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REVIEW

PET imaging in breast cancer

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ABSTRACT

The application of Positron Emission Tomography (PET) using 2-[F18] fluoro-2-deoxy-D-Glucose (FDG) and the more recently fused technique of Computerized Tomography and PET (PET/CT) in patients with breast cancer is reviewed. Their role in diagnosis of primary tumour, staging, chemotherapy monitoring and radiotherapy planning, follow-up and restaging is introduced. The advantages of combination of anatomical and functional images are emphasized and the comparison with other imaging techniques is highlighted.

INTRODUCTION

During the past decade, the application of positron emission tomography (PET) has remarkably improved the management of cancer patients. The radiotracer most widely used in clinical practice is the glucose analogue 2-[F18] fluoro-2-deoxy-D-glucose (FDG). PET is showing increasing value in the distinction between malignant and benign lesions, in disease staging and re-staging and in therapy planning. Combined PET/CT systems have recently been developed and allow functional PET and anatomical CT images to be acquired in one session and rapidly co-registered [1].

In this review, we evaluate the possible impact of PET and PET/CT on breast cancer diagnosis and on clinical management of breast cancer patients, in comparison with conventional imaging modalities, such as mammography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) imaging.

DIAGNOSIS OF PRIMARY TUMOUR

At present, diagnosis of primary breast cancer is principally based on mammography. Although this technique has a high sensitivity (85-90%), its major limitation is a low specificity and a low positive predictive value (10-35%) [1,2]. Mammography has also a low negative predictive value in patients with dense breasts or breast implants or after previous treatment for breast cancer [3].The false negative results in these women range between 25% and 45% [4]. Therefore, other non-invasive diagnostic imaging methods have been evaluated. The specificity of ultrasound is reported to be superior to that of mammography, especially in distinguishing solid and cystic lesions [5]. MRI imaging presents a sensitivity higher than 90%, but its specificity is lower than that of mammography [6]. In conclusion, the combination of these examinations is not sufficiently conclusive to significantly reduce the use of invasive diagnostic procedures in the primary diagnosis of breast cancer [1].

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Several investigations have been conducted to assess the role of [18F] FDG-PET in detecting primary breast cancer. PET has yielded very encouraging results, showing a diagnostic sensitivity ranging between 80% and 96% and a specificity between 83% and 100% [7-10] but its ability to detect breast cancer greatly depends on tumour size. Regarding small tumours, only 68.2% of breast carcinomas at stage pT1 (<2cm) are correctly identified compared to 91.9% of these at stage pT2 (>2-5cm) [7]. Because of its limited spatial resolution, PET is not recommended for lesions smaller than 1cm in diameter [11].

In addition, PET imaging accuracy is affected by tumour histology. Invasive lobular carcinomas are more often false negative (65.2%) than invasive ductal carcinomas (23.7%) [7]. Indeed there is higher glucose metabolism for invasive ductal carcinomas (median SUV of 5.6) versus invasive lobular carcinomas (median SUV of 3.8) [12]. Standardized uptake value (SUV) is a commonly used parameter in PET imaging and it is defined as the fractional uptake of FDG relative to the injected activity normalized to the body weight [13].

The identification of multifocal or multicentric breast cancer plays an important role in decisions about therapy, as it limits breast-conserving surgery. The sensitivity of PET is quite low, but it is twice as sensitive in detecting multifocal lesions (sensitivity 63%, specificity 95%) than the combination of mammography and ultrasound (sensitivity 32%, specificity 93%) [7,8].

The diagnosis of in situ carcinomas has increased over the past decade, but data suggest that PET imaging cannot contribute to an improved diagnosis of non-invasive breast cancer. Nevertheless, it is important to note that focally increased FDG accumulation provides a high positive predictive value (96.6%) in diagnosing breast cancer [7].

In general, benign breast masses display low FDG uptake. About 10% of fibroadenomas take up FDG. Fibrocystic changes often do not reveal any significant FDG uptake, even though some false positive imaging results have been obtained in proliferative dysplasia (diffuse uptake), ductal ectasia, tubular angiomyoepithelioma and cystosarcoma phyllodes [14]. False positive results have also been observed in infectious and inflammatory lesions, including hemorrhages after biopsy or surgery [14].

The dual system PET/CT solves the problem of lesion localization -fusing the two imaging modalities-and allows differentiation between pathological uptake and the normal physiological variants of radiotracer uptake (in the urinary tract, bowel, brown fat and muscles) [3]. The frequency of definite lesion characterization is increased by 38% (from 65% to 90%) with PET/CT as compared to PET and the frequency of equivocal lesion characterization is decreased by 83% [15].

