image coregistration of the abdomen or the thorax. In the future, however, this technology may play an important role in allowing correction of misregistration due to patient motion or breathing artifacts, which may also arise from integrated SPECT/CT.

Besides anatomic referencing, the added value of CT coregistration is also based on the attenuation correction capabilities of CT. Cardiac imaging poses a particular problem in attenuation correction because of respiratory and cardiac motion in the thorax. Individual CT-based attenuation correction of brain studies using SPECT may also lead to improved image quality and more accurate data evaluation. Furthermore, radionuclide treatment planning using attenuation correction of imaging data and assessment of organ or target volumes derived from simultaneously performed CT may be more accurate and potentially allows safe and effective therapy.

A similar discussion on the need for integrated hybrid scanners has already been raised after the introduction of hybrid PET/CT systems to clinical medicine. As indicated for PET/CT, image fusion is faster, more reliable, and more accurate using an integrated scanner than using separately performed imaging modalities (*4*). In addition to these technical issues, hybrid image acquisition of both modalities in a single clinical visit (1-stop) offers apparent logistic advantages and is obviously more comfortable for the patient. PET/CT scanners represent the imaging modality with the most rapid growth worldwide and play an increasing role in routine patient care, especially in oncologic applications. Yet, there is a lack of evidence that the same holds true for hybrid SPECT/CT systems. CT coregistration, however, has been recognized to result in higher specificity and sensitivity of scintigraphic imaging and to markedly reduce the number of indeterminate findings. The superiority of SPECT/CT over planar scintigrams or SPECT has been clearly demonstrated for imaging skeletal diseases, parathyroid adenomas, and neuroendocrine cancers and for mapping sentinel lymph nodes in various cancers (*1*). Studies demonstrating superiority in other clinical applications are lacking; however, pilot studies encourage the use of SPECT/CT in cardiac and neurologic imaging.

Regarding the growing number of studies demonstrating an added value of hybrid SPECT/CT over separately performed imaging modalities (*1*), it appears likely that this promising technique will gain an important role in clinical routine practice. The broad spectrum of existing SPECT tracers and their widespread availability suggests SPECT/CT as a complementary imaging modality to PET/CT procedures. In summary, we agree with Knoll and colleagues that advanced software-based coregistration procedures do have a legitimate relevance for image fusion, particularly if no hybrid technology is available. However, we believe that hardware-based hybrid acquisition offers several apparent advantages regarding accuracy, reliability, logistics, and comfort for the patient, which cannot be easily outweighed by software-based image fusion approaches.

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Tumor Metabolic Phenotypes on ^{18}F FDG PET

TO THE EDITOR: With great interest, we have read the article by Iagaru et al. (*1*) in the November issue of *The Journal of Nuclear Medicine*. The paper raises several issues on the use of functional imaging in oncology. The study assumed that refractory or relapsed non-Hodgkin lymphoma always maintains the same tumor phenotype as at the initial diagnosis and had been treated correctly before ^{90}Y-ibritumomab therapy. The authors suggested that the bulky disease revealed by pretreatment ^{111}In-ibritumomab imaging showed a less favorable response, although there are no well-cited references to suggest that ^{111}In-ibritumomab accumulation is proportional to tumor load. Furthermore, ^{111}In-ibritumomab imaging is usually for biodistribution only, as the authors have pointed out in the paper. Figure 1 is convincing for complete response because it shows negative PET findings after treatment. However, no quantitative parameters such as standardized uptake value (SUV) tables (*2–4*), glucose sensitivity calculations (*2*), or tumor load assessments (*5*) to characterize tumor phenotype are reported for the initial pretreatment PET. On the basis of our clinical experiences, the tumor load appears visually to be in the low to medium range and the ^{18}F-FDG uptake is moderately intense in Figure 1, suggesting an intermediate grade of lymphoma by the presented pretreatment PET findings. Figure 2 shows an increased extent and magnitude of metabolically active foci on PET after treatment. On the corresponding pretreatment PET scan, tumor load appears to be in the medium range and the degree of uptake appears to be less intense than that in Figure 1. Thus, it would be of interest to readers from both the nuclear medicine/radiology and the oncology disciplines for the authors to clarify and characterize tumor metabolic phenotypes and tumor load assessment on PET. These 2 pieces of additional biologic information from PET have gradually been found to be useful in various cancers, including many types of lymphoma, for systemic and organ-directed or regional therapies (*4–6*).

