The Need for Prudence When Using ^{18}F-FDG PET as a Reference Standard for Lymphoma Detection

TO THE EDITOR: With interest we read the article by Kaste et al. (*1*) entitled "Comparison of ^{11}C-Methionine and ^{18}F-FDG PET/CT for Staging and Follow-up of Pediatric Lymphoma" that was recently published in *The Journal of Nuclear Medicine.* Kaste et al. mention ^{18}F-FDG PET to be a valuable tool for staging and response monitoring in lymphoma, with a particularly high sensitivity but limited specificity due to nonmalignant etiologies that may mimic tumor uptake. Therefore, another tracer, ^{11}C-methionine, was investigated and compared with ^{18}F-FDG for both staging and monitoring response to therapy in 21 pediatric patients (19 with Hodgkin lymphoma and 2 with diffuse large B-cell lymphoma). At staging, 3 nodal groups demonstrated discordant metabolic activity, whereas all others had concordant metabolic activity. Eight weeks after treatment, paired ^{18}F-FDG and ^{11}C-methionine PET images were available for 15 patients, of whom 14 (93.3%) had concordant ^{18}F-FDG PET and ^{11}C-methionine PET results. In the remaining patient, metabolic activity was minimally discordant: ^{18}F-FDG PET had normalized, but the ^{11}C-methionine PET study remained slightly positive. This particular patient remained well for more than 3 y from diagnosis without further treatment (i.e., false-positive results on end-of-treatment ^{11}C-methionine PET). During follow-up, 3 patients developed disease relapse and 1 patient developed a secondary diffuse large B-cell lymphoma (importantly, it was not reported how these events related to the end-of-treatment ^{18}F-FDG and ^{11}C-methionine PET results), and no deaths occurred. Kaste et al. concluded ^{11}C-methionine uptake to be elevated in most lymphomatous regions, both at baseline and at the end of treatment.

However, we disagree with Kaste et al.'s (*1*) conclusion. Their claim that increased ^{11}C-MET uptake is observed in most regions involved with lymphoma cannot be determined by a comparison with staging and response assessment ^{18}F-FDG PET scans, due to a suboptimal sensitivity and specificity of this imaging modality. First, ^{18}F-FDG can accumulate in many other types of cancer and in several benign alterations, particularly infections (and treatment-induced inflammatory changes), as already noted by Kaste et al. themselves. Studies have also shown that tumor-associated ^{18}F-FDG uptake is due not only to viable tumor cells but also to a considerable proportion of nonneoplastic cellular elements (such as macrophages) (*2*). Hodgkin lymphoma, in particular, is an extreme example of this phenomenon, since malignant Reed–Sternberg tumor cells occupy only 0.1%–1.0% of the pathologic substrate, with the remainder consisting of inflammatory cells. In addition, after the start of chemotherapy, an increase in the apoptotic and necrotic tumor fraction is followed by an early (4–6 d afterward) influx of inflammatory cells that consume ^{18}F-FDG (*3*). Therefore, ^{18}F-FDG avidity during or after treatment generally does not reflect lymphomatous tissue, as has already been demonstrated by several studies that showed a high rate of biopsied false-positive ^{18}F-FDG–avid residual lesions (*4*). On the other hand, negative ^{18}F-FDG PET results cannot exclude lymphomatous tumor involvement, particularly after treatment. This has been convincingly shown by several studies reporting absence of ^{18}F-FDG–avid bone marrow lesions in patients with lymphoma-positive bone marrow biopsies (*5*). Furthermore, antilymphoma therapy has been reported to reduce glucose uptake by malignant cells as a result of downregulation of glucose membrane transporters or hexokinase activity (*6*), generating false-negative results. Finally and most importantly, because the spatial resolution of current PET systems is only 6–7 mm, involvement by small lymphomatous deposits cannot be excluded (*7*). This hypothesis is supported by findings such as the occurrence of disease relapse in many patients who acquired a ^{18}F-FDG PET–negative status (*8,9*), the lower relapse rate in patients with negative ^{18}F-FDG PET results after chemotherapy plus radiation therapy than after chemotherapy alone (*10*), and the huge proportions of patients with incurable, indolent lymphomas who acquire a negative ^{18}F-FDG PET status after noncurative chemotherapy. However, this last finding by no means implies the absence of residual lymphomatous disease after treatment.