A considerable number of studies have shown the value of FDG PET imaging in breast cancer patients. However, PET imaging may not be used as a routine application for evaluation of primary breast tumors, because of the low sensitivity, but it provides a high positive predictive value to represent malignancy in patients that present metabolically active lesions [13].

PRE-OPERATIVE STAGING

Pre-operative staging of breast cancer is extremely important as it influences treatment decisions [11].

In the TNM staging system, T stage depends on the precise size of the primary tumour. Conventional imaging techniques such as mammography and ultrasonography are better than PET in determining tumour size (13). MRI can detect small tumours 2-3mm while sensitivity of PET for tumours less than 1cm in diameter (T1a &b) is 25% [13]. Therefore PET has not adequate spatial resolution for the determination of T stage.

The axillary lymph node status is considered the single most important prognostic indicator in patients with breast cancer. Clinical examination and conventional imaging techniques are generally unreliable for the determination of N stage. Recent experience with lymphoscintigraphy has shown that the intraoperative gamma probe has a greater than 90% accuracy for detecting sentinel lymph nodes [16].

In anatomic based imaging modalities, such as CT, ultrasound and MRI, the size of a particular lymph node is of crucial importance in determining the tumour involvement. Acccordingly, lymph node enlargement over 1 cm in diameter is the decisive criterion. In contrast, metabolic imaging with PET seems to provide more specific information based on detecting increase glucose consumption of cancer tissue. The results of most studies indicate that PET is highly sensitive and specific for the presence of nodal disease in the axilla with a sensitivity ranging from 79% to 100%, a specificity ranging from 50% to 100% and an accuracy ranging from 77% to 89.8% [8,17-20]. Small axillary metastases were frequently missed,suggesting that detection of micrometastases and small tumour-infiltrated lymph nodes is limited by the currently achievable spatial resolution of PET (approximately 6-8mm). PET has been found to be insensitive for minute foci of metastatic disease and therefore cannot replace lymphoscintigraphy and sentinel lymph node mapping [21]. Compared to conventional imaging modalities, PET seems to be more accurate in determining the locoregional lymph node status, particulary in women with locally advanced breast cancer although it does not allow determination of the number of tumour-involved lymph nodes. In lymph node regions in which histological or clinical follow-up results revealed the existence of malignancy, PET demonstrated definitely positive findings in all of them while CT showed positive, equivocal and negative findings in 56%, 24% and 20%, respectively [15]. In a PET/CT study aiming at staging breast cancer patients, sensitivity, specificity

and accuracy in detecting lymph node metastases were 80%, 90% and 86.7%, respectively. In comparison with PET alone. PET/CT provided additional information in terms of detection and lesion localization in 46% of cases, [22].

Although there are only a few studies available which directly compare the diagnostic accuracy of PET with sentinel node biopsy in breast cancer patients, sentinel node biopsy seems to be the method of choice in early stages of disease, whereas PET excels with a high diagnostic accuracy in locally advanced stages [23].

Detection of internal mammary lymph nodes has long been a challenge for imaging modalities, as metastases in this region are often clinically occult [15]. The sensitivity, specificity and accuracy of PET seems to be higher than those of CT (85%, 90% and 88% vs 54%, 85% and 73%, respectively) [24]. Using PET/CT findings of abnormal focal uptake in the region of the internal mammary chain appear to be more frequent than when using PET alone. PET/CT can improve the diagnostic confidence to almost 100%, in the internal mammary region [11,15]. This may be the result of a higher localisation accuracy of PET/CT in comparison with PET, allowing the detection of lesions considered on PET alone as showing non-specific uptake [11].

Another advantage of PET in breast cancer staging is that, being a non-invasive technique, allows the study of all lympatic basin of the breast (axilla, supraclavicular and mammary chain) and it permits the characterization of breast lesions and the complete viewing of the entire body in a single examination [14].

