EDITORIAL

To AC or Not to AC: That Is the Question

Whether 'tis nobler in the mind to suffer
The slings and arrows of outrageous fortune,
Or to take arms against a sea of troubles,
And by opposing, end them.

William Shakespeare
Hamlet, Prince of Denmark (3.1.57–60)

It is unlikely that even the great William Shakespeare could have been prescient enough to consider the question of attenuation correction (AC) in oncologic PET while writing his timeless tragedy *Hamlet, Prince of Denmark*. My observations of discussions concerning AC in the nuclear medicine community suggest a Shakespearean drama, however. Strong advocates of AC insist that it is equal to the light of the sun, whereas naysayers suggest that it is a waste of precious scanner time and resources with little practical gain. In this issue of *The Journal of Nuclear Medicine* Bleckmann et al. (*1*) present some practical clinical data from 28 women with breast cancer to address this vexing question.

PET of cancer using ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is of undeniable clinical value in many patients. The movement by Medicare and private carriers to pay for clinical PET applications in common tumors supports this observation, as does the proliferation of clinical articles that show the improved accuracy of imaging tumor metabolism and anatomy with PET compared with traditional anatomic methods such as CT (*2*). There appears to be significant growth in the number of clinical PET studies performed at most medical centers on the basis of these factors. Consequently, scanner time is increasingly a precious and limited resource, and efforts to speed and optimize clinical PET are in order.

Most clinical articles that show PET to be superior to CT have used PET with AC performed (*2*). This is not surprising because clinical PET of cancer evolved from quantitative research applications in the brain and other organ systems. In research applications, PET has the attributes of a metabolic imaging technique that is quite accurate both quantitatively and anatomically for lesions of sufficient size (*3*). Attenuation effects are greater in PET than in SPECT, especially for deeper structures, because both emitted photons are potentially attenuated, not just the single photon. Deep structures in oncologic PET may have 50-fold or more count reductions (versus if nonattenuating material were present) caused by attenuation and scatter events, a greater reduction than for SPECT (*4*). To achieve quantitative radioactivity counts with anatomic precision, a variety of AC algorithms have been used. The most common, however, has been by direct measurement of 511-keV photon attenuation of the body. It should be noted, however, that not all AC methods are identical. As is well reviewed elsewhere, the attenuation of the paired 511-keV photons emitted after positron annihilation allows for a potentially quantitatively accurate correction of the absorption of photons by the body (*2*). This sounds all well and good, but what are the pros and cons of AC in a clinical setting?

The pros of AC methods include the following:

1. Radioactivity concentrations in the body and tumors are quite accurately measured—and these values, such as standardized uptake value or standardized uptake value corrected for lean body mass, can be useful in helping to characterize lesions as malignant or benign.
2. Lesion size, shape and location are generally not distorted.
3. The intensity of lesions deep in the body appear to be comparable with those located superficially.
4. This more comparable apparent tracer uptake between deep and superficial structures likely makes image interpretation easier for inexperienced readers.
5. The transmission maps can be reconstructed as images that can be useful in image fusion and tumor localization.
6. Many clinical studies that have been performed with AC show that PET is superior to CT in many diseases (*3–6*).

However, the cons regarding AC are many:

1. From a practical standpoint, the attenuation scans add both considerable time and slightly more radiation exposure to the patient study.
2. The directly measured ^{68}Ge transmission scans are intrinsically noisy. This is a particular problem in obese patients or if the emission sources are aged and have reduced photon flux versus their youth. In addition, this noise degrades image quality.
3. Patient motion between attenuation measurements and emission data (misregistration) can lead to serious image artifacts.
4. Methods to perform AC after tracer injection can lead to quantitative artifacts if not corrected.
5. Faster AC algorithms based on segmentation can produce artifacts if segmentation is inaccurate.
6. Not all AC methods are the same.
7. The time spent performing transmission images to allow for AC

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potentially could have been spent acquiring emission data and thus improving signal-to-noise ratio —or have allowed another patient to be imaged (*7–9*).

