Use of Anthropometric Factors in ^{18}F-FDG PET Bone Marrow SUVs

TO THE EDITOR: The findings of Prévost et al. (*1*) on bone marrow standardized uptake value (SUV) as a survival predictor in lung cancer are interesting. The authors substituted a height (H) algorithm for the customarily used body weight (W) to calculate the SUV in the case of bone marrow. This substitution made it possible to find a statistical significance that supports the conclusions of this investigation. However, tumor SUV was calculated with the traditional W.

The literature shows W substitution algorithms falling into the following classes of functional dependencies:

1. Ideal body weight: f(H, sex) (*2*);
2. Lean body mass: f(W, H, sex) (*3*);
3. Geometric body surface area: f(W, H) (*4*);
4. ^{18}F-FDG body surface area: f(W, H) (*5,6*); and
5. ^{18}F-FDG-tissue body surface area: f(W, H optionally, tissue class) (*7*).

For bone marrow, the authors tried an incorrect adaptation of the first algorithm. They selected the algorithm for the female ideal body weight (sometimes called lean body mass, as the authors here preferred) used in a study of females (*2*) instead of using separate expressions for males and females. Criticism (*3*) of the ideal-body-weight approach for correcting SUVs compared with the usual uses of lean body mass or body surface area has led to data reevaluation. The conclusions of Prevost et al. (*1*) may have remained unchanged had other choices for W replacement been made, noting that the ratio of bone marrow to liver (traditionally a ratio of uncorrected activity densities) was found to be a significant survival predictor. However, especially considering the rather noticeable effect of age on liver SUV (using W or presumably also a W substitute) (*8*), use of the liver as a reference may require additional considerations. In contrast to the SUV increasing with age for the liver, it was recently reported that SUV decreases with age for bone marrow (*9*). Could the healthy group be younger than the cancer patients?

Sixteen markers are examined for statistical significance to predict survival. These 16 (and perhaps others investigated and not reported) are somewhat large in number. Thus, the statistical issue of multiple comparisons arises. If addressed, this issue might change opinions about the significance of some markers.

Perhaps not generally appreciated is the possibility of certain tissue classes, in the case of ^{18}F-FDG, for which a traditional SUV (i.e., using W rather than a W substitute) is preferable. Normal bone marrow in females has been reported to be such a class (*2*): Its traditional SUV had no trend with W in this population and so would be the correct approach. Zasadny et al. (*2*) also demonstrated that using the inappropriate ideal body weight in the SUV (i.e., the approach of Prevost et al. (*1*) here for bone marrow) led to an undesirable significant inverse correlation between such a corrected SUV and increased weight.

The above 5 classes are in approximate order of their capabilities to reduce the variability encountered in ^{18}F-FDG traditional SUVs caused by the fat portion of body weight. Fat, differing from patient to patient, is low in ^{18}F-FDG uptake. Classes 4 and 5 are optimal in that they find parameters to improve on the geometric body-surface-area algorithm in order to minimize population variability in ^{18}F-FDG SUVs that result from using these parameters. It is interesting to speculate on the multitude of ^{18}F-FDG investigations to date: whether some missed discovering statistically significant effects because of a commonplace failure to implement improved SUV calculations, which, to their credit, the authors recognized as something to try here for bone marrow.

In general, it is possible to predict when it can be worthwhile to substitute for W in SUV calculations. The coefficient of variation of weights encountered in populations is typically approximately 0.15. The residual influence of this parameter on the traditionally calculated SUV is not linear because of a fractional-power-law effect (*7*), and SUVs, if there were no other influences, would thereby have coefficients of variation of approximately 0.1. In practice, however, traditionally calculated SUVs also have various (mostly physiologic) influencing factors. When these lead to SUV coefficients of variation not greatly exceeding approximately 0.1, it can be worthwhile to replace W (such as by fractional-power-law body-surface-area algorithms) and reduce variability for most tissues.

A good point made by the authors is that additional studies are needed to understand factors associated with ^{18}F-FDG uptake in the bone marrow of cancer patients. If these studies are done, consideration could also be given to more intensive analysis of weight, height, and age influences on various tissue SUVs in both patients with cancer and patients without cancer. Evidence has already been presented and commented on (*2*) that because of the fat content of bone marrow, its traditional SUV does not exhibit the same population behavior with W as that of other tissues. Thus, an appropriate SUV calculation for the bone marrow of patients with cancer and patients without cancer might use different parameters than were used by the authors here or than appear in reports of the above 5 classes. Ideally, dynamic scans might be added to the list of additional studies to shed light on bone marrow quantification issues—a methodology already demonstrated as useful in SUV algorithm development (*6*). Dynamic scans separate out the confounding factor of the blood input function, which is known to be responsible for anthropometric influences on SUVs (*5*). Then, the bone marrow rate constants obtained in this manner have the potential to provide fundamental insights.

REFERENCES

1. Prévost S, Boucher L, Larivée P, Boileau R, Bénard F. Bone marrow hypermetabolism on ^{18}F-FDG PET as a survival prognostic factor in non–small cell lung cancer. *J Nucl Med.* 2006;47:559–565.
2. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology.* 1993;189:847–850.
3. Sugawara Y, Zasadny KR, Neuhoff AW, Wahl RL. Reevaluation of the standardized uptake value for FDG: variations with body weight and methods for correction. *Radiology.* 1999;213:521–525.
4. Kim CK, Gupta NC, Chandramouli B, Alavi A. Standardized uptake values of FDG: body surface area correction is preferable to body weight correction. *J Nucl Med.* 1994;35:164–167.

