INVITED COMMENTARY

Adding Structure to Function

When cross-sectional anatomic imaging emerged over two decades ago, Henry N. Wagner, Jr., recognized that the nuclear medicine community should focus on tissue and organ function rather than anatomy (*1*). The value of functional imaging has not only become clear since that time but is now recognized as the future of diagnostic imaging. Structural and functional imaging are also increasingly understood as complementary rather than competing imaging modalities. Over the past decade, manufacturers have considered developing combined CT and PET or SPECT imaging devices. CT, PET, and SPECT are, in fact, closely related imaging devices and share a common origin. In some respects, x-ray CT is the stepchild of transmission computed tomography (*2*), which was first used by Kuhl and Edwards (*2*) with a collimated radionuclide source, as a direct extension of their work in emission computed tomography (*3*). The 2 articles by Beyer et al. (*4*) and Patton et al. (*5*) in this issue of *The Journal of Nuclear Medicine* mark the beginning of a new era in the growing integration of functional and structural imaging into clinical practice.

The work reported by Beyer et al. (*4*) and Patton et al. (*5*) is part of a broad trend toward the fusion of complementary diagnostic imaging modalities. The merging of biologic imaging, embodied in PET, with the rapid and detailed structural imaging provided by x-ray CT may well be among the most fruitful direction of this trend. The impetus to build combined scanners has emerged with the rapid growth of whole-body oncology PET imaging. The diagnosis and staging of malignant neoplasm by FDG PET are technically demanding. A large portion of the body must be imaged quickly, small deposits of neoplasm detected accurately, and the PET findings interpreted in the context of the patient's corresponding normal and abnormal anatomy. At present, 2 practical, related considerations drive the merging of PET and CT: the need for a rapid, noise-free transmission scan for attenuation correction of the PET emission data and a need for an anatomic framework for the physiologic information provided by PET.

Without attenuation correction, PET images are spatially distorted, and there is marked radial nonuniformity in the depiction of tracer activity (*6*). The application of a 511-keV transmission map to the reconstruction of the PET emission data yields a spatially and quantitatively accurate depiction of the tracer activity. High-quality, attenuation-corrected FDG PET images contain recognizable anatomic structure; yet, debate continues over whether the use of current technology for attenuation correction is truly advantageous over noncorrected PET for clinical oncology diagnosis (*7*). At a practical level, the additional scanner time needed for the transmission scan using current technology can nearly double total PET study time, imposing increased likelihood of patient-movement artifacts and decreased patient throughput, ultimately decreasing the diagnostic accuracy and increasing the cost of PET imaging, respectively. Because the typical transmission scan is very count poor, substantial statistical noise is propagated into the reconstructed attenuation-corrected emission scan, resulting in apparent decreases in lesion contrast and small-lesion detectability (*8–10*). Anecdotal evidence of the value of attenuation correction in FDG PET imaging is widespread, but generalized evidence that more accurate results are obtained with attenuation-correction versus emission-only images is lacking. Centers continue to use noncorrected images for whole-body oncology FDG PET, and when attenuation correction is performed, noncorrected images are often consulted, in addition to corrected images, before the final interpretation is rendered (*7*).

In response to the above needs, rapid advances have been made in the past 5 years in the attenuation-correction hardware and software. The capacity to perform transmission scans after tracer injection has made routine whole-body (cf. torso) attenuation-corrected FDG PET feasible in clinical practice. High-activity single sources have been developed to improve counting statistics of the transmission scan (*11*), and segmentation methods allow elimination of the noise propagation, although with risks of segmentation error (*12*). However, these developments have not fully solved the limitations of attenuation correction. Ideally, attenuation correction would add very little to the scanner time imposed by the emission-image acquisitions, and there would be essentially no noise and no possible segmentation errors propagated into the final attenuation-corrected emission images. Kinahan et al. (*13*) have shown that it is possible to use CT imaging data to construct an attenuation map scaled to 511 keV. This essentially noise-free attenuation map, in which there is no need for segmentation assumptions, can then be used for attenuation correction of the PET imaging data. The time imposition for this approach is limited only by the speed of contemporary spiral CT technology, which is measured in seconds for each PET emission bed position. Thus, PET/CT presents a plausible solution to the need for a very rapid, low-noise, and quantitatively correct method of PET attenuation correction. Furthermore,

