^{18}F-FDG PET of Thyroid Nodules with Inconclusive Cytologic Results

TO THE EDITOR: We read with great interest the paper by Lioe-Fee de Geus-Oei et al. (*1*). There is no doubt that the main objective of preoperative evaluation of patients with thyroid nodules is to avoid unnecessary surgery. This will pose no problem for patients with a positive result for cancer on fine-needle aspiration biopsy (*2*). However, fine-needle aspiration biopsy will fail to give either a clearly positive (malignant) or clearly negative (benign) result in an important percentage of patients; the result will instead be inconclusive. For these patients, diagnostic/therapeutic surgery may be indicated as the next step (*3,4*), but for most the final diagnosis will be that of a benign lesion. Therefore, a large number of unnecessary surgical interventions are still being performed around the world, adding to the morbidity and mortality of thyroidectomy.

Lioe-Fee de Geus-Oei et al. (*1*) reported a negative predictive value of 100% for ^{18}F-FDG PET in 44 patients (only 6 with cancer). Recently, our group addressed this problem using ^{99m}Tc-methoxyisobutylisonitrile (MIBI) thyroid scanning (*5*), which is a less expensive and more readily available diagnostic test than ^{18}F-FDG PET.

Our results on 130 consecutive patients who had hypofunctioning thyroid nodules and underwent thyroidectomy (50 patients with proven thyroid cancer) showed that lack of ^{99m}Tc-MIBI uptake in the nodules always ruled out thyroid cancer (negative predictive value of 100%).

Lioe-Fee de Geus-Oei et al. (*1*) concluded that ^{18}F-FDG PET reduces the number of futile hemithyroidectomies and outweighs the costs of unnecessary thyroid surgery, but ^{99m}Tc-MIBI thyroid scans are considerably less expensive than ^{18}F-FDG PET studies. We believe that ^{99m}Tc-MIBI scans should be the first study to be performed in the diagnostic algorithm of patients with thyroid nodules and inconclusive cytologic results to avoid unnecessary thyroid surgeries.

However, because of the higher resolution of PET over conventional γ-cameras, research with ^{18}F-FDG PET should be undertaken on patients with small-size incidentalomas to determine if the diagnostic test can help in the diagnostic algorithm of those patients.

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REPLY: We thank Martínez-Duncker and Hurtado-López for their comments about our paper on ^{18}F-FDG PET in thyroid nodules with inconclusive cytologic results (*1*). We agree with them that several other radiopharmaceuticals besides ^{18}F-FDG PET can be considered for evaluation of solitary thyroid nodules. They refer to their recent paper on the use of ^{99m}Tc-MIBI for this purpose (*2*). Like ^{18}F-FDG PET, ^{99m}Tc-methoxyisobutylisonitrile (MIBI) was positive in all patients with thyroid cancer (*1,2*). For ^{18}F-FDG PET, this is in line with data in the literature (*3,4*). However, several studies in the literature do report false-negative ^{99m}Tc-MIBI findings in thyroid cancer (*5,6*).

Furthermore, their study (*2*) was designed differently from ours (*1*). First, 78 of 130 patients (60%) underwent diagnostic fine-needle aspiration biopsy (FNAB). These patients do not require any additional imaging—neither ^{18}F-FDG PET nor ^{99m}Tc-MIBI. This type of group was not included in our study. The remaining 52 patients (40%) had inconclusive FNAB results (*2*). This is a relatively large percentage of patients, because inconclusive aspirates typically are reported in up to 20% of cases (*7,8*). The number of patients in the inconclusive-FNAB group who ultimately had thyroid cancer was also relatively high (18/52, or 35%) (*2*), whereas approximately 20% is typical (*9*). In our series, the prevalence of thyroid cancer was 14% (*1*).

When they separately analyzed the results of ^{99m}Tc-MIBI imaging in the 52 patients with inconclusive FNAB results (*2*), 20 of 52 patients (38%) showed negative findings on ^{99m}Tc-MIBI scintigraphy and were diagnosed with benign disease. In our study (*1*), ^{18}F-FDG PET findings were negative in 25 patients (57%), all of whom had benign thyroid nodules.