5. Shiozaki T, Sadato N, Senda M, et al. Noninvasive estimation of FDG input function for quantification of cerebral metabolic rate of glucose: optimization and multicenter evaluation. *J Nucl Med.* 2000;41:1612–1618.
6. Graham MM, Peterson LM, Hayward RM. Comparison of simplified quantitative analyses of FDG uptake. *Nucl Med Biol.* 2000;27:647–655.
7. Thie JA, Hubner KF, Isidoro FP, Smith GT. Reducing variability of uptake by a $(weight)^n$-normalized percent injected dose per gram (WPND) and corresponding SUV [abstract]. *J Nucl Med.* 2005;46(suppl):462P.
8. El-Haddad G, Bozkurt MF, Kumar R, et al. Liver FDG uptake increases with age: implications for detection of focal disease [abstract]. *J Nucl Med.* 2004; 45(suppl):293P.
9. Houseni M, Chamroonat W, El-Haddad G, et al. Effects of age on red marrow metabolism as determined by FDG-PET imaging [abstract]. *J Nucl Med.* 2006; 47(suppl):23P.

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REPLY: We thank Dr. Thie for his interest in our paper (*1*). Because we observed a very strong correlation between bone marrow standardized uptake value (SUV) and actual weight of the patient (as opposed to what was previously reported by Zasadny et al. (*2*) for a population of 28 females), we examined several approaches to calculate SUV, based mainly on lean body mass or body surface area, including those approaches reported by Sugawara et al. (*3*). We chose the method that showed the weakest correlation coefficient between weight and bone marrow SUV in our population—a method that turned out to be the one Dr. Thie accurately refers to as "female ideal body weight" in his letter.

Nevertheless, SUV calculations using either the male ideal body weight or the correct ideal body weight (f(H, sex)) gave similar results in correlation coefficients between bone marrow ^{18}F-FDG uptake and weight (Table 1) and in the prognostic value of bone marrow hypermetabolism. This finding led us to the arguable choice of using a unique formula for the sake of simplicity in day-to-day clinical practice although possibly less accurate from a rigorous scientific point of view.

Table 1 shows that, unlike Houseni et al. (*4*), we did not observe a significant correlation between bone marrow metabolism and patient age. We did observe a slight tendency toward a negative correlation but not reaching statistical significance. Moreover, the ratio of bone marrow activity to liver activity was obtained by comparing bone marrow metabolism to a patient's own liver, not to the livers of a healthy population. The only effect of a rising liver SUV with age would be a decrease in the likelihood of detecting abnormal bone marrow activity in older patients. However, as reported by El-Haddad et al. (*5*), there seemed to be a plateau after the fifth decade of life, an age group that comprises most lung cancer patients.

TABLE 1
Effect of Correlation Parameter on SUV Calculation

Correlation parameter	*r*	*P*
Body mass vs. weight	0.54	1.76×10^{-10}
Body mass vs. weight (female)	0.73	1.05×10^{-7}
Body mass vs. ideal body weight (female)	0.03	0.78
Body mass vs. ideal body weight (male)	0.05	0.59
Body mass vs. ideal body weight	0.09	0.34
Body mass vs. lean body weight	0.54	1.63×10^{-10}
Body mass vs. body surface area	0.19	0.04
Liver vs. age	0.25	0.05
Body mass vs. age	−0.08	0.42

To evaluate the prognostic value of tumor SUV, most authors in the literature up to now have used the standard weight-corrected SUV. We preferred to use this approach as well, considering that this factor was one of the few, along with stage of disease-related variables, that were consistently reported in multivariate analyses in similar studies. Again, the calculation of the SUV with the correct ideal-body-weight approach provided a similar prognostic value.

We agree that multiple comparisons can sometimes be misleading for variables with borderline significance. The impact of the number of variables is more complex in multivariate analyses. To minimize this problem, we adhered to a rule of thumb that recommends that a Cox model should have at least 10 outcomes per variable included (*6*). According to the size of our sample (120 patients, 84 deaths), we would be allowed to include as many as 8 different factors in a single model. With the backward-deletion approach, a maximum of 10 factors was entered simultaneously in a model because variables that were obviously not independent were not all included. For example, among all the stage-related factors, only the most significant factor was included in the model (N factor). Using the forward-selection method, no more than 7 factors were entered simultaneously.

We are confident that the prognostic value of bone marrow hypermetabolism we reported is not just a statistical aberration but reflects some real underlying pathophysiologic processes. We certainly agree that further investigations are of interest to understand the physiology of ^{18}F-FDG uptake in bone marrow. Dynamic acquisitions could shed additional light by decoupling uptake rate from distribution issues, but this was unfortunately not an option in a retrospective analysis of clinical scans.

REFERENCES

1. Prévost S, Boucher L, Larivée P, Boileau R, Bénard F. Bone marrow hypermetabolism on ^{18}F-FDG PET as a survival prognostic factor in non–small cell lung cancer. *J Nucl Med.* 2006;47:559–565.
2. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology.* 1993;189:847–850.
3. Sugawara Y, Zasadny KR, Neuhoff AW, Wahl RL. Reevaluation of the standardized uptake value for FDG: variations with body weight and methods for correction. *Radiology.* 1999;213:521–525.
4. Houseni M, Chamroonat W, El-Haddad G, et al. Effects of age on red marrow metabolism as determined by FDG-PET imaging [abstract]. *J Nucl Med.* 2006; 47(suppl):23P.
5. El-Haddad G, Bozkurt MF, Kumar R, et al. Liver FDG uptake increases with age: implications for detection of focal disease [abstract]. *J Nucl Med.* 2004; 45(suppl)293P.
6. Katz MH. Multivariable analysis: a primer for readers of medical research. *Ann Intern Med.* 2003;138:644–650.

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