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For correspondence or reprints contact: Paul D. Shreve, Division of Nuclear Medicine, University Hospital, University of Michigan, B1G 505-UH-Box 2008, 1500 E. Medical Center Dr., Ann Arbor, MI 48109.

anatomic information in the CT images can be incorporated into the image reconstruction process, potentially enhancing the speed and accuracy of numerical reconstruction algorithms and scatter and partial volume corrections (*14,15*).

Many technical hurdles still remain. The rapid acquisition capabilities of contemporary spiral CT can effectively freeze respiratory motion in the chest and upper abdomen, resulting in misregistration of the transmission scan with the PET emission data, for which respiratory motion is averaged. Intravenous contrast when given as a bolus can result in intravascular attenuation during the CT acquisition, which inadvertently scales to bone rather than soft tissue, creating attenuation-correction errors. These are solvable problems, however. CT for radiation therapy planning is conducted without the person holding their breath and with slowed table motion to average respiratory movement. Currently, it is not uncommon to perform spiral CT sequentially during 2 or 3 phases of intravenous contrast enhancement in some body applications (e.g., precontrast, arterial phase, venous phase). Thus, a CT of the whole torso for PET attenuation correction (with lowered beam current to reduce dosimetry) could be followed by a rapid intravenous contrast–enhanced CT as needed. In any case, the need for the aggressive use of intravenous contrast in CT for oncology diagnosis may need reconsideration in light of the superior ability of FDG PET to detect malignant neoplasm; the FDG is the "smart" contrast. Finally, the ability of the CT-derived transmission scan to freeze respiratory motion may be useful in the attenuation correction of respiratory gated PET emission data (*16*), a strategy used to improve small-lesion detection in the lung bases and upper abdomen.

The second, and in some ways, more compelling driving force for the merger of PET and structural imaging is the need for an anatomic framework for the physiologic information provided by PET. For cancer diagnosis and staging, FDG PET scans are nearly always performed in response to a finding, or lack of findings, on CT. For larger neoplasms (i.e., >1.5–2 cm), anatomic correlation often can be performed by visual reference within the attenuation-corrected PET images and to the CT images. For example, fused PET and CT images added little to diagnostic accuracy in an early study of mediastinal lymph node staging in lung cancer (*17*). As the size of detected neoplasm gets smaller, however, "eyeball" correlation becomes increasingly inadequate, particularly in the neck, abdomen, and pelvis. Data showing that fused PET and CT images improve accuracy compared with separate interpretation of the FDG PET and CT images in these more challenging situations have yet to be published, because the hardware and software for true image fusion is only now becoming available.

Clinical PET imaging in oncology is already moving beyond cases requiring straightforward interpretive skills, such as pulmonary nodules, enlarged mediastinal lymph nodes, and well-circumscribed masses. Increasingly, practitioners are asked to identify and locate deposits of malignant neoplasm that are not detected on CT scans, evaluate the precise location of recurrent neoplasm for biopsy, and provide accurate delineation of true neoplasm extent for radiation therapy planning. Experience at the University of Michigan is that true image fusion would be highly valuable and possibly indispensable for interpretation or subsequent procedural applications in up to 20% of our current whole-body oncology clinical FDG PET studies. Because of the perceived need for fused PET and CT images for interpretation and the demand for fused PET and CT images from practitioners in radiation oncology, surgery, and interventional radiology, image-fusion algorithms are now being applied that are capable of warped geometric deformations (*18*), although for the abdomen and pelvis, the algorithms are expected to be inaccurate at times. It is becoming clear that the use of the powerful metabolic images provided by PET will require, at times, an anatomic scaffolding for interpretation, procedural planning, and communication of findings to practitioners.

