

Emerging Opportunities for c-MET Visualization in the Clinic

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In this issue of *The Journal of Nuclear Medicine*, Arulappu et al. present results of c-MET–specific peptide ¹⁸F-AH113804 PET screening for local regional recurrence after surgical excision of orthotopically implanted HCC1954 human basal-like breast cancer (BLBC) xenografts. ¹⁸F-AH113804 PET could visualize this locoregional recurrence as early as 6 d postoperatively, whereas CT did so after day 20, and tumors were first palpable only by day 27. They were also able to differentiate between high and low c-MET–expressing tumors. On the basis of these results, the authors concluded that ¹⁸F-AH113804 c-MET PET has potential as a clinical screening tool for earlier detection of locoregional BLBC recurrences (1).

c-MET is an interesting target for molecular imaging and treatment in solid tumors. It is a tyrosine growth factor receptor and together with ligand hepatocyte growth factor (HGF), c-MET is often dysregulated in cancers, including breast cancer. Increased activation of the c-MET/HGF pathway leads to invasion, angiogenesis, motility, and cell proliferation (2).

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Breast cancers are subdivided in molecular subtypes. One of these is triple-negative breast cancer (TNBC), which is characterized by lack of human epidermal growth factor receptor 2 (HER2) and estrogen and progesterone receptor overexpression. BLBC, which served as a model for Arulappu et al. (1), expresses gene characteristics for normal basal or myoepithelial breast cells. BLBCs comprise around 80% of TNBCs, and 80% of BLBCs are classified as a TNBC. Although not completely overlapping, BLBC is often used interchangeably with the term TNBC (3,4). About 15%–20% of all breast cancer patients have TNBC (5). Locoregional relapses develop in 12%–14% of these patients, and the overall recurrence rate is 35%–40% within 5 y (6,7).

After primary breast cancer treatment, current guidelines advise regular physical examinations approximately every 3–12 mo and yearly mammography for the first 5 y. In the absence of clinical signs and symptoms suggestive of recurrent disease, no laboratory

or imaging studies for metastases screening are advised (8–10). Most locoregional recurrences present themselves by clinical signs and symptoms such as lumps, swelling, or inflamed skin, whereas mammography and physical examination detect most other locoregional recurrences (11).

Although screening for locoregional recurrences using PET seems enticing, this reasoning incurs potential pitfalls. In contrast to the preclinical model in which local recurrences were already present 6 d after surgery, recurrences in TNBCs peak between 1–2 y after surgery (6). Therefore, follow-up of these patients would likely encompass numerous, costly, PET scans during the first 5 y next to the advised yearly mammographies. Moreover, the inherent spatial resolution of whole-body PET scans is currently around 10–15 mm, whereas locoregional recurrences this size are likely to be detected by palpation or conventional mammography. When whole-body PET scanning is performed, distant metastases may also be visualized. Modern PET/CT cameras and dedicated positron emission mammography could improve the spatial resolution of PET tracers (12), with the dedicated positron emission mammography at a loss of whole-body detection capability for possible distant metastases. Risk associated with radiation exposure induced by PET scans would have to be justified by potential outcome benefits. For instance, a single ¹⁸F-FDG PET scan incurs around 3.99 (European Association of Nuclear Medicine Research Ltd. guidelines) to 6.2–7.1 mSv (13). The 60%–65% of TNBC patients who will not relapse would receive additional radiation exposure if routinely screened by c-MET PET, next to the approximately 0.4 mSv dose per annual mammography (13). The patient population that might be considered for c-MET PET imaging could possibly be initially enriched by selecting for known local recurrence risk factors such as primary tumor size, vascular invasion, and node positivity (14). However, a follow-up protocol of patients using a 1-target approach is likely to result in a significant number of false-negative results. This is mainly due to the lack of expression of the c-MET receptor in about half of the TNBC patients (5). However, a selection for c-MET imaging based on expression in primary tumors might underestimate the c-MET expression, because conversion from low-expressing primary tumors to high c-MET levels in recurrent lesions has been observed (15). It will, however, be difficult for c-MET to compete with more general tumor characteristics such as elevated glucose consumption reflected by ¹⁸F-FDG PET imaging, because ¹⁸F-FDG performs relatively well in TNBC (16). Given these arguments, we do not at this moment foresee a routine place for the ¹⁸F-AH113804 PET tracer for broad local recurrence screening. However, there may well be other future reasons to target c-MET for imaging.

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There are several other successfully tested preclinical c-MET PET tracers, including ^{64}Cu -labeled HGF (17), ^{89}Zr -labeled anticalin PRS-110 (18), ^{124}I - and ^{89}Zr -labeled full-length murine antibody DN30 (19), 1-armed antibody ^{89}Zr -onartuzumab (20), and a ^{89}Zr -labeled H2 cys-diabody and H2 minibody (21). They have different properties, such as binding site, residualizing radiometals for improved contrast and varying tumor targeting kinetics, and clearance rates. Some strategies involve labeling of existing drug candidates as proxy for drug tumor deposition, whereas others involve specially generated c-MET-targeting proteins.

Next to c-MET imaging with a PET tracer, imaging with a fluorescent tracer might be of interest. Recently, GE-137, a fluorescent c-MET probe of which the targeting moiety is based on the same peptide used by Arulappu et al., was successfully applied to detect polyps in individuals at risk for colorectal cancer. These individuals underwent regular screening colonoscopies and GE-137 served as an add-on red-flag fluorescent imaging technique (22). Benefits of this strategy compared with radionuclide-based imaging are a less costly infrastructure and availability of off the shelf nonradioactive tracers. It is especially of interest when information of a limited body area is needed because no whole-body information can be obtained. In the future, potentially multiple fluorescent tracers with different distinct wavelengths targeting several targets could be used simultaneously in a multiplexed imaging setting to gain even more insight. Fluorescence imaging of growth factor receptors/ligands in the breast is currently actively pursued in the intraoperative setting, with the ultimate goal to obtain superior information concerning tumor-free margins. Moreover, recent developments in multispectral optoacoustic imaging allows for noninvasive real-time imaging using a hand-held probe in the outpatient clinic. This strategy combines superior resolution with high signal penetration for visualization of tissues. It might therefore be a tool for local breast recurrence screening purposes without radiation burden (23), whereas a c-MET fluorescent tracer could be part of the multispectral optoacoustic imaging screening with a tracer cocktail against often-expressed breast cancer targets.

TNBCs are characterized by a generally poor prognosis compared with other breast cancer subtypes as well as a lack of targeted treatment options (24). This has stimulated the search for drugable targets for this particular subgroup. It is of interest that several c-MET-targeted therapeutics are currently evaluated in breast cancer trials, such as the small-molecule tyrosine kinase inhibitors tivantinib, cabozantinib and foretinib, 1-armed c-MET antibody onartuzumab, and autologous cMET-redirected T cells. Preliminary clinical efficacy of such compounds in TNBC is modest (5). Pretreatment c-MET PET scans as a noninvasive accompanying biomarker could potentially enrich the patient population that might benefit from c-MET/HGF-targeted drugs (25), by providing insight in whole-body c-MET target distribution. When imaging c-MET obtains a role in the clinic, the answers required for patients will ultimately guide selection of the imaging modality and optimal tracer.

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