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From Small to Large Primary Breast Cancer: The Role of 18F-Fluorodeoxyglucose Positron Emission Tomography

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Depending on the size of the breast and the density of breast tissue, most tumors do not become palpable until greater than 1 cm in diameter. In the last years, many efforts have been made for the early detection of primary breast cancer, increasing the performance of common radiological imaging modalities, such as mammography and Magnetic Resonance Imaging (MRI), or improving functional imaging, such as scintigraphy and Positron Emission Tomography (PET). Although standard radiological imaging methods are used for the initial diagnosis of breast cancer, the information provided by these modalities is purely structural and does not reflect the degree of the metabolic activity of this malignancy. From 1986 to 2012, 339 English journal articles in "humans breast cancer and PET" by a Pubmed research for were found, while the number of reports were 374 when the "18F-Fluorodeoxyglucose (FDG)" word has been added. Many of the reports are focalized on the early detection of loco-regional or distant metastasis of breast cancer, on breast cancer recurrence, on the response to treatment and on prognostic evaluation, while few papers had evaluated the role of FDG PET in primary breast cancer [1-9]. According to the literature, the sensitivity of FDG PET for the detection of breast cancer is 85-95% with a specificity ranging from 80 to 100% and a positive predictive value greater than 90% [9-11], nevertheless, the accuracy tends to change with the size of primary breast cancer. In the report by Avril et al. [12], FDG PET scanning of the breast was performed in 144 patients (60 patients were clinically identified as premenopausal, 18 as perimenopausal, and 66 as postmenopausal). Conventional image reading was obtained by regarding only focal FDG tracer accumulation as to represent malignancy, and Sensitive Image Reading (SIR) was achieved by including probable (grade 2) and definite (grade 3) malignant lesions. Visual analysis identified a total of 88 focal tracer accumulations within the breast, classified as grade 3 (definitely malignant). Thirty-one lesions were classified as grade 2 (probably malignant), and 66 lesions were classified as grade 1 (unlikely to represent breast cancer). Depending on tumor size, there was considerable variation in diagnostic accuracy. Sensitivity was found to be low for tumors smaller than 1 cm, being 41.7% for Tis, 25.0% for T1a and T1b (<0.5 and from 0.5 to 1.0 cm), 84.4% for T1c (from 1.0 to 2.0 cm) and increasing to 91.9% in stage T2 (2.0 to 5.0 cm), and finally shifting to 100% for breast carcinomas ≥ 5 cm (stage T3). These results suggested that the number of unnecessary invasive procedures may not be significantly reduced by the use of PET imaging techniques. Also from the study by Cermik et al. [2] in patients with invasive breast cancer, there was significant variation in diagnostic accuracy depending on primary tumor size. In particular, the sensitivity of FDG PET increase as the size of the lesion detected increases, being sensitivity of 53% (8/15) in T1mic and T1a, 63% (15/24) in T1b, 80% (36/45) in T1c and 92% (49/53) in T2/T3. When the stage of disease was considered as end-point, the sensitivity were: 72% (18/25) in stage 0, 69% (34/49) in stage I, 80% (44/55) in stage II, 90% (18/20) in stage III and 92% (12/13) in stage IV. Scheidhauer et al. [7], found that 21 of the 23 patients with breast carcinomas showed focal FDG uptake in the tumour area (sensitivity: 91%). Two carcinomas (pTlc, N0, M0, G3; pTlc, Nx, M0, G2) were not discovered (false-negatives), one of them occurring in the patient with elevated blood glucose due to diabetes. The results by Scheidhauer et al. [7] suggested that the accuracy of breast cancer detection becomes lower in tumors with a diameter below 10 mm and Zangheri et al. [13] underlined that the diagnostic performance reduced in subtypes with known hypometabolic histology such as tubular carcinoma or noninvasive cancer and such as ductal or lobular carcinoma in situ, although a moderate sensitivity (41.7%) in these latter histological pattern was reported by Avril et al. [12]. Moreover, the increasing levels of glucose lead to inhibition of FDG uptake in breast cells [9].

