^{123}I-MIBG Versus ^{18}F-FDG: Which Is Better, or Which Can Be Eliminated?

TO THE EDITOR: The excellent paper by Dr. Sharp and colleagues compared the diagnostic utility of ^{123}I-metaiodobenzylguanidine (MIBG) with ^{18}F-FDG (*1*). They found that ^{18}F-FDG is superior to ^{123}I-MIBG in stage 1 and 2 neuroblastoma and that ^{123}I-MIBG is superior to ^{18}F-FDG in stage 4 neuroblastoma.

The authors comment that for socioeconomic and radiation exposure reasons, a reduction in the total number of imaging procedures may be desirable in neuroblastoma patients. In this setting, what is important is not necessarily which test is superior. Rather, we want to know if one of these imaging tests can be safely eliminated. The answer is no. Not in early-stage neuroblastoma, and not in late-stage neuroblastoma.

The authors found that in 10 of 10 patients with early disease, ^{18}F-FDG was equivalent or superior to ^{123}I-MIBG. But the 95% confidence interval for this ranges from about 72% to 100%. Thus, it remains statistically possible that ^{18}F-FDG may be inferior to ^{123}I-MIBG in up to 3 of 10 patients. We thus conclude that ^{123}I-MIBG scanning cannot be safely eliminated in early neuroblastoma, although ^{18}F-FDG works particularly well.

In stage 4 disease, ^{123}I-MIBG was superior in 24 of 40 patients, whereas ^{18}F-FDG was better in 8 of 40 patients. Yes, 24 of 40 is different from 8 of 40 ($P < 0.001$), but so what? The more pressing question is whether 8 of 40 is significantly different from 0 of 40. That is, can we safely eliminate ^{18}F-FDG scanning in stage 4 patients? No. Their data indicate that up to 3 of 10 late-stage patients will benefit from ^{18}F-FDG scanning, even though ^{123}I-MIBG performs better.

The authors make a valuable contribution by giving us the relative superiority of each agent during the course of neuroblastoma. However, their data also indicate that ^{123}I-MIBG scanning cannot yet be safely eliminated, nor can ^{18}F-FDG scanning be safely eliminated, in the evaluation of early- or late-stage neuroblastoma.

REFERENCE

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^{123}I-MIBG Scintigraphy and ^{18}F-FDG PET in Neuroblastoma

TO THE EDITOR: We read with great interest a recent article by Sharp et al. (*1*) in which the authors compared the diagnostic utility of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy and ^{18}F-FDG PET in neuroblastoma. In this retrospective study, a total of 113 paired ^{123}I-MIBG and ^{18}F-FDG PET scans of 60 patients were compared.

The authors concluded that ^{18}F-FDG PET was superior to ^{123}I-MIBG scanning in detecting stage 1 and 2 neuroblastoma. Only 10 patients, however, had stage 1 or 2 disease, and of these, 5 patients were undergoing imaging for diagnosis and 5 for follow-up, indicating nonuniform patient groups with different clinical questions. Because the methods of statistical analysis were not described in the article, it was difficult to comprehend the results of the confidence intervals. The calculation of confidence intervals usually requires the assumption that the distribution of the sample population is normal; however, given the small sample size of the studied groups with stage 1 and 2, a normal distribution could not be expected. Thus, the conclusion that ^{18}F-FDG PET is superior for depicting stage 1 and 2 neuroblastoma is doubtful. We would appreciate information about the authors' methods of statistical analysis and their comments on the results for stage 1 and 2 neuroblastoma in regard to the statistical power of the tests.

The authors further concluded that ^{123}I-MIBG scanning was superior to ^{18}F-FDG PET in the evaluation of stage 4 neuroblastoma, "especially during initial chemotherapy, primarily because of the better detection of bone or marrow metastases." In contrast to these findings, Kushner et al. (*2*) reported a study of 51 patients with high-risk neuroblastoma in which ^{18}F-FDG PET was equal or superior to ^{123}I-MIBG scanning for "identifying neuroblastoma in soft tissue and extra-cranial skeletal structures, for revealing small lesions, and for delineating the extent and localizing sites of disease." Sharp et al. (*1*) mentioned and discussed the findings of Kushner et al. briefly and from another angle; for example, that Kushner et al. "primarily addressed appropriate follow-up for patients with progressive disease after primary tumor resection in the absence of cranial vault lesions." The authors, however, did not discuss the discrepancy of the results between the 2 studies. We would appreciate a discussion by the authors in this regard.

