PET/XT: Optimizing Breast Cancer Therapy Using Quantitative Positron Emission Tomography

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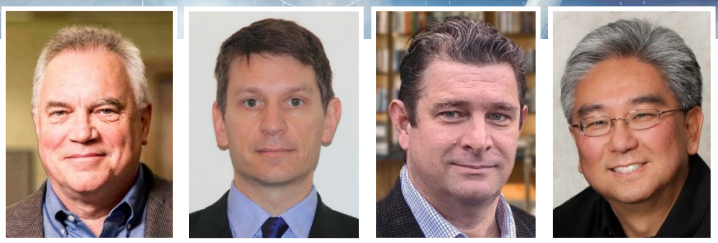
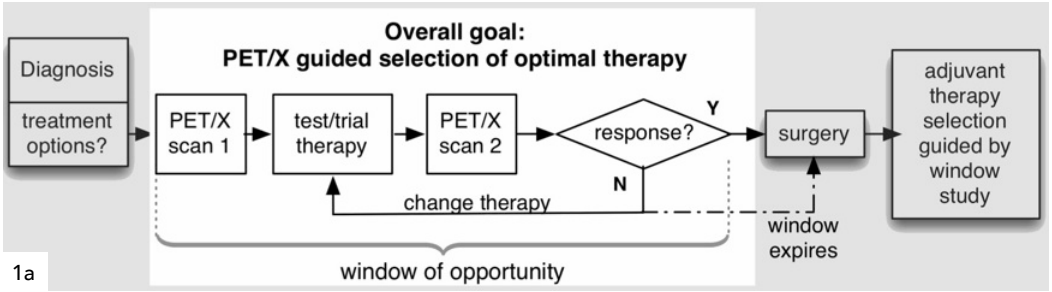


Dedicated breast imaging scanners using radiotracers, such as positron emission mammography (PEM) scanners, positron emission tomography (PET) scanners, and gamma cameras (single-photon planar imaging devices), have been evaluated since the late 1980s.[1] These systems trade the size of the imaging field of view for improved resolution, with potentially lower cost, higher sensitivity, and a smaller form factor. The higher resolution can improve detection and quantitation of subtle concentrations of radiotracer, although tomographic imaging is mandatory for quantitation. Several commercial dedicated breast PEM, PET, and gamma camera systems have been marketed.[2]

Despite the sustained level of interest in molecular breast imaging scanners, dedicated systems have not been widely adopted,[3] at least in part because breast imaging technology is a crowded field. In breast cancer imaging, multiple modalities are used in screening, diagnosis, treatment planning, and follow-up. Additionally, clinical PET and nuclear medicine procedures in general are categorized as "usually not appropriate" in the ACR Appropriateness Criteria. These procedures have a similar lack of endorsement in the influential National Comprehensive Cancer Network guidelines. When the first dedicated breast PEM, PET, and gamma camera systems were deployed before the emergence of routine breast magnetic resonance imaging, the focus was on improving detection, diagnosis, and staging (eg, improving sensitivity and specificity when mammography findings were equivocal).[1,2] The lack of guideline recommendations and limited clinical adoption reflect the challenges of using radionuclide imaging in this setting.

Quantitative PET Imaging of Breast Cancer

Patient-specific evaluation of breast cancer therapy has become a compelling application of quantitative PET imaging over the last decade. With the advent of neoadjuvant therapies, it has been shown repeatedly that molecular imaging with clinical PET scanners can be used to gauge response of breast tumors to therapy within days. Recently, the TBCRC026 multicenter phase 2 trial demonstrated that early changes in radiotracer uptake accurately predicted response to 4 cycles of neoadjuvant therapy with pertuzumab and trastuzumab for estrogen receptor–negative, human epidermal growth factor receptor 2 (ERBB2 or HER2)–positive breast cancer.[4] At least another 10 studies over the last decade have shown the same general results, especially for the role of PET in predicting early response.[5] In the adjuvant therapy approach, a window of opportunity between diagnosis and surgery (Figure 1) allows early evaluation of the effectiveness of adjuvant treatment before resection. After a baseline PET image and short regimen of targeted therapy, a posttherapy PET scan can evaluate treatment response and guide selection of postsurgical adjuvant therapy when the tumor is no longer visible.



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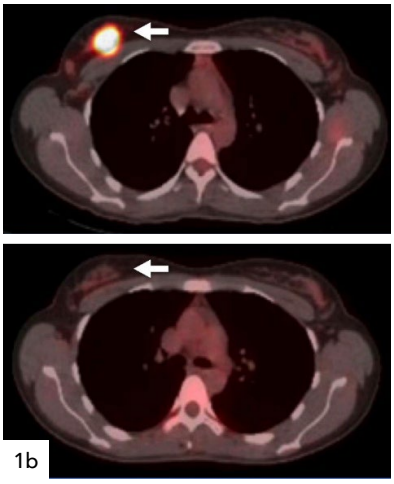


1b

Figure 1. 1a: The role of PET in patient-specific window-of-opportunity assessment of response to breast cancer therapy. **1b:** Fused fludeoxyglucose–PET/computed tomography images of a breast cancer patient in the Neo ALTTO trial, with a baseline study (top) showing tumor (arrow) and an image after 2 weeks of anti-HER2 treatment (bottom) showing metabolic response. The patient later had pathologic complete response. This example was a large tumor (>3 cm) imaged on a standard whole-body PET scanner.