Conversely, Groheux et al. [4] and Segaert et al. [8] suggested that the use of FDG PET/CT at initial staging of breast cancer patients might be appropriate starting with clinical stage IIB and primary operable stage IIIA. Groheux et al. [4], evaluating 131 patients with locally advanced stage cancer (stages from IIA to IIIA) who underwent FDG PET/CT, demonstrated that the nuclear imaging was able to modify the stage in 5.6% of IIA, in 14.6% of IIB and in 27.6% of IIIA patients.

Multi centric breast cancer represents a significant limitation for use of breast-conserving therapy. Identification of multi centricity was suggested to be improved by means of PET imaging [6]. Even by applying SIR, Avril et al. [12] identified nine (50%) of 18 patients with multifocal or multi centric breast cancer. In contrast, MRI reported to provide a greater sensitivity for the detection of multi centric breast cancer [14]. Presumably because of its excellent soft-tissue contrast, MRI is able to correctly predict the T stage in significantly more patients than FDG PET/CT did. With CT as part of the FDG PET scan, tumor margins are more difficult to determine than with MRI, especially in dense breast tissue. T staging seems to be a limitation of FDG PET/CT, when compared with MRI. Berg et al. [1] reported a statistically significant difference when assessing the T stage of breast cancer, particularly MRI classified the T stage correctly in 77% of cases while FDG PET/CT, in 54% of cases. On the other hand, the authors found that FDG PET/CT detected 75% of small carcinomas being in contrast to a report by Avril et al. [12], when assessed with PET alone. Heusner et al. [5] tried to explain the differences in the findings of both reports by two possible reasons. First, the combination of CT with PET: the limited spatial resolution of PET may compromise detection of small tumors within the breasts, even when a dedicated positioning device is used. Adding contrast-enhanced CT to PET can

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reveal small contrast-enhancing breast lesions. The second reason may be the time point at which PET was acquired: Avril et al. [12] acquired PET scans 40–60 min after 18F-FDG injection. In accord with Kumar et al. [15] and Mavi et al. [16], a significant increase in the maximum standardized uptake value (SUVmax) of breast cancer lesions over time was found.

The main limitation of the link between FDG uptake on PET/CT scans and tumor size is due to little information available regarding the relationship between metabolic activity and tumor extension. Glucose metabolism and subsequent FDG uptake may initially be low, increasing with tumor growth, thus preventing the detection of small tumors. Moreover, partial volume effects impact on the accuracy of radioactivity measurement in small lesions by causing a spread of the signal over a larger area than it actually occupies [17]. Depending on the spatial resolution, which is usually between 5 and 8 mm for the PET scanners, the tracer accumulation is significantly underestimated in small tumors. In phantom studies, Avril et al. [18] found only 28% of the true radioactivity concentration in spheres of 1 cm in diameter. This means that at small sizes, only highly metabolic active tumors can be visualized. Several studies have demonstrated that breast tumors with unfavorable prognostic characteristics show a higher degree of FDG uptake [19,20], but, due to the limited resolution of most common whole-body PET/CT scanners, suboptimal patient positioning, and the partial volume effect, sensitivity for the visualization of small primary tumors was found to be low [2,3,12].

Therefore, the ways for improving the accuracy of PET/CT scanner in detection of small breast tumors are: 1) the optimal patient positioning (i.e. prone position, hanging breasts), and reconstruction protocols for tumor visualization (i.e. image reconstruction to 2×2×2 mm voxels as suggested by Koolen et al. [21]). This latter approach provides high resolution images of the breasts and loco-regional lymph nodes without tissue compression and results in improved tumor delineation and less breathing artifacts [22]. Further, it enables image comparison with MRI.

In conclusion, the number of invasive procedures required by patients presenting with breast masses suggestive of abnormality cannot be reduced by PET or PET/CT imaging. On the other hand, PET excels with high positive-predictive values that are superior to mammography, ultrasound, and MRI. Further improvements in spatial resolution will be provided by new generations of PET scanners, by dedicated breast imaging devices and new hybrid techniques (i.e. PET/MRI or time of flight PET/CT). However, the diagnostic limitations linked to partial volume effects could be not expected to be completely resolved.

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