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An Overview on Positron Emission Mammography in Breast Cancer Detection and Follow up: Particular Concerns in Iran as a Developing Country

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Generally, about 2 million new patients with breast cancer are diagnosed annually.[1] Breast cancer is the most prevalent cancer among females and it causes a considerable burden on both patients and health system.[2] The screening and diagnostic procedures including staging, restaging, and evaluating the response to treatment are costly. Yet, the need for rapid detection and diagnosis of the tumor and its recurrence pushes the imaging methods to the edge of science for incremental accuracy. The currently available breast imaging methods cover most encountered clinical needs, but certain areas may still be in need of increasing accuracy and preciseness. The possible clinical use of positron emission mammography (PEM) was reviewed in the current study and cons and pros as well as indications for clinical use were compared with other imaging modalities. Clinical indications for any imaging of breast can be purified into 5 categories: screening, diagnosis and staging, restaging, evaluating the response to treatment, and directing the biopsy tools.[2] The advantages and drawbacks of routine available breast imaging are roughly addressed in the following lines for every available tool.

Mammography is the essential method for breast cancer screening and diagnosis. The sensitivity is highly variable ranging from optimal to modest (95%-40%) in different populations, while the specificity is not also favorable. Nevertheless, the risk benefit ratio of the mammography is obviously confirmed and mammography is documented as the only diagnostic tool to reduce the mortality.[3] Albeit, there are certain concerns regarding the cost effectiveness of the breast cancer screening.[4] The reports of accuracy of breast specific gamma imaging (BSGI), a newly revived functional imaging, for lesion detection and diagnosis are noticeable. The sensitivity is reported to be more than 90% and the specificity is seemingly superior to that of MRI.[5] Whatever the result of the debits would be, mammography is the milestone method for the detection and diagnosis of breast cancer.[3]

Ultrasonography (US) is a complementary diagnostic tool for mammography and clinical examination for detection and characterization of lesions. It is not expensive; it imposes no ionizing radiation to the patient or the operator. US is valuable for the diagnosis of primary lesion and recurrences, the evaluation of the axilla, and guiding the biopsy. US has perfect negative predictive value (i.e. 100%) in optimal operating condition for the diagnosis of malignancy in palpable mass; the diagnosis of ill-defined masses including invasive lobular carcinoma are the weak points. US has proved its sufficient accuracy to locate additional foci of malignancy.[6,7]

Although the mammography and US are the essential imaging tools for diagnosis, the MRI is required in particular populations including those with dense breasts and those with post-surgical scars as well as BRCA positive patients or their first relatives. MRI illustrates the extent of the tumor and detects the ipsilateral and contralateral tumors and assists determining the need for neo-adjuvant therapy.[8] The role of MRI is underscored for the detection of the invasive component of ductal carcinoma in situ, primary lesion in node positive patients without known primary, and in breast Paget's disease.[9] MRI is also used to follow up the patients under 50 years, who are at high risk (>20%)

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for recurrence. MRI is, likewise, radiation free with perfect sensitivity (>90%) and moderate specificity (>70%).[9]

The detectors of conventional PET scanners are rings with trans-axial field of view of about 20 to 40 cm. These devices are designed to image the whole body and patient's bed; the detector may move to cover the bed length. The spatial resolution of the PET/CT state-of-art scanners are smaller than 10 mm.[10] The indication of ^{18}F-FDG-PET/CT is for the evaluation of distant metastases in high risk patients, restaging, and the assessment of response to treatment. Apparently, there is no place for ^{18}F-FDG PET/CT for screening or the diagnosis of primary lesion.[11] The physical limitations of PET scanners, which unfavorably reduce spatial resolution, are many comprising that the detected line of response (LOR) contains the annihilation, not the emission source, acollinearity effect, relatively large size of detector element, and the depth of interaction error (parallax effect). Despite the fact that the contrast of the PET/MR is better and the privileges of MR are added to those of PET, the technical issues are more concerning, because the attenuation correction cannot be done as perfectly as in PET/CT. PEM is a dedicated breast PET with smaller field of view and minimal distance between the detectors and detector to the breast. The smaller detector elements and reduced parallax effect provided better in-plane full width at half maximum (FWHM) and spatial resolution was improved to 2 to3 mm. The sensitivity is also optimal and scatter is low because the detectors are in proximity and even touching the breast.[12] ^{18}F-FDG accumulates in the hypermetabolic areas, the specification of malignant tumor cells. The detection of ipsilateral malignant lesion by conventional PEM is superior to MRI. Furthermore, PEM is a perfect alternative to MRI with similar expenses when MRI is prohibited for a certain contraindication including small metallic clips and foreign bodies in the eye or brain, cardiac defibrillator, and spinal prostheses as well as in patients susceptible to renal failure or sensitive to Gadolinium.[13,14]