In conclusion, caution is warranted when using staging and (particularly) response-assessment ^{18}F-FDG PET scans as a reference standard for determining the presence or absence of lymphoma deposits throughout the body, since this test suffers from a nonnegligible proportion of false-positive and false-negative results. Because Kaste et al. reported ^{11}C-methionine PET results to closely match ^{18}F-FDG PET results, they should have concluded that the former appears to be as good as, or as bad as, the latter in terms of lymphoma detection, rather than that ^{11}C-methionine uptake is elevated in most lymphomatous regions.

REFERENCES

1. Kaste SC, Snyder SE, Metzger ML, et al. Comparison of ^{11}C-methionine and ^{18}F-FDG PET/CT for staging and follow-up of pediatric lymphoma. *J Nucl Med.* 2017;58:419–424.
2. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med.* 1992;33:1972–1980.
3. Brepoels L, De Saint-Hubert M, Stroobants S, et al. Dose-response relationship in cyclophosphamide-treated B-cell lymphoma xenografts monitored with [^{18}F] FDG PET. *Eur J Nucl Med Mol Imaging.* 2010;37:1688–1695.
4. Adams HJ, Kwee TC. Proportion of false-positive lesions at interim and end-of-treatment FDG-PET in lymphoma as determined by histology: systematic review and meta-analysis. *Eur J Radiol.* 2016;85:1963–1970.
5. Adams HJ, Nievelstein RA, Kwee TC. Opportunities and limitations of bone marrow biopsy and bone marrow FDG-PET in lymphoma. *Blood Rev.* 2015;29:417–425.
6. Banning U, Barthel H, Mauz-Korholz C, Kluge R, Korholz D, Sabri O. Effect of drug-induced cytotoxicity on glucose uptake in Hodgkin's lymphoma cells. *Eur J Haematol.* 2006;77:102–108.
7. Adams HJ, Kwee TC. A negative ^{18}F-FDG-PET scan can never exclude residual disease [letter]. *Nucl Med Commun.* 2016;37:102–103.
8. Adams HJ, Nievelstein RA, Kwee TC. Systematic review and meta-analysis on the prognostic value of complete remission status at FDG-PET in Hodgkin lymphoma after completion of first-line therapy. *Ann Hematol.* 2016;95:1–9.
9. Adams HJ, Nievelstein RA, Kwee TC. Prognostic value of complete remission status at end-of-treatment FDG-PET in R-CHOP-treated diffuse large B-cell lymphoma: systematic review and meta-analysis. *Br J Haematol.* 2015;170:185–191.
10. Hu C, Deng C, Zou W, Zhang G, Wang J. The role of consolidative radiotherapy after a complete response to chemotherapy in the treatment of diffuse large B-cell lymphoma in the rituximab era: results from a systematic review with a meta-analysis. *Acta Haematol.* 2015;134:111–118.

Hugo J.A. Adams*
Thomas C. Kwee
**Deventer Ziekenhuis*
Nico Bolkesteinlaan 75
7416 SE Deventer, The Netherlands
E-mail: h.j.a.adams@gmail.com

Published online Dec. 1, 2016.
DOI: 10.2967/jnumed.116.187096

REPLY: Thank you for allowing us to respond to Drs. Adams and Kwee, who caution readers about the utility of ^{18}F-FDG in this letter, as they have done in many others (*1–6*). We thank them for their comments on our article (*7*) and appreciate their perspective on ^{18}F-FDG, which, though imperfect, remains internationally regarded as the functional imaging agent of choice for patients with lymphoma.

REFERENCES

1. Adams HJ, Kwee TC. Interim PET-CT scan in advanced Hodgkin's lymphoma [letter]. *N Engl J Med.* 2016;375:999.
2. Adams HJ, Kwee TC. A negative ^{18}F-FDG-PET scan can never exclude residual disease [letter]. *Nucl Med Commun.* 2016;37:102–103.
3. Adams HJ, Kwee TC. Prevention of large-scale implementation of unnecessary and expensive predictive tests in Hodgkin's lymphoma [letter]. *Lancet Haematol.* 2017;4:e63–e64.
4. Adams HJA, Kwee TC. Do not abandon the bone marrow biopsy yet in diffuse large B-cell lymphoma [letter]. *J Clin Oncol.* 2015;33:1217–1218.
5. Adams HJA, Kwee TC. In regard to Ceriani et al. [letter]. *Int J Radiat Oncol Biol Phys.* 2017;97:869–870.
6. Adams HJ, Kwee TC. Neither posttreatment PET/CT nor interim PET/CT using Deauville criteria predicts outcome in pediatric Hodgkin lymphoma [letter]. *J Nucl Med.* 2017;58:684–685.
7. Kaste SC, Snyder SE, Metzger ML, et al. Comparison of ^{11}C-methionine and ^{18}F-FDG PET/CT for staging and follow-up of pediatric lymphoma. *J Nucl Med.* 2017;58:419–424.