There are arguments against the merger of PET and CT in the form of a single scanner. If PET is expensive, would not the addition of CT make it more so? First, PET is not expensive. Even high-end PET scanners have been, and remain, priced in the mid to upper range of MRI scanners. Second, PET scanners already have transmission CT capability built in them in the form of the transmission scan sources. Substituting a widely used CT tube and detector, for which development and manufacturing costs are distributed over many units, for the transmission scan sources and related mechanicals results in a modest increase in cost for a new generation PET scanner. If the incorporation of CT reduces overall scan time to roughly 30 min for imaging the torso, patient throughput becomes comparable with MRI and effectively reduces the cost of PET imaging. Incorporation of CT into the next generation of PET should be seen, then, as an upgrade in the transmission scan capability over that of the current generation PET scanners.

The same concept applies to SPECT and coincidence-SPECT devices. The work by Patton et al. (*5*) demonstrates how a low-cost CT tube and detector system incorporated into a dual-head SPECT gamma camera can provide relatively rapid low-noise transmission scans and provide useful anatomic information for interpretation of the functional images. This innovative approach not only could solve some of the current limitations of sealed source transmission devices applied to attenuation correction of cardiac SPECT but may aid interpretation of gallium-, antibody-, and peptide-based single photon tracers. The incremental cost of the tube and detectors used in their system over the cost of a sealed source transmission device for SPECT attenuation correction is modest considering the potential advantages for both single photon SPECT and coincidence FDG images. Although the structural images are not of diagnostic quality, they may well suffice for many of the SPECT

and coincidence applications; regardless, diagnostic CT images can be aligned and fused with the structural images as needed.

Methods for fusion of PET and structural images of the brain performed on separate scanners are well developed. The application of such rigid realignment fusion methods to nonrigid body structures (*19*) has advanced to image fusion with warped geometric deformation capability (*18*). For the chest and neck, this may be useful for interpretive applications; however, in the abdomen and pelvis, movement of bowel and bowel gas between the structural and PET imaging sessions could result in interpretive difficulties. To take full advantage of image fusion, especially if the structural imaging is used for attenuation correction and related anatomic information incorporated into PET image reconstruction algorithms, the structural and PET imaging need to be temporally and geographically as close as possible.

There is general consensus that the PET capability of a PET/CT scanner should be high end. Debate remains, however, over the required structural imaging capability that is appropriate for a combined scanner. Even low-end contemporary CT scanners produce image quality that is suitable for most diagnostic applications. High-end CT, for the most part, translates into very fast scan acquisition in an attempt to squeeze some additional information out of the intravenous contrast–enhanced studies. For oncology diagnosis, however, FDG PET renders the small incremental advantages of such high-intensity contrast exams largely obsolete. The older spiral CT used in the prototype PET–CT scanner developed by Beyer et al. (*4*) may have adequate image quality. The CT images of these older scanners may not be entirely satisfactory to some diagnostic radiologists, but newer generation CT, even the lower priced systems, will generate better CT images at acquisition rates entirely suitable for a combined scanner. In any case, as the power of PET imaging becomes more appreciated, the need for exquisite structural image quality may diminish somewhat in the minds of diagnostic radiologists and referring physicians.

The trade-offs of cost versus performance will be addressed over the next 5 years, with increasing experience in clinical practice. Combined PET/CT scanners with contemporary diagnostic CT capability are currently under development. The approach used by Patton et al. (*5*) is already a marketable product and is being disseminated into the clinical work environment. These differing approaches of adding structure to function will be shaped by clinical experience, even as clinical practice is being shaped by these technologies.

Combined PET/CT scanners may be a catalyzing development for clinical PET. The combination has the potential to solve some current limitations on whole-body oncology imaging, with substantial shortening of imaging times and possible improved overall PET image quality. Grafting the metabolic information of PET onto the familiar anatomic depiction of the body may speed acceptance and use of PET by referring physicians. Most important, the integration of structural and biologic imaging will provide a bridge for the fundamental shift in medicine from viewing disease as an overall anatomic process to a fundamentally molecular process. If "form and function form the future" (*20*), the functional capability of PET will play a major role.

Paul D. Shreve
University of Michigan
Ann Arbor, Michigan

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