Non-AC images of the body have considerable distortion present in lesion shape because of nonuniform attenuation. Zasadny et al. (*5*) reported an apparent 30% lengthening of clinical lung cancers in the thorax in the anteroposterior dimension for non-AC images versus AC images or CT truth. Similarly, they reported increased apparent tracer activity at the skin surface caused by limited superficial photon attenuation. However, for detection of simulated tumor lesions in realistic phantom studies, Raylman et al. (*10*) recently reported comparable results between AC and non-AC images in terms of lesion detectability, using both two- or three-dimensional acquisitions. Bengel et al. (*11*) have reported that lesion distortion occurs in the non-AC images, similar to that described by Zasadny et al., but that the apparent target-to-background ratios were actually higher in the non-AC images than those with AC regardless of lesion localization. Although this latter finding could be caused, in part, by the method of AC or analysis used, the data in phantom studies indicate that no serious loss in lesion detection capability is seen on non-AC images in studies with two different types of dedicated PET systems. Indeed, there may be improved results, possibly because of loss of noise by eliminating the transmission data.

Although phantom studies are of interest and suggest that lesion size or shape and actual activity are not accurately measured on non-AC images, does it really matter in clinical practice? If lesion detection is the issue, what are the results in clinical practice for lesion detection? Is it still appropriate for AC to be the standard in routine clinical practice, especially if it significantly lengthens the study? Bleckmann et al. (*1*) suggest that the answer, at least for metastatic breast cancer detection, is no. In their brief report, only 5 of 189 lesions were disparately characterized between AC and non-AC PET images in metastatic breast cancer. These 5 small lesions were detected with non-AC but not with AC imaging. One could ask how final truth was determined in these patients and why the authors concluded that AC was less accurate (the results seem to be quite comparable between AC and non-AC), but it seems that AC added a lot of time and very little benefit in this study and even impaired detection of lesions <1 cm in diameter in a few instances.

These practical results are in keeping with at least three other clinical series comparing AC and non-AC images in tumor PET for lesion detection. Yasuda et al. (*12*) showed that 104 of 106 lesions (98.1%) seen on AC PET were detected on non-AC PET. Their detection problems occurred when a large primary lesion in the breast was near internal mammary nodes and obscured visualization, as well as in a case of para-aortic lymph nodes that were hard to detect, presumably because of the attenuation of signal from deep in the body. Kotzerke et al. (*13*) recently reported in a study of 51 lymphoma patients that the AC and non-AC imaging performed quite comparably, with minor discrepancies not in lesion detection but in lesion localization. They believe that lesion contrast was largely comparable between AC and non-AC lesions, and the more important issue stems from differences in reader experience than whether AC was done. These results are consistent with those of Bengel et al. (*11*), who showed in a series of 34 patients that the apparent tumor-to-background ratios in patients were higher for non-AC than for AC images (5/1 versus 3.1/1).

One has to be very cautious in interpreting target-to-background data in non-AC PET, however. Wahl et al. (*14*) have shown that in lung cancer, the target-to-background (i.e., lesion-to-blood) ratios are significantly higher for non-AC images than for AC images. This increase is, in large measure, caused by the "loss" of mediastinal blood-pool activity due to uncorrected attenuation effects, which reduces apparent signal from the blood. Thus, algorithms to characterize lesions as malignant or benign on the basis of contrast versus background must be revisited if non-AC images are used, to avoid false-positive results. These data from multiple studies suggest that AC (at least as performed in these clinical trials in these patients) is not adding a great deal to lesion detection capabilities over non-AC imaging. It should also be noted that several important clinical studies showing the accuracy of PET were conducted without AC algorithms being applied (*15,16*). These data suggest that performing 30 min or more of transmission imaging plus an hour of emission imaging may not be well justified—at least with the AC methods used in these studies.

Although these clinical data make a reasonable case that non-AC images are quite acceptable, it should be realized that non-AC images have some problems. The accuracy of non-AC images versus AC images has not been rigorously compared in all clinical settings. As an example, our own clinical experience has shown that some superficial lesions, such as in the breast and skin, can be inapparent on non-AC images because of skin artifacts of increased apparent tracer uptake. Also, for new interpreters of PET images, reading the non-AC images may be challenging, because deep structures have much less apparent activity than superficial ones, and these can fail to be detected (because they appear much less intense). However, familiarity with these image artifacts is essential. Varying the contrast level on the computer screen is also essential because it is hard to capture, in a single image, a suitable appearance for both deep and superficial structures. In addition, the transmission images can be helpful for tumor localization. In a study in which Wahl et al. (*17*) reported PET to be more accurate than CT for mediastinal tumor localization, the anatomic imaging data from the reconstructed transmission images were helpful for more precisely locating lymph nodes, i.e., mediastinal or hilar. Meyer et al. (*6*)

also found transmission images to be of considerable value to image fusion, which first allows fusion of transmission PET images to CT and then realignment of emission data with the transmission data.