The authors described ^{123}I-MIBG as being inferior to ^{18}F-FDG PET in stage 1 and 2 neuroblastoma and superior to ^{18}F-FDG PET in stage 4 neuroblastoma, based on the numbers of scans and patients for which either of the 2 modalities detected more lesions. The authors, however, did not discuss whether the better performance of either modality resulted in a change in clinical stage or clinical management. We would appreciate information from the authors on this subject.

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REPLY: Dr. Heston emphasizes an important point with which we agree. As stated in our conclusions (*1*), any generalized statements regarding the use of ^{123}I-metaiodobenzylguanidine (MIBG) and ^{18}F-FDG in neuroblastoma will have clinically significant exceptions. It was not our intention to imply that either scan can be safely eliminated from the imaging evaluation of neuroblastoma. However, as most neuroblastoma patients are primarily diagnosed and followed with ^{123}I-MIBG, the question is not whether scans can be safely eliminated; rather, the question is when addition or substitution of an ^{18}F-FDG scan can give important information. ^{18}F-FDG may be the preferred agent for most follow-up scans in patients with stage 1 or 2 disease when the tumor is better demonstrated with ^{18}F-FDG at diagnosis and bone marrow involvement is highly unlikely. ^{123}I-MIBG is likely to be the preferred agent for most follow-up scans in stage 4 patients with ^{123}I-MIBG–avid disease. It is probably unnecessary for all neuroblastoma patients to undergo both functional imaging studies at all time points during their disease course, as long as it is recognized that addition or substitution of the second study will be beneficial in some clinical situations, in particular when there are discrepancies between anatomic evaluations and the functional imaging study, and at important decision points when completeness of the imaging evaluation may be particularly important.

Regarding the confidence intervals given by Dr. Heston, the 95% confidence interval for a proportion uses the estimated proportion from the study sample and allows for sampling error. If a study is conducted and an event occurs 0 times in n subjects, we need to examine the "upper limit" of the 95% confidence interval. In our study, the 95% "upper limit" for observing zero events would be 30.85%, which means that it is statistically possible that ^{123}I-MIBG was superior to ^{18}F-FDG in up to 3 of 10 patients.

Regarding the statistical questions raised by Drs. Nguyen and Osman, the methods of statistical analysis were not described in the article because no formal statistical testing was done. The estimated proportions presented in the paper were based on the total number of scans that were examined at each disease stage rather than in individual subjects. The proportions were meant to be descriptive in nature, and the confidence intervals were included to allow for sampling error. For calculation of confidence intervals, the simplest method is to approximate the binomial distribution with a normal distribution. This approximation applies well even when the sample size is less than 30, as long as the proportion is not too close to 0 or 1. Results presented were based on the normal approximation. When the confidence intervals are estimated using the Exact and the Wilson score interval, the results are nearly the same.

Our study included 13 scans of 10 patients with stage 1 or 2 disease. We agree with Drs. Nguyen and Osman that larger, multiinstitutional prospective trials may provide further information, as stated in our conclusions.

Drs. Nguyen and Osman also ask whether the better performance of either modality resulted in a change in clinical stage or clinical management. We did not specifically look at this question, but we do know of patients in whom management was altered on the basis of positive findings seen on only one of the studies. A stage 2 patient imaged after tumor resection had a normal ^{123}I-MIBG scan, but was found to have a large amount of ^{18}F-FDG–avid retroperitoneal disease (also seen on CT); the patient had repeat surgery with resection of residual retroperitoneal neuroblastoma. Follow-up imaging of a stage 4 patient showed ^{123}I-MIBG–avid skull lesions not identified on ^{18}F-FDG; the patient received local radiation therapy. Nine ^{18}F-FDG scans showed uptake in neuroblastoma when the corresponding ^{123}I-MIBG scans were negative. Eleven ^{123}I-MIBG scans showed uptake in neuroblastoma when the corresponding ^{18}F-FDG scans were negative. Clinical management could have been impacted in each of these cases.

In contrast to Kushner et al. (*2*), we found that ^{123}I-MIBG was more reliable than ^{18}F-FDG in the detection and follow-up of bone and marrow disease. Possible reasons for the differing results are consistent use of ^{123}I-MIBG in our study, use of cell-stimulating factors in some patients in our study (resulting in intense marrow uptake of ^{18}F-FDG), and inclusion of cranial findings in our study.

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