Sue C. Kaste*
Monika Metzger
Barry L. Shulkin
**St. Jude Children's Research Hospital*
262 Danny Thomas Place, Mail Stop 220
Memphis, Tennessee 38105
E-mail: sue.kaste@stjude.org

Published online Apr. 27, 2017.
DOI: 10.2967/jnumed.117.190652

Linear No-Threshold Hypothesis at the Hospital: When Radioprotection Becomes a Nosocomial Hazard

TO THE EDITOR: The article by Siegel, Pennington, and Sacks, "Subjecting Radiologic Imaging to the Linear No-Threshold Hypothesis: A Non Sequitur of Non-Trivial Proportion," is an important and timely contribution (*1*).

Because of the irrational fear of radiation fostered by the linear no-threshold hypothesis, patients forgo necessary medical examinations and scientific societies issue guidelines that actually may harm patients. Radioprotection at the hospital has become a nosocomial hazard, and the patients who are likely to suffer the most from this radiophobia are children and pregnant women.

Without any clear scientific rationale, aggressive policies of dose reduction are being implemented for pediatric imaging, especially for CT scans (*2*). It has been estimated that, because of excessive dose reduction, 1 in 20 pediatric abdominal CT scans may be nondiagnostic (*3*). Moreover, flagging any amount of dose as dangerous has the predictable effect of spreading radiophobia to the parents: more than 5% of emergency CT scans for children are refused by parents concerned about radiation risk (*4*).

Pregnant women are subjected to imaging protocols that would be deemed unethical if used for any other patient. According to the lung scintigraphy guidelines of the European Association of Nuclear Medicine and Molecular Imaging, pregnant women with suspected embolism should undergo a 2-d lung scan protocol, especially during the first trimester: a perfusion scan on the first day followed by a ventilation scan on the next day only if indicated (*5*). When evaluating this approach on 27 first-trimester pregnant women, Bajc et al. found that the ventilation scan could be avoided in only 14 of them. Among the 5 women who eventually were diagnosed with embolism, the diagnosis was postponed until the following day in 4 (*6*). The fact that official guidelines propose delaying the diagnosis of a life-threatening disease to avoid a fetal dose smaller than that received during a few hours of air travel is an egregious example of how modern radioprotection thinks inside a box. The goal of dose reduction is pursued single-mindedly regardless of scientific evidence, countervailing goals, side effects, and societal costs.

REFERENCES

1. Siegel JA, Pennington CW, Sacks B. Subjecting radiological imaging to the linear no-threshold hypothesis: a non sequitur of non-trivial proportion. *J Nucl Med.* 2017;58:1–6.
2. Cohen MD. Point: should the ALARA concept and Image Gently Campaign be terminated? *J Am Coll Radiol.* 2016;13:1195–1198.
3. Brody AS, Guillerman RP. Don't let radiation scare trump patient care: 10 ways you can harm your patients by fear of radiation-induced cancer from diagnostic imaging. *Thorax.* 2014;69:782–784.
4. Boutis K, Cogollo W, Fischer J, Freedman SB, Ben David G, Thomas KE. Parental knowledge of potential cancer risks from exposure to computed tomography. *Pediatrics.* 2013;132:305–311.
5. Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy: part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. *Eur J Nucl Med Mol Imaging.* 2009;36:1356–1370.
6. Bajc M, Olsson B, Gottsater A, Hindorf C, Jogi J. V/P SPECT as a diagnostic tool for pregnant women with suspected pulmonary embolism. *Eur J Nucl Med Mol Imaging.* 2015;42:1325–1330.

Paolo Zanotti-Fregonara*
Elif Hindie
**Houston Methodist Research Institute*
6670 Bertner St.
Houston, TX 77030
E-mail: pzanottifregonara@houstonmethodist.org

Published online Mar. 2, 2017.
DOI: 10.2967/jnumed.117.190983