Experience with coincidence systems without AC has indicated difficulties in detection of lesions, especially in the abdomen (*18*). Examination of these images has shown a marked apparent deficit in counts from deep in the body, and some manufacturers have now implemented AC regimens. It is not certain how results from dedicated PET systems operating in two dimensions and three dimensions with filtered backprojection or iterative methods will translate to these hybrid systems. However, one would expect, on the basis of the dedicated PET data, the advantages of implementing AC to be relatively modest, because noise will be added to already count-poor images. Empirical evaluation of the methods in patients and phantoms will still be necessary before firm conclusions can be reached regarding the importance of AC in dual-head coincidence imaging.

It is likely that if AC images could be obtained rapidly and accurately the benefits they add to whole-body PET would be considered sufficient to offset the increased acquisition time. Fortunately, several methods are in development or have already been implemented to allow more rapid, accurate and less noisy AC to be performed. Although the earliest PET studies had transmission images performed before the injection of tracer, the uptake phase and emission imaging, such algorithms are considerably time consuming. Methods to acquire transmission images after tracer injection are now more commonly applied (*19*). Such methods save time but may have disadvantages, with potential artifacts if FDG activity is changing in location or intensity during the acquisition of the AC image. However, a promising development is the use of "segmentation" algorithms both to reduce the noise from the AC images and to reduce the time of acquisition—by computer-aided classification of tissue density into a few discrete categories based on the transmission scan data and prior knowledge of expected tissue attenuation coefficients. Indeed, algorithms with only a few minutes of acquisition per level have been developed using ^{68}Ge sources (*9,19*). With such mathematic segmentation algorithms, the correction is only as good as the segmentation, and artifacts can occur. More rapid collection of data using either higher photon flux single sources or x-ray sources is also promising for the future (*20*). Indeed, combined CT and PET devices soon may be able to provide rapid solutions to the AC problem, as well as aid in image fusion (*21*).

From the available data, non-AC dedicated PET images appear to be comparable with dedicated AC PET images for lesion detection in many clinical oncologic imaging settings. It should be noted that this conclusion applies only to the scanner and AC algorithm (and specific radioactive source or activity) used, because they are not all created equal. Whether non-AC images will suffice for lesion therapy monitoring, lesion characterization, image fusion and lesion location remain somewhat an open issue. If throughput is a problem with current PET technologies, it seems rational that elimination of AC—particularly if such acquisitions are time consuming, perhaps even lengthening the time of emission acquisition—may be reasonable for certain whole-body screening applications. The current clinical approach at the University of Michigan Medical Center has been to move toward shorter, postinjection AC acquisitions using segmented ordered-subset expectation maximum approaches but to also reconstruct all non-AC images and examine both AC and non-AC image sets before rendering final image interpretation. In this way, potential artifacts of AC and non-AC can be recognized. It is my opinion that a very rapid, low-noise and quantitatively correct AC method that allows for precise quantitation and anatomic fidelity would, if available, be used on all PET studies. Indeed, approaches attempting to refine such methods are under way at several centers. For example, there are investigations of statistical methods of transmission image reconstruction that yield less noisy AC factors and avoid the artifacts caused by conventional segmentation methods as well as x-ray or CT-based methods.

Although there will be progress in AC algorithms and ultimately all oncologic PET likely will be done with rapid and accurate AC, the literature to date indicates that for many clinical applications both the AC and non-AC PET images are valuable tools in PET of cancer. The benefits of AC may not outweigh the costs (in time and noise) in some clinical applications. Or, as Shakespeare wrote, "Out, damned spot! out, I say!" (*Macbeth* 5.1.32) to AC—at least sometimes.

