Nuclear Imaging and Early Breast Cancer Detection
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Abstract
The present report discusses about the most important roles of nuclear medicine related to the early detection of breast cancer. We summarize describe the established and emerging diagnostic techniques, their indications and clinical impact for planar and tomographic breast scintigraphy, positron emission tomography (PET)/computed tomography (CT) and positron emission mammography (PEM).

Keywords: Breast cancer; Positron emission tomography; Computed tomography; Nuclear imaging; Initial staging

Introduction
The concept of early detection of breast cancer (BC) is wide and can be considered as the early identification of primary cancer at different phases of disease, it means at initial staging, during and after treatment (neoadjuvant or adjuvant), and during follow-up.

Molecular breast imaging uses short-term radioactive agents that absorbed into tissues and can be imaged with a special camera. From planar to tomographic images, from technetium to fluoride, many efforts have been made for earlier individualizing the BC and for understanding the molecular pathways of tumour.

Here in, we described the usefulness of nuclear imaging modalities, considering the pros and cons of each others based on the last clinical applications, particularly for initial staging.

Conventional Nuclear Imaging
Breast scintigraphy
Since 1980s numerous pioneer studies demonstrated the usefulness of 99mTc-methoxyisobutyl isonitrile (MIBI) scintigraphy in the evaluation of different types of neoplasms. Waxman and Khalikhal et al. [1-3] generated the clinical interest in evaluated BC with this tracer. Therefore, close to conventional imaging for the detection of primary BC in order to select patient for biopsy and spare an unnecessary surgical procedures, nuclear medicine breast imaging was added. Nowadays, breast scintigraphy or scintimammography (SM) is considered a supplemental breast exam that may be used by a dedicated breast camera (DBC), that is a high resolution small field of view dedicated breast camera mounted on a mammography unit. This diagnostic tool has shown a sensitivity rate of 81-90%. In particular, DBC proved an extremely highly sensitive diagnostic method in the detection of cancer in patient with ipsilateral multifocal/multicentric carcinomas, either invasive or in situ, and in those with synchronous bilateral tumours, resulting positive in 93.2% of cases. As reported in literature, conventional mammography detected multifocality/multicentricity in only the 47.5% on cases, demonstrating lower performance than DBC which identified a significantly higher number of additional invasive tumour foci (89.6% vs. 37.9%), most clinically occult and small in size [11,12]. The preoperative underestimation of local disease can lead to surgical under-treatment, resulting in a higher risk of local and distant recurrence. Bearing in mind that the tendency of BCs to metastasize reflects total tumour rather than the size of the largest focus, there is the risk that patients will not receive adjuvant chemotherapy or radiotherapy if additional smaller foci are missed. Therefore the early detection of multifocal/multicentric BC becomes extremely important both prognosis and therapeutic strategy.

SPET/CT
Conventional nuclear medicine imaging, such as planar or tomographic scintigraphy, is also precious in the preoperative evaluation of the effectiveness of neoadjuvant treatment in primary tumour and in lymph nodes draining the site of the tumour. The increasing development of hybrid devices, based on an X-ray tube for low-dose computed tomography (CT) added to a conventional single photon emission tomography (SPET) system had opened a new era for SPET application. The advantages of SPET/CT essentially rely

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on the attenuation correction capabilities and on precise anatomical landmarks that permits an exact localization of a focal-uptake. SPET/CT significantly increases the diagnostic accuracy of both conventional planar and SPET imaging in several cancer fields, reducing considerably the number of indeterminate findings [13-16]. In particular, 99mTc-MIBI or 99mTc-Tetrofosmin SPET/CT is able to detect residual BC, although false negative findings occurred in some patients with microscopic residues and in those with low-cellularity histotype tumours. The few data present in literature about the employment of SPET/CT in diagnosis of BC appear encouraging. They shown a sensibility values ranging from 89.2% to 90.7% in overall lesions an from 71.4% to 78.3% in the subgroup of small size (≤ 10 mm) [17,18]. Also lymph node status was evaluated in these few studies, reporting a sensitivity value of 78.3%. Spanu et al. [19] suggest a wider application of SPET/CT in the preoperative evaluation of BC patients after neoadjuvant therapy to guide the surgeon to the most appropriate breast surgical treatment and to eventually select the most suitable axillary sampling, i.e. axillary lymph node dissection (ALDN) vs. sentinel lymph node biopsy (SLB). Considering that SPET/CT cannot replace the pathologic examination for the assessment of lymph nodes status, given the low sensitivity for axillary lymph nodes (36.8%) and that at present ALDN is the standard procedure for nodal staging following neoadjuvant therapy, the authors hypothesize that patients with SPET/CT study positive at the axillary site should undergo ALND directly, given the high probability that there is lymph nodal involvement. On the contrary, patients with a SPEC/CT negative study, especially patients with partial or complete response of primary tumour to neoadjuvant therapy and clinically negative axilla should be selected for SLB. In these latter cases, ALND could be avoided if the sentinel node is negative, with the well known advantages in terms of reduced morbidity and cost.

