Nuclear Medicine Imaging in Breast Cancer: Current Strategies and Future Directions

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The article “PET Scan in the Diagnosis and Management of Breast Cancer” by Jame Abraham and coworkers is a complete, updated review of the existing scientific literature about clinical indications for positron-emission tomography (PET) in this malignancy.

Preoperative Axillary Staging

We agree with the authors that PET has limited indications in primary breast cancer, but we think that the role of PET in preoperative axillary staging deserves more discussion. In this field, the main drawback of PET is the high rate of false-negative results in the presence of a small volume of disease—specifically, axillary micrometastases—due to the limited spatial resolution of current PET technology scanners (about 5 mm). This limitation has been highlighted by the introduction of very accurate pathologic techniques, such as multislice sectioning and immunocytochemistry staining, coupled with sentinel lymph node biopsy (SLNB). These techniques have significantly increased the rate of detection of micrometastases in removed axillary nodes. As a result, SLNB after lymphoscintigraphy is the current standard diagnostic approach for staging axilla.

However, any discussion about the possible role of PET in preoperative axillary staging should take into consideration the fact that, despite the higher sensitivity, SLNB also showed a nonnegligible false-negative rate in the detection of axillary metastases in almost all studies. Moreover, the importance of axillary micrometastases in the clinical history of breast cancer remains to be clarified.

At our Institute, a prospective nonrandomized study was carried out with 401 T1-2, N0 breast cancer patients who had undergone breast surgery without axillary lymph node dissection (ALND). With a median follow-up of 5 years, only 27 patients (6.7%) had axillary recurrence of disease, with no major impact on overall survival.[1]

In addition to axillary status, PET provides a noninvasive evaluation of supraclavicular and internal mammary lymph nodes as well as a total body evaluation. At our Institute, the combined use of SLNB and [18F]-fluorodeoxyglucose (FDG)-PET has been proposed. In patients with clinically negative axillary lymph nodes, PET could be used to differentiate patients eligible for ALND (those with positive PET) from patients who should undergo SLNB (those with negative PET). Of course, this strategy will need to be validated through a large prospective study with adequate follow-up, but in this way, we might combine the strength of the two methods with potential benefits for patients.

Response to Therapy

Until now, PET has played a minor role in the evaluation of response to therapy in breast cancer. Despite promising results, its use has been confined to a few clinical trials of response assessment after neoadjuvant chemotherapy in locally advanced disease or therapy monitoring in metastatic disease. However, as demonstrated in other malignancies (ie, lymphoma and gastrointestinal stromal tumor [GIST]), PET is currently the most accurate imaging tool for early assessment of treatment response, providing an evaluation of the kinetics of tumor cell kill. Nevertheless, for meaningful clinical use, PET should be applied when early identification of responders and nonresponders can alter treatment strategy. This is probably not a key issue in the routine management of nonoperable primary breast cancer. PET might play a role in evaluation at the end of standard chemotherapy, to spare unnecessary surgery, but its use is limited by possible false-negative results in the presence of microscopic foci of residual disease.

In our experience, the area where PET is most beneficial in breast cancer is in follow-up, where it can
play an important role in the metabolic characterization of inconclusive abnormalities detected by other imaging modalities (ie, hepatic nodules or bone alterations), the restaging of recurrent or metastatic disease, the evaluation of patients with elevated tumor markers and negative conventional imaging, and the monitoring of therapy for metastatic disease. To date, however, we have no evidence of the impact of PET-guided changes in decision-making on patient outcomes in curative and palliative settings.

**Alternative Radiopharmaceuticals**

Although [18F]-FDG is the one radiopharmaceutical used worldwide for tumor detection with PET, the role of alternative radiopharmaceuticals has become of increasingly greater interest, in order to overcome limitations of this tracer in certain clinical conditions. For example, some cancers (eg, lobular carcinoma of the breast) show low FDG avidity, and inflammatory alterations can produce false-positive results.

Interesting PET radiopharmaceuticals include [18F]-FCH and [18F]-FLT, which provide information on cell proliferation and predict response to chemotherapy. Different fluorinated estrogen analogs have been developed as diagnostic probes for treating breast cancer. [18F]-FES binds estrogen receptors and can help select patients who are candidates for endocrine therapy. The integrin alpha(v)beta(3) is a key player in angiogenesis and metastasis. [18F]-galacto-RGD has demonstrated elevated and highly variable expression of receptors in breast cancer and is under evaluation for planning therapy with antiangiogenic drugs. [2]

On the other hand, studies on hypoxia led to the development of radiopharmaceuticals that predict resistance to radiotherapy. The radiosynthesis of [18F]-FMISO and other MISO derivatives, such as [18F]-FETA and [18F]-FAZA, enabled the imaging of hypoxic tissues. Among the hypoxia markers is a bioreductive metal complex trapped only in hypoxic tissues that can be labelled with the positron-emitting radionuclide 62Cu. This isotope can be produced by a small generator, avoiding the use of the cyclotron—the resulting tracer is [62Cu]ATSM. [3]

**Conclusions**

Despite the important results achieved with PET in studying breast cancer, the role of PET in this disease is still not defined for several indications, as we need further validation through large prospective clinical trials. The development of PET imaging in breast cancer is headed in two main directions: (1) the technologic improvement (more efficient detectors, hybrid systems, hardware and software implementation) and (2) new PET radiopharmaceuticals, especially the non-[18F]-FDG tracers. We have no doubt that these efforts will continue to bring improvements to the diagnosis and management of breast cancer.

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