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How can we optimize modern imaging techniques for breast cancer, with main reference to breast recurrence?

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Worldwide, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women.[1-2] Generally, modern imaging techniques consider two broad groups of women: 1) early (stage I-III) disease, which is limited to the breast and regional (axillary) lymph nodes and 2); metastatic (stage IV) disease that involves distant organ sites. After surgical resection of primary breast cancer, locoregional recurrences predominately affect the breast, skin, chest wall and the axillary and supraclavicular lymph nodes. In terms of metastatic sites, the pleura and lung parenchyma as well as internal mammary and mediastinal nodes, are the most common sites of intrathoracic recurrence.[2, 3] Extrathoracic metastases often occur in bone, liver and brain. In the follow-up of patients with early breast cancer, the presence of suspicious symptoms generally prompts clinical consideration for a change in systemic therapy, a process which requires the correct identification of local recurrences and distant metastases.[4] Therefore, modern imaging techniques focus broadly on detecting either premalignant or malignant conditions of the breast and systemic imaging is tailored towards distant metastatic sites.

In this special edition of the Quarterly Journal of Nuclear Medicine and Molecular Imaging a series of articles discusses the current status of imaging in breast cancer and future research directions, mainly focusing the interest on breast recurrence.

Breast cancer is biological heterogeneous, an observation that has important implications for treatment. Tumor expression of the estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2) separates breast cancer into broad phenotypes, with distinct natural histories. In the first of the articles in this special edition, Cadoo *et al.*[5] discuss the clinical behavior of breast cancer along these categories. The authors delineate the patterns of tumor spread associated with subtypes of breast cancer, with particular emphasis on the implications for imaging and treatment.

Breast cancer that metastasizes to distant organs may be treatable but is generally not considered curable. Following a diagnosis of early stage breast cancer, early detection of metastases by repeated conventional imaging tests (computed tomography [CT], ultrasound [US], and bone scintigraphy [BS]) has not been shown to be of major benefit over routine clinical follow-up. Therefore, a major focus of imaging after early stage breast cancer diagnosis is the detection of new (and potentially curable) disease within the breast itself. In the second of the reviews in this special edition, Cuccurullo *et al.*[6] examine the

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major challenges in diagnostic imaging of the breast following the treatment of a primary breast cancer. In general, physical examination and mammography are used routinely to detect such abnormalities but their sensitivity is reduced when surgery and radiotherapy have induced deleterious changes in breast tissue.[7, 8] In such cases, the diagnostic performance of mammography might be improved by the use of other techniques such as US or recent non-invasive techniques including colordoppler US, contrast-enhanced CT and magnetic resonance imaging (MRI) which detect the neovascular changes relatedto malignancy, Promising, although not yet well defined, are the possible contributions of positron emission tomography (PET) and of breast Tomosynthesis, allowing a 3D mammography.[6, 9-11] In the following review titled: "*Post breast conservation therapy imaging and local recurrence*" Lee *et al.*[12] discuss intervals for screening and various mammographic appearances of local recurrence, underlying the performance of such modalities in differentiating benign versus malignant disease. In addition, the authors review preliminary data on the utility of breast MRI and US in supporting the work-up of mammographic findings, although no conclusive data are currently available.

In the past ten years, technological advances have led to improvements in breast imaging both in the radiological and nuclear medicine fields. One such novel technique is 99mTc sestamibi/tetrofosmin scintimammography, which has been proposed as a sensitive and specific imaging technique before and following surgical interventions for breast cancer. In addition, it may be that the combination of conventional imaging procedures with nuclear techniques such as single photon emission tomography (SPECT) images might improve the diagnostic performance of either approach alone. A detailed discussion of the utility of conventional scintimammography in detecting primary breast tumors is provided by Schillaci *et al.*[13] in their review entitled "*Molecular breast imaging with gamma emitters*", also analyzing possible improvements allowable by dedicated gamma cameras and hybrid SPECT-CT machines.

Some data have suggested that contrast enhanced MRI of the breast is a sensitive imaging tool for the detection of breast tumor recurrence.[11] Furthermore, nuclear medicine techniques such as 18F-Fluorodeoxyglucose (FDG) PET provide an accurate assessment of metabolic activity, and, possibly tumor behavior. The current use of these imaging techniques is described by Gaeta *et al.*[14] The authors go on to discuss how these sophisticated tools and novel radiopharmaceutical compounds might be used in the future for depicting loco-regional recurrences or distant breast cancer metastases.

The major goal of a powerful and reliable imaging modality is to modulate therapeutic strategies and, therefore, improve outcomes for patients. In fact, local recurrences can often be treated with localized surgery or completion mastectomy in cases of prior breast-conserving surgery with/without radiation and systemic therapy, and may sometimes result in long-term survival.[15] Moreover, alongside advances that have been made in surgical and radiotherapeutic techniques, new chemotherapeutic and targeted agents are being developed, which have the potential to bring significant clinical benefits to patients. Evangelista *et al.*,[16] in their review article discuss the role of PET and PET/CT in guiding local therapies for breast cancer recurrences, with a particular emphasis on the interpretation of available data for current and possible future clinical practice.

Despite extensive research, many questions about breast cancer recurrences and its earlier detection remain. For example: 1) the optimum timing for performing imaging examinations; 2) the appropriate order in which these imaging studies should be conducted; and 3) the true impact of the benefits of these techniques for patients. It is hoped that future research will build on available data to optimize imaging for breast cancer. Collectively, this series of articles addresses these issues and examines current and future imaging techniques in the diagnosis of breast cancer and its recurrence. We hope that the readers will find this a useful and valuable resource.

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