In conclusion, ^{18}F-FDG seems to be less prone to accumulation in benign thyroid nodules than is ^{99m}Tc-MIBI, thereby allowing better selection of patients with inconclusive FNAB results who require surgical intervention. Furthermore, unlike ^{18}F-FDG PET, the literature contains evidence that false-negative ^{99m}Tc-MIBI findings do occur in thyroid cancer. For these reasons, we do not support the recommendation of Martínez-Duncker and Hurtado-López that ^{99m}Tc-MIBI scans should be the first study performed in the diagnostic algorithm of patients with thyroid nodules and inconclusive cytologic results to avoid unnecessary thyroid surgery. However, a definite conclusion in favor of either ^{18}F-FDG PET or ^{99m}Tc-MIBI can be drawn only in a prospective comparative study with appropriately selected patients, especially in view of the high percentage of inconclusive FNAB results and the high prevalence of thyroid cancer in their series (*2*).

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Adequate Evaluation of Image Registration in Hybrid PET/CT

TO THE EDITOR: In a recent paper (*1*), Brechtel et al. evaluated the impact of different CT acquisition protocols on imaging with an integrated PET/CT scanner. We fully acknowledge that breathing protocols and accurate image registration in PET/CT are highly relevant and require adequate evaluation. Brechtel et al. analyzed the relationship between various breathing protocols and the accuracy of PET/CT image registration. We believe that the applied methodology merits some comments.

The evaluation of image registration in hybrid PET/CT is a delicate matter. When CT images are used for correction of photon attenuation in PET images, the 2 imaging modalities are no longer independent. Artifacts in attenuation-corrected PET images may be caused by differences in the attenuation of low-energy CT photons and high-energy PET photons or by positional differences in attenuating masses during the acquisition of CT and PET images. The latter plays an important role in the diaphragmatic area, where a sharp change in tissue density exists that may have shifted between the PET acquisition and the CT acquisition. The result of this phenomenon is that—in hybrid PET/CT—the CT image *defines* the visual position of the diaphragm on the attenuation-corrected PET image rather than *correlates* with it. This may lead to clinically relevant problems such as apparent displacement of the diaphragm (*2,3*) or even the disappearance of lesions (*4*). As a consequence, correlation of CT images only with uncorrected PET images allows evaluation of image registration in the diaphragmatic area. This applies *a fortiori* when evaluating the position of liver borders and, unabatedly, when performing software image fusion between PET from a hybrid scanner and CT.

Brechtel et al. (*1*) appear to have analyzed PET/CT image registration by determination of liver borders on attenuation-corrected PET images. Consequently, their evaluation suffers from bias because of attenuation correction artifacts, as can be recognized in their results. For example, the authors stated that the average image registration error in the diaphragmatic area was only 6.2 mm (range, 3.2–9.4 mm) when they used an unforced expiration breath-hold protocol in single-phase CT. Such accuracy in intentional positioning of the diaphragm by breathing commands can hardly be expected from living subjects. In our experience, correlation of CT images and uncorrected PET images can reveal much larger errors. This was also recognized in a comparable analysis by Goerres et al., who found differences in diaphragmatic position of −24.7 to 18.9 mm in the vertical direction (*5*). The same reasoning holds when free-breathing CT is used for attenuation correction. Brechtel et al. stated an average error of 9.4 mm (range, 5.7–12.1 mm), whereas Goerres et al. reported differences of −29.1 to 18.9 mm. Therefore, it is likely that the presented results were caused by evaluation of attenuation-corrected PET images containing artifacts.

In another protocol, Brechtel et al. (*1*) presumed that PET images that had been corrected for attenuation using free-breathing CT images were suitable for correlation with breath-hold multiphase CT images, or with a different set of free-breathing multiphase CT images, after software fusion. Evaluation of image registration between such image sets will undoubtedly be affected by attenuation correction artifacts.

In conclusion, the applied methodology and the subsequent results are not straightforward. If the results were indeed derived from analysis of attenuation-corrected PET data, reanalysis using the uncorrected PET data will provide more realistic (and probably less encouraging) results for the accuracy of PET/CT image registration. The effects of the attenuation correction procedure itself are not negligible and can be analyzed separately.

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