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REFERENCES

1. Bleckmann C, Dose J, Bohuslavizki KH, et al. Effect of attenuation correction on lesion detectability in FDG PET of breast cancer. *J Nucl Med.* 1999;40:2021–2024.
2. Wahl RL. Progress in nuclear medicine imaging of cancers. *Prim Care.* 1998;25:341–360.
3. Huang SC, Hoffman EJ, Phelps ME, Kuhl DE. Quantitation in positron emission computed tomography: 2. Effects of inaccurate attenuation correction. *J Comput Assist Tomogr.* 1979;3:804–814.
4. Ostertag H, Kubler WK, Doll J, Lorenz WJ. Measured attenuation correction methods. *Eur J Nucl Med.* 1989;15:722–726.
5. Zasadny KR, Kison PV, Quint LE, Wahl RL. Untreated lung cancer: quantification of systematic distortion of tumor size and shape on non-attenuation-corrected 2-[fluorine-18]fluoro-2-deoxy-D-glucose PET scans. *Radiology* 1996;201:873–876.
6. Meyer CR, Boes JL, Kim B, et al. Demonstration of accuracy and clinical versatility of mutual information for automatic multimodality image fusion using affine and thin-plate spline warped geometric deformations. *Med Image Analysis.* 1997;1:195–206.
7. Huang SC, Carson RE, Phelps ME, Hoffman EJ, Schelbert HR, Kuhl DE. A boundary method for attenuation correction in positron computed tomography. *J Nucl Med.* 1981;22:627–637.
8. Xu EZ, Mullani NA, Gould KL, Anderson WL. A segmented attenuation correction for PET. *J Nucl Med.* 1991;32:161–165.
9. Meikle SR, Dahlbom M, Cherry SR. Attenuation correction using count-limited transmission data in

positron emission tomography. *J Nucl Med.* 1993; 34:143–150.
10. Raylman RR, Kison PV, Wahl RL. Capabilities of two- and three-dimensional FDG-PET for detecting small lesions and lymph nodes in the upper torso: a dynamic phantom study. *Eur J Nucl Med.* 1999;26: 39–45.
11. Bengel FM, Ziegler SI, Avril N. Whole-body positron emission tomography in clinical oncology: comparison between attenuation corrected and uncorrected images. *Eur J Nucl Med.* 1997;24:1091–1098.
12. Yasuda S, Ide M, Takagi S. Cancer detection with whole-body FDG PET images without attenuation correction. *Jpn J Nucl Med.* 1996;33:367–373.
13. Kotzerke J, Guhlmann A, Moog F. Role of attenuation correction for fluorine-18 fluorodeoxyglucose positron emission tomography in the primary staging of malignant lymphoma. *Eur J Nucl Med.* 1999;26:31–38.
14. Wahl RL, Neuhoff A, Kison P, Zasadny K. Qualitative criteria for determining if a solitary pulmonary nodule is malignant or benign on FDG PET: impact of not accounting correctly for soft tissue attenuation [abstract]. *J Nucl Med.* 1999;39(suppl):44P.
15. Bury T, Dowlati A, Paulus P, et al. Whole-body ^{18}FDG positron emission tomography in the staging of non-small cell lung cancer. *Eur Respir J.* 1997;10: 2529–2534.
16. Rigo P, Paulus P, Kaschten BJ, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med.* 1996;23:1641–1674.
17. Wahl RL, Quint LE, Greenbough RL, Meyer CR, White RI, Orringer MB. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. *Radiology.* 1994;191:371–377.
18. Shreve PD, Steventon RS, Deters EC, Kison PV, Gross MD, Wahl RL. Oncologic diagnosis with 2-[fluorine-18]fluoro-2-deoxy-D-glucose imaging: dual-head coincidence gamma camera versus positron emission tomographic scanner. *Radiology.* 1998;207:431–437.
19. Meikle SR, Bailey DL, Hooper PK, et al. Simultaneous emission and transmission measurements for attenuation correction in whole-body PET. *J Nucl Med.* 1995;36:1680–1688.
20. Karp JS, Muehllehner G, Qu H, Yan XH. Singles transmission in volume-imaging PET with a ^{137}Cs source. *Phys Med Biol.* 1995;40:929–944.
21. Kinahan PE, Townsend DW, Beyer T, Sashin D. Attenuation correction for a combined 3D PET/CT scanner. *Med Phys.* 1998;25:2046–2053.