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.

REFERENCES

1. Iagaru A, Gambhir SS, Goris ML. ^{90}Y-ibritumomab therapy in refractory non-Hodgkin's lymphoma: observations from ^{111}In-ibritumomab pretreatment imaging. *J Nucl Med.* 2008;49:1809–1812.
2. Wong CYO, Thie J, Parling-Lynch KJ, et al. Investigating the existence of quantum metabolic values in non-Hodgkin's lymphoma by F-18 FDG PET. *Mol Imaging Biol.* 2007;9:43–49.
3. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol.* 2005;23:4643–4651.
4. Wong CYO, Thie J, Parling-Lynch KJ, et al. Glucose-normalized standard uptake value (SUV) from F-18 FDG PET in classifying lymphomas. *J Nucl Med.* 2005;46:1659–1663.
5. Wong CYO, Qing F, Savin M, et al. Reduction of metastatic load to liver after intraarterial hepatic Y-90 radioembolization as evaluated by F-18 FDG PET imaging. *J Vasc Interv Radiol.* 2005;16:1101–1106.
6. Khong PL, Pang CB, Liang R, Kwong YL, Au WY. Fluorine-18 fluorodeoxyglucose positron emission tomography in mature T-cell and natural killer cell malignancies. *Ann Hematol.* 2008;87:613–621.
7. Wong CY, Salem R, Raman S, Gates VL, Dworkin HJ. Evaluating ^{90}Y-glass microsphere treatment response of unresectable colorectal liver metastases by [^{18}F]FDG PET: a comparison with CT or MRI. *Eur J Nucl Med Mol Imaging.* 2002;29:815–820.
8. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with ^{18}F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. *Ann Oncol.* 2002;13:1356–1363.
9. Kostakoglu L, Coleman M, Leonard JP, Kuji I, Zoe H, Goldsmith SJ. PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. *J Nucl Med.* 2002;43:1018–1027.

Ching-yee Oliver Wong
William Beaumont Hospital
Royal Oak, Michigan

Pek-lan Khong
University of Hong Kong
Hong Kong Island, Hong Kong

DOI: 10.2967/jnumed.108.061010

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

of visualization with the therapeutic agent or its analog could not be used (by itself) to predict response or, conversely, that lack of visualization is not (as has been claimed) a contraindication to treatment with that agent.

3. The discourse about PET is interesting but does not invalidate the point, which is, in general, that low tumor burdens make imaging findings less likely to be positive but make cure more likely.
4. Perhaps we could have mentioned that macroscopic imaging is a poor predictor of microscopic dosimetry.

The views expressed in the letter may be valid for an article regarding ^{18}F-FDG PET evaluation of response to therapy in non-Hodgkin lymphoma.

REFERENCES

1. Iagaru A, Gambhir SS, Goris ML. ^{90}Y-ibritumomab therapy in refractory non-Hodgkin's lymphoma: observations from ^{111}In-ibritumomab pretreatment imaging. *J Nucl Med.* 2008;49:1809–1812.

Andrei H. Iagaru
Sanjiv Sam Gambhir
Michael L. Goris
Stanford University Medical Center
Stanford, California

DOI: 10.2967/jnumed.109.061945