**Positron emission imaging devices**

New nuclear diagnostic imaging tools are, nowadays, considered in the early detection or in subsequent pre-surgical planning of women with BC. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has revolutionized the diagnostic opportunities of malignancies; however, it has still a controversial role in the management of BC. In particular, PET and PET/CT provide new methods of both locally advanced BC staging and assessment of the early chemo/endocrine therapy response. The development of new radiotracers and the value in predicting treatment response represent a great area of research interest.

**FDG PET/CT**

In clinical practice, the application of FDG PET/CT covers different settings: from the definition of disease extension (i.e. lymph node or distant involvement) to identification of unknown foci of BC, so defined incidentalomas. Following, we described in separate paragraphs these different topics.

**Primary tumour**

NCCN guidelines recommend against the use of PET or PET/CT scanning in the staging of clinical stage I and II or operable III (IIIA) BC [20]. The recommendations against the use of PET are supported by several findings: the high false negative rate in the detection of breast tumours that are small (<1cm) or of low grade, the low sensitivity for detection of axillary nodal metastasis, the low prior probability that these patients have detectable metastatic disease, and the high rate of false positive scan findings [21].

Paradoxically, many are the neoplasm incidentally discovered during conventional imaging or PET/CT imaging performing for other reasons. Sometimes, these lesions result as benign findings, but in other cases they are metastatic foci by other tumour or primary tumours. Beatty et al. [22] suggested that the incident breast lesions should be better evaluated because in 55% of the cases they represent a BC. Litmanovich et al. [23] reported a percentage of 57% of unaware foci with high FDG-uptake concluding that these lesions should be considered as a second primary tumour, a lymphoma or a metastasis with higher FDG-uptake rather than benign findings. The major number of FDG-avid “incidentalomas” are positive at histological staining, but considering the low positive predictive value (PPV=25%) of the biopsy, should be necessary to perform other evaluations, such as a new mammography scan and a tissue sample by ultrasound. In incidental lesions with a low FDG-uptake, the presence of abnormal morphological pattern should be considered of a great clinical relevance.

**Lymph node metastases detection**

Evaluation of axillary lymph node metastases is important for BC staging and treatment planning. Monzawa et al. [24] assessed the diagnostic performance of FDG-PET/CT compared with that of ultrasonography and contrast-enhanced CT for the detection of axillary lymph node metastasis in subjects with early (clinical stage I or II) BC, taking the histopathological results of ALDN and SLB as the reference standard. Their results showed that the sensitivity of PET/CT was disappointingly low and only 20%, and was inferior to that of ultrasonography and contrast enhanced CT, which were also hardly sufficient for staging. Recently a study by Cooper et al. [25] evaluated the diagnostic accuracy, cost-effectiveness and effect on patient outcomes of PET, with or without CT, and MRI in the evaluation of axillary lymph node metastases in patients with newly diagnosed early-stage BC. PET/CT resulted less sensitive than PET only (56% vs. 66%) but with a similar specificity (96% vs. 93%). PET performed less well for small metastases; the mean sensitivity was 11% for micrometastases (≤ 2 mm). Conversely, PET/CT detected extra-axillary lymph node involvement in almost one-third of the patients with stage II-III BC, including regions not evaluable with ultrasound. PET/CT may be useful as an additional imaging tool to assess extra-axillary lymph node metastasis, with an impact on the adjuvant radiotherapy management [26]. As suggested by Wahl et al. [27] and Eubank et al. [28] PET/CT may be useful in assessing patients with medially or superiorly situated BCs that may drain preferentially or exclusively to internal mammary or supraclavicular lymph nodes.

**Early distant metastases detection**

The evidence of occult metastasis, missed by staging examination can be detected by PET/CT scan according to Koolen et al. [29]. The authors demonstrated that in 80% studied patients, additional lesions were exclusively seen with PET/CT, leading to a change in treatment in 8% of them. Furthermore, they showed that in 84% of patients with a negative staging PET/CT, no metastases developed during the follow-up.

The report by Groheux et al. [30] included 39 patients with stage II or III BC after conventional work-up. PET/CT revealed occult metastases in four patients. These were bone metastases in three patients and pleural involvement in one patient. Fuster et al. [31] studied 60 consecutive patients with BC stage IIb or higher. PET/CT sensitivity and specificity in detecting distant metastasis were 100 and 98%. Citation: Evangelista L, Burei M, Cervino AR (2012) Nuclear Imaging and Early Breast Cancer Detection. J Cancer Sci Ther S7:003. doi:10.4172/1948-5956.S7-003.
respectively, versus 60 and 83% for conventional work-up (contrast-enhanced chest CT, liver ultrasonography, 99mTc-HDP bone scan). Metastases missed by conventional work-up were visualized in eight patients. The sites of involvement were bone (six cases), and/or lung (two cases) and/or liver (two cases). PET/CT is also highly sensitive in detecting pleural, mediastinal, abdominal and pelvic metastases. In this study PET/CT diagnosed both patients with liver metastases, whereas liver ultrasound detected only one of the two cases. PET performs well to assess lung nodules larger than 8 mm [32], but it lacks sensitivity in smaller lesions, due to partial volume effect and respiratory motion.