There are 2 major types of dedicated positron emission breast scanners: 2 planar or curved separated detector heads integrated with compression paddles (i.e. conventional PEM) and rotating detectors or ring shaped detectors (i.e. fully tomographic). The major drawbacks of both designs are image in quality of degradation at the edge of field of view, radiation, and high operation cost. In conventional PEM, the detection of chest wall lesions is further hesitated. Conventional PEM is 2 dimensional with notable limitation for the deep breast near the chest wall. The only commercial PEM in US, Flex Solo II (Naviscan, San Diego, USA)[15] , has 6 ×16.4 cm^2 paired moving detectors with 24×16.4 cm^2 compression paddles. PEM tubes are position sensitive and lutetium yttrium oxyorthosilicate (LYSO) crystal is cutted at 2×2×13 mm,[3] making a construction of 13×13 arrays of crystal. Scan time is about 7 to10 minutes, 60 to80 minutes after 5 to13 mCi ^{18}F-FDG injection. For bilateral craniocaudal and mediolateral oblique views, 28 to 40 minutes is required. The scanner enables direct biopsy of the lesion employing an isotope guiding rod. In Iran, MAMMI (OncoVision, Valencia, Spain)[16] is logistically available with less than a half of investment for a whole body PET scanner. The scanner has 1 or 2 moving complete LYSP rings and images are fully tomographic (trans-axial × long-axial field of view 17×4 cm^2). Scan time is between 5 to15 minutes; 1 hour after about 5 mCi^{18} F-FDG injection. Because the injected dose and the device costs are half of those of ^{18}F-FDG PET/CT, the scan would plausibly cost 20% to 40% of ^{18} F-FDG PET/CT scans.[1,12]

In the advent of ^{18}F-FDG production in Iran as a developing country, ^{18}F-FDG PET/CT and PEM would be more available in future. While the indication of the PET is well documented and its cost is radically high compared to US and MRI, about 10 times more expensive and not covered by the insurance, the PEM is expected to be available with more reasonable cost and possibly indication for lesion detection, characterization of the tumor, evaluation of the extent of the invasion, local recurrence and response to treatment, and guiding the biopsy.[17] The compound of ^{18}F-FDG PET/CT and ^{18}F-FDG PEM at a single visit may be the optimal diagnostic tool admixing the whole body advantages of ^{18} F-FDG PET/CT with high local resolution of PEM with reduced total cost. It is noteworthy that had the PET/MR passed its current technical problems including attenuation correction, it may become the standard procedure in future.[18] In the perspective of nuclear medicine, better diagnosis and follow up are expected for patients with breast cancer in the horizon of perfect screening in which the BSGI may play a role and optimal follow up of the patients with PET/MR and ^{18}F-FDG PET/CT in addition to PEM.

According to the meta-analysis by Caldarella *et al*., PEM is specific and sensitive for the evaluation of suspicious breast lesion with device.[19] Eight studies were included in the meta-analysis comprising 873 women with early breast lesions. The sensitivity and specificity values of PEM using FDG were 85% (95% CI, 83%-88%) and 79% (95% CI, 74%-83%), respectively; however, high statistical heterogeneity was observed among the included studies.

To sum up, mammography is the gold standard for screening, concerning the sensitivity in particular populations.[3] US assists the screening, diagnosis, and confirmation of the findings in mammography and further assessments of the findings in other

imaging modalities and examinations at any stage through the follow up.[6] MRI, with its optimal spatial resolution, is a powerful tool for the evaluation of local extension, multiplicity, and multi-centricity at staging time. MRI can evaluate response to therapy after chemotherapy either adjuvant or neo-adjuvant.[8,9] BSGI promotes lesion diagnosis.[20] PET overwhelming power is the ability to assess the metabolic activity and the nature of whole body imaging. ^{18}F-FDG PET/CT is optimal for metastasis workup, restaging, and the evaluation of response to treatment. PEM may fill certain gaps in this scenario. The drawback for ^{18}F-FDG PET/CT is its low spatial resolution; had the spatial resolution been improved,^{18}F-FDG PET/CT would have been an optimal imaging modality. Even though the whole body imaging privilege is lost in PEM, it has become a potent scanner with high spatial resolution, which makes the method suitable for diagnosis, staging, the detection of local recurrence, and response to therapy. Not only the cost and availability of PEM has already hindered its clinical use, but also notable inherited drawbacks including the radiation remain to be addressed.

It may be concluded that simultaneous PEM and whole body FDG-PET with a single injection promise optimal staging and restaging diagnostic performance. The high spatial resolution of PEM for the evaluation of local recurrence and the strength of whole body PET for the detection of distant metastases add up to optimize the diagnostic performance. Also, PEM may be useful for the diagnosis of suspected breast lesions and future studies should be directed to evaluate the clinical cost benefit concerns for screening and diagnostic performance of PEM.

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