The lack of response on PET could be due to the following causes: invalid assumption of the tumor phenotype before treatment, lack of chemosensitivity, or possible transformation or grade migration (as in Fig. 2, with more diffuse disease and higher ^{18}F-FDG uptake after treatment). Thus, the suggestion of progression alone in Figure 2C may not be entirely accurate. The additional

metabolic phenotypic and tumor load information from both pretreatment and posttreatment PET is important. The correct biologic interpretation of PET has profound clinical implications. If transformation into an aggressive tumor phenotype occurs, ^{90}Y-anti-CD20 will not be totally effective and a different treatment regimen may be required. The fact that the tumor was refractory to initial chemotherapy may be due to sampling error in the initial biopsy or lack of chemosensitivity, leading to an incorrect assumption that the tumor was pure, low-grade lymphoma. Thus, consideration of metabolic phenotype in the very first and all other prior PET scans is crucial, as is the fact that the patients included were quite heterogeneous because they had been treated with rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), external radiation, or marrow transplantation in the study (*1*). Thus, knowing details of the prior treatment regimens, PET findings, and repeated biopsies on these patients would help one to better understand the results. In these patients, was the diagnosis made through PET-guided biopsy of the area of highest metabolic activity before chemotherapy or ^{90}Y ibritumomab treatment? In addition, only about 60% of the population was followed up by PET, which is well recognized to be more sensitive than conventional anatomic imaging (*7*). What kind of statistical tests were used to draw the conclusions? No *P* values or detailed case-by-case follow-up methods were presented in Table 2.

The role of PET in lymphoma management has been evolving recently because of research on tumor metabolic phenotypes (*2–4*) and tumor metabolic load (*7*). The use of ^{18}F-FDG PET/CT in following lymphoma treatment should no longer be just about remission, recurrence, or progression. It should also include information about tumor metabolic phenotype (*2–4*), chemosensitivity (*8*), and possible transformation (*2,3*). For instance, if a patient with follicular grade I or II lymphoma has an initial maximum SUV of 5; receives treatment with rituximab or with cyclophosphamide, vincristine, and prednisone; and then has a maximum SUV of 25 on follow-up PET, one should suspect transformation into a different cell type, such as diffuse large B-cell lymphoma, or migration into aggressive follicular grade III lymphoma (*2,3*). In this case, tissue diagnosis would be essential, and treatment then might be altered using regimens such as R-CHOP or E-POCH (etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin). Therefore, for Figure 2 (*1*), which was also featured on the cover of the journal, the legend for panel C should entertain the quantitative PET data and the possibility of transformation, not merely the progression alone that appears at first glance. Moreover, if the treatment had been directed toward the wrong phenotype, as suggested by the discrepancy between the initial histologic sampling and the metabolic phenotype given by the whole-body maximum SUV (*2,3*), a good response would not be expected.

In addition, the concept of "bulky disease" may be an old one with regard to treatment implications, and aggressive or toxic treatment regimens may be avoided or modulated by early or mid-therapy PET assessment. For example, a young female patient who shows bulky disease in the chest or pelvis on CT may no longer have met the criterion for full-dose radiation therapy in combination with chemotherapy, because of the subsequent risk of breast cancer or infertility, respectively. Thus, assessment of chemosensitivity after the first or second cycle of chemotherapy will be important (*9*) to determine chemosensitivity and to decide whether extended cycles of chemotherapy or lower-dose radiation is warranted instead of traditional full-dose radiation. Similar considerations should be accorded to young, developing patients to prevent bony deformity due to radiation.

PET should transcend the conventional concept of staging and response or positive and negative findings. The role of ^{18}F-FDG PET/CT is not only diagnosis, staging, or restaging but also characterization of tumor metabolic phenotype and assessment of tumor load, which covers a spectrum between the usual positive and negative metabolic findings. By reducing uncertainties about TNM stage, chemosensitivity, and biologic treatment volumes, PET aims at individualizing therapy so as to maximize symptom-free survival and minimize toxicity and complications. PET/CT is thus performed not only for the sake of current treatment but also for the future of the patient.

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REPLY: We thank Drs. Wong and Khong for their attention to our article (*1*). Although their comments about ^{18}F-FDG PET in lymphoma may be valid, our article was not about ^{18}F-FDG PET but rather about observations from biodistribution imaging before ^{90}Y-ibritumomab administration. The figures included ^{18}F-FDG PET scans only to illustrate the extent of disease before and after treatment. Furthermore:

1. Our paper did not raise issues about functional imaging in oncology but about the significance of the results of imaging with the therapeutic agent or its analog.
2. Tumor transformation, changes in antigen expression, and changes in grade are all possible. The point was that the degree