Bone is the main site of metastatic spread in BC history and bone scintigraphy and/or MRI are the gold standard for its diagnosis. Bone marrow metastases represent metabolic bone changes that appear before morphologic ones [33,34]. PET/CT imaging is more efficient than contrast enhanced CT in this latter case and its ability to detect osteolytic lesions is significantly better than that of bone scintigraphy [35]. Osteolytic lesions are more common than sclerotic type (80 vs. 15–20%). FDG may miss sclerotic lesions, but a better specificity for PET/CT than for bone scintigraphy in its detection has been recently reported [36,37].

CT is the imaging modality of choice for evaluating suspected liver metastases. Unenhanced CT is useful in a few cases, especially for detecting calcifying or hemorrhagic metastases from colon or BC. If the clinical suspicion of a lesion is high and the CT scan is negative, MRI or PET can be considered as alternative tests for further assessment. In a meta-analysis comparing ultrasound, CT, MRI, and PET in the detection of hepatic metastases from gastrointestinal tract cancers, Kinkel et al. [38] reported the highest sensitivity for FDG-PET. The main limitation of PET is its low sensitivity for brain metastases.

In literature, only some studies report with detail about the diagnostic accuracies of PET/CT at early diagnosis of BC [24,25,29,31,39-42], as depicted the (Table 1).

PEM

Due to the limited resolution of PET equipment and the space limitations of the current protocols for CT acquisition, small-size breast tumours are not visible using this technique, until they reach a certain size, and they can be visualized with other techniques like MRI. This is what has led to the development of a PET device dedicated to the breast, such as positron emission mammography (PEM). There are several commercial firms which have developed the PEM and, although they are still in early clinical development, initial results show sensitivity levels of 93% [43], similar to MRI and also high specificity levels 93% [44] higher than MRI. With dedicated configurations, the recent PEM system has high spatial resolution, up to 2.4 mm. In the prospective study from Eo et al. [45], the imaging sensitivity of PEM was compared with that of PET/CT in relation to tumor size. The results showed that PEM had significantly higher sensitivity in small-sized tumours <2 cm than PET/CT. However, in literature the data is controversy about the diagnostic power of PEM being reported different rates of accuracies [46-50] (Table 2).

An issue to resolve is which will be the interrelation between MRI and PEM and if a coexistence of both techniques is possible or if one of them will prevail over the other. PEM proved to be complementary to MR imaging for defining preoperative disease extent in the ipsilateral breast of women with newly diagnosed BC.

PEM was more specific than MR imaging and less likely prompt unnecessary biopsies. The advantage of PEM-guided biopsy is that the lesion can be easily re-imaged to determine whether the region of FDG uptake has been removed or reduced sufficiently to ensure adequate sampling without injecting additional contrast as in MRI or additional radiation dose as is required during stereotactic biopsies. In addition, the specimen scan allows the physician to evaluate the radiotracer distribution in the biopsy cores, without the interference of normal background breast tissue radiotracer uptake, thus providing information of adequate sampling and to help direct the pathologist’s attention to the areas of interest [51].

Conclusion

Until now, many efforts have been made for the detection of primary tumour and metastasis but the future challenge is to apply specific tracers as histological, molecular and biochemical markers of several cellular processes including apoptosis, proliferation, P-glycoprotein expression and neoangiogenesis. Furthermore, an integration of the

<table>
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<th>Authors (ref)</th>
<th>N. of pts</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
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<td>Monzawa et al. [24]</td>
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<td>56%</td>
<td>96%</td>
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<td>97</td>
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<tr>
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<td>70 (axillary nodes)</td>
<td>100</td>
<td>-</td>
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<td>98</td>
<td>-</td>
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<td>-</td>
<td>58 (axillary nodes)</td>
<td>92</td>
<td>79</td>
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<td>97</td>
<td>-</td>
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<td>100</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>97.4</td>
<td>91.2</td>
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*axilla and loco-regional lymph nodes

Table 1: Diagnostic accuracies of FDG PET/CT in detection of primary and metastatic foci of breast cancer.
new emerging techniques with the established ones in order to take advantage of the combination of both should be evaluated. The work in a multimodality environment could represent the way for reaching these purposes.

References


Table 2: Diagnostic accuracies for detection of primary breast cancer according to PEM.

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<tr>
<th>Authors (ref)</th>
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<th>N of patients</th>
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<th>Specificity (%)</th>
<th>PPV (%)</th>
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<th>Accuracy (%)</th>
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<td>PEM flex</td>
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<td>87</td>
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<td>88</td>
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<td>Naviscan</td>
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<td>41</td>
<td>79.9</td>
<td>66</td>
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<td>Tafra et al. [48]</td>
<td>Am J Surg</td>
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<td>Laboratory PEM System</td>
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<td>Ann Surg Oncol</td>
<td>Laboratory PEM System</td>
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<td>86</td>
<td>91</td>
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<td>89</td>
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<td>PEM flex Solo II; Naviscan</td>
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<td>95</td>
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*18 lesions


