 2	Combined	
2	0.839	0.812	0.821	0.888	0.815	0.850	
5	0.806	0.831	0.807	0.833	0.830	0.828	
P-value	0.563	0.280	0.674	0.470	0.442	0.595	



**Figure 4.** Surgical outcome sensitivity. The sensitivity of  $^{18}\text{F}$ -FDG PET for predicting a positive surgical outcome for the two OSEM reconstructions studied. There was no statistically significant difference in the sensitivities of the reconstructions for either of the readers, or with their results combined. Excluding the scans acquired on the GE Discovery VCT did not alter the results.

cal outcome at a moderate level of diagnostic confidence (images rated 3 or higher counted as positive reads) are shown in **Figure 4**. There was no significant difference between the two reconstructions for each reader separately or with their results combined. This was true at all other levels of diagnostic confidence as well (data not shown). As with the ROC curves for surgical candidacy, excluding the scans acquired on the Discovery VCT did not alter the results.

### Discussion

The aim of this study was to retrospectively investigate the impact of the number of iterations performed during OSEM reconstruction on the sensitivity and specificity of  $^{18}\text{F}$ -FDG PET for predicting surgical candidacy and surgical outcomes in TLE. This was done with a blinded reader study comparing two OSEM reconstructions, differing in the number of iterations performed. The ability of  $^{18}\text{F}$ -FDG PET to predict surgical candidacy was evaluated with a ROC analysis of the two reconstructions, and the

sensitivities of the two reconstructions for predicting surgical outcomes were compared. In the cases studied here, the number of iterations performed during OSEM reconstruction had no statistically significant impact on the sensitivity and specificity of  $^{18}\text{F}$ -FDG PET for predicting surgical candidacy, or its sensitivity for predicting surgical outcome. The nuclear medicine physicians' interpretations of the PET studies were essentially unchanged by the different reconstructions, illustrated by the consistency with which they interpreted the images between the two reconstructions studied. Therefore using physician preference to determine reconstruction parameters seems justified and acceptable in this case. These results should be tempered by the limited statistical power of our data.

The hypometabolic regions identified by nuclear medicine physicians tended to be more global decreases in FDG uptake in the temporal lobe (**Figure 1**). Smaller lesions may not have been identified in either reconstruction, as they may have remained too blurred in the original reconstructions, and obscured by noise in the recon-

structions with more iterations. It is possible that reconstructing with a number of iterations between 2 and 5 would be more optimal and would result in a better trade-off between image sharpness and noise variance.

We did not consider partial volume correction methods that aim to increase image sharpness while suppressing noise to improve the identification of small hypometabolic regions on  $^{18}\text{F}$ -FDG-PET or on SPECT studies [5-7]. Such methods are not yet available as clinical tools, whereas changing the number of iterations used in OSEM reconstructions can readily be performed and therefore may have a more immediate impact. Given that our results do not indicate any benefit to using the sharper but noisier images obtained with more iterations, more advanced partial volume correction methods might be needed to identify smaller regions of hypometabolism. However, if physicians rely on identifying a pattern of globally reduced  $^{18}\text{F}$ -FDG uptake, such methods may make little difference in subjective interpretation. If this is the case, one of the more objective methods of detecting small regions of hypometabolism might be required [20, 21].

We have focused on the number of iterations performed during OSEM reconstruction in order to study the tradeoff between bias and variance (resolution and noise in this case), but there are a number of other factors that will influence resolution and noise. The most notable extraneous factors in this study are the two PET cameras that were used, the GE Advance and the Discovery VCT, and the different acquisitions and reconstruction used for each scanner, 2D acquisition with 2D OSEM reconstruction for the Advance and a shorter 3D acquisition with 3D OSEM reconstruction using more subsets (35 versus 28) for the Discovery VCT (**Table 1**). The overall impact of these differences on the images from the two scanners is difficult to determine. The 3D acquisition and reconstruction of the Discovery VCT images should result in better noise properties in the images, but this may be offset by the shorter acquisition time. Likewise, the greater number of subsets used during reconstruction should give sharper images for the same number of iterations, though image sharpness is also likely influenced by the 3D acquisition. We do not attempt to address each of these issues, but instead try and focus only on the impact of iteration number by demonstrat-

ing that excluding the Discovery VCT scans does not significantly alter the results. In addition, the smooth, clinically standard reconstructions from the two scanners are qualitatively closer to each other in their resolution and noise properties than to the corresponding sharper reconstructions (**Figure 1**).

All reconstructions used for PET imaging have parameters that will affect the tradeoff between bias and variance. While these parameters are frequently determined by physician and institutional preference, it is possible that they could have an impact on diagnostic outcomes. Our investigation here indicates that this may not be the case with OSEM reconstructions of  $^{18}\text{F}$ -FDG PET images acquired for the diagnosis of TLE, as we found little difference between the two reconstructions studied. Our results are limited by their statistical power, by extraneous variables such as the two PET cameras used, and in that we only examined two possible numbers of iterations. However, the consistency with which the readers interpreted the images indicates that a substantial number of scans would have to be read to identify any difference between reconstructions. Different reconstruction parameters, such as an intermediate number of iterations between 2 and 5, may have made a greater impact on the interpretation of scans, but the consistency of the interpretations makes this unlikely as well. If changing the number of iterations performed in reconstruction had potential to change interpretations, less consistency would be expected in the data presented here, even if the area under the ROC curves and the sensitivities are nearly equivalent. As such it appears perfectly reasonable to use images that nuclear medicine physicians are most familiar and comfortable with. Nevertheless, such studies could be helpful in validating and optimizing the reconstruction and image processing methods used in different clinical imaging tasks. And in the case of  $^{18}\text{F}$ -FDG PET for the diagnosis of TLE a more rigorous study could be performed with more patients and varying more reconstruction parameters to validate the results presented here.

### Conclusions

In this retrospective blinded analysis, we have investigated the impact of the number of iterations performed during OSEM reconstruction on the interpretation of  $^{18}\text{F}$ -FDG PET scans ac-

quired for the diagnosis of TLE. We found no difference between the reconstructions studied. This implies that the reconstructions used for the subjective clinical interpretation of  $^{18}\text{F}$ -FDG PET scans acquired for TLE can be determined by physician preference. More sophisticated means of partial volume correction may have a more significant impact on the diagnostic interpretation of such scans.

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