The advantage of PET imaging is the potential for quantitative measurement of radiotracer uptake. However, this advantage is lost when imaging small objects (<2 cm) in whole-body PET scanners because of limited resolution. This creates a mismatch between current technological capability and clinical need: whole-body PET is accurate down to roughly 2 cm, but lesions smaller than 2 cm are the most prevalent at breast cancer diagnosis. Thus a dedicated breast imaging high-resolution PET scanner would enable patient-specific optimization of therapy in early-stage breast cancer.

PET/XT Scanner

We are building the PET/XT scanner, which is a breast PET scanner attached to an x-ray mammography (X) or preferably a digital breast tomosynthesis (T) system. Our goal for the PET/XT scanner is to precisely measure changes in radiotracer uptake after an initial or test dose of therapy. Since measurement accuracy is paramount, a fully tomographic system with all data corrections (attenuation, scatter, etc) is needed. The design of the PET/XT system is shown in Figure 2 along with initial results using the micro Derenzo phantom.

On the basis of discussions with radiologists and medical oncologists regarding clinical impact, the system performance target is that a measured 20% change in tracer uptake in 5-mm lesions should correspond to at least 95% specificity (<5% false-positive rate for detecting a true change in uptake). Our goal is to achieve this performance with 3- to 5-minute scans of no more than 185 MBq (5 mCi) of injected fludeoxyglucose F 18 or other radiotracer. This dose is half of the typical radiation dose of a clinical whole-body PET scan. This procedure is intended for patients who have confirmed breast cancer, so the relative risk consideration of the radiotracer dose is much different than in screening or diagnostic scenarios.

Integration of the PET and mammography/tomosynthesis systems occurs on multiple levels. The mammography or tomosynthesis images can be used for the needed PET data corrections, much as in a PET/computed tomography scanner, to enable quantitative imaging. In addition, the anatomical x-ray imaging can aid in the positional tracking of breast lesions between scans. The modular and movable design of the PET/XT scanner allows imaging to occur without patient motion between the PET and x-ray scans. The x-ray imaging is done under only light compression because the images are not collected for diagnosis.

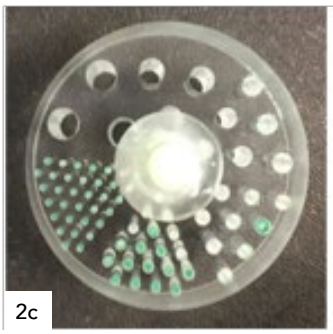
The PET/X scanner is a unique PET design that integrates with existing mammography equipment. The system was designed to quantitatively measure PET tracer uptake in known breast cancers to optimize adjuvant breast cancer therapy. Simulations show that the system will be readily capable of measuring a 20% change in tracer uptake in lesions 5 mm in diameter. The full system has been completed, and the initial measured image resolution is 2.5, 2.6, and 1.6 mm full width at half maximum in the transverse, coronal, and axial directions, respectively. Although data corrections for photon attenuation and scattered and random coincident photons are still under development, initial images from the system are encouraging.

Paul Kinahan, PhD, and Larry MacDonald, PhD, are cofounders of PET/X LLC.

References

1. Hruska CB, O'Connor MK. Nuclear imaging of the breast: translating achievements in instrumentation into clinical use. *Med Phys.* 2013;40(5):050901.
2. Narayanan D, Berg WA. Dedicated breast gamma camera imaging and breast PET: current status and future directions. *PET Clin.* 2018;13(3):363-381.
3. *Medical Radiation Exposure of Patients in the United States.* National Council on Radiation Protection and Measurements; 2019. NCRP report No. 184.
4. Connolly RM, Leal JP, Solnes L, et al. TBCRC026: Phase II trial correlating standardized uptake value with pathologic complete response to pertuzumab and trastuzumab in breast cancer. *J Clin Oncol.* 2019;37(9):714-722.
5. Wahl RL. Quo vadis: PET and single-photon molecular breast imaging. *J Nucl Med.* 2016;57 Suppl 1:3S-8S.


2a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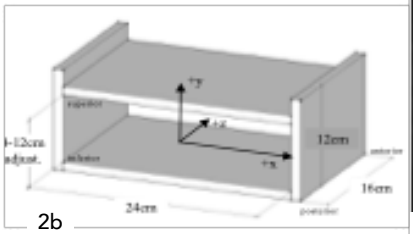

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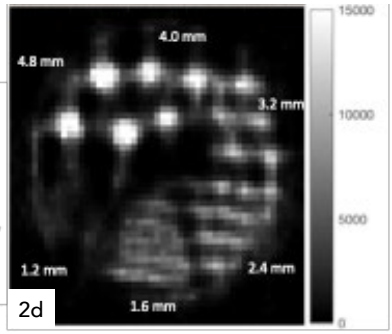

2d

Figure 2. Left: The PET/X prototype attached to a mammography scanner (2a) and a schematic illustration of the PET/X scanner consisting of 4 removable planar detector panels (2b). **Right:** Initial images of a test phantom (2c) showing partial resolution of 2.4-mm sources and full resolution of 3.2-mm sources (2d).