M stage is characterised by the presence of distant metastases. In breast cancer, distant metastases are frequently found in lymph nodes, lungs, liver and bones. Therefore, chest X-ray, abdominal ultrasound, bone scintigraphy, CT and MRI are useful for staging. As PET imaging became more easily available, different groups of investigators have evaluated the role of PET in staging breast cancer. In a study, PET imaging correctly identified 97% of patients with lymph node involvement, 100% of those with bone metastases, 83% of those with lung metastases and 100% of those with liver metastases [25]. Furthermore, the diagnostic accuracy of PET imaging was compared with CT and MRI. PET detected additional lymph node (27%) and bone metastases (46%) missed by conventional imaging techniques [25]. Even though CT and MRI imaging show superior spatial resolution, PET provides more accurate information in discriminating between viable tumour, fibrotic scar or necrosis. PET can identify metastatic disease with a sensitivity and specificity of 85%-86% and 79%-90%, respectively [26,27] where the sensitivity and specificity of chest X-ray, bone scintigraphy and ultrasound of the abdomen are 36% and 95% respectively [27]. With respect to the location of metastases, the sensitivity of PET was superior in detecting pulmonary metastases and particularly mediastinal lymph node metastases compared with chest X-ray. The sensitivity of PET in detecting bone and liver metastases is of the same magnitude compared with bone scintigraphy and ultrasound of the abdomen, respectively [27].

Particular attention should be paid to skeletal involvement because 8-10% of breast cancer patients develop skeletal metastases early in their disease and the frequency of bone metastases is around 70% in patients with advanced disease [14]. Bone scintigraphy visualises the osteoblastic response to bone destruction by cancer cells, while PET visualises primarily the metabolic activity of the tumor cells [14]. Clinical studies have demonstrated that PET detects significantly more lesions than bone scintigraphy. However, this higher FDG uptake was confined to osteolytic lesions [28]. Therefore, PET is superior to bone scintigraphy in the detection of osteolytic not osteoblastic breast cancer metastases [28].

There is evidence that PET imaging in breast cancer patients leads to a shifting in clinical staging in 36% and in a change in the treatment strategy in 60% of patients, respectively as a result of a higher number of distant metastases [29]. The advantage of whole-body PET imaging is its ability to detect metastases in different sites and organs, whereas various other methods need to be added when using conventional imaging [13].

PET/CT adds incremental diagnostic confidence to PET in 33% to 100% of cases, depending on location of metastases with the exception of the liver (0%) [15]. Equivocal lesions decrease by 83% with PET/CT in comparison with PET while PET/CT showed definitely positive foci in 28% of cases with equivocal or negative CT findings. The sensitivity, specificity and accuracy of PET/CT are 87%, 62% and 83%, respectively compared with 68%, 69% and 68% of CT alone [15].

In a retrospective analysis of the impact of PET on clinical management of patients with breast cancer, it was found that PET was 69% sensitive and 80% specific in predicting clinical stage at 6 months and there was a significant association between PET results and clinical outcome [30]. More specifically, 69% of the patients who demonstrated progression at 6 months were PET positive while 80% of the patients who were stable or improving at 6 months were PET negative [31]. PET influenced treatment decisions in 74% of the patients referred for study [30].

TREATMENT MONITORING

Up to now, anatomical imaging modalities are mostly used to evaluate response to treatment, by evaluating changes in tumour size. Nevertheless, these modalities do not usually allow the determination of early response or differentiation between viable tumour tissue and scar tissue. PET imaging seems highly useful in monitoring therapeutic effects at an earlier stage in the course of treatment. It is known that anticancer treatment primarily influences tumour metabolism,

which only at a later stage is followed by a decrease in tumour mass [14]. A reduction in the FDG uptake (SUV) can predict for a subsequent decrease in the diameter of the tumour [32]. Unchanged or enhanced FDG uptake indicates tumour progression [11]. Early identification of non-responders would significantly improve patient management by reducing the use of ineffective therapies, preventing prolonged side-effects, reducing the delay in initiation of more effective treatment and minimizing costs [14].

While data on PET monitoring in radiotherapy and chemotherapy of advanced disease are in general inadequate some valid data are available regarding the monitoring of primary chemotherapy.

PRIMARY (NEO-ADJUVANT) CHEMOTHERAPY

It is increasingly used for patients with locally advanced breast cancer as it can increase the rate of breast-conserving surgery by preoperatively reducing the tumor volume [34]. Patients with complete pathological response after neoadjuvant therapy have significantly higher disease-free and overall survival rates than non-responders [13]. Approximately 70% of the patients undergoing primary chemotherapy show clinical response, but only 20-30% demonstrate partial or complete response at histopathological level [33]. Therefore, the therapeutic effect cannot be accurately evaluated until definitive breast surgery is performed [13].

Because of the significant side-effects of chemotherapy, there is a need for early identification of non-responding patients [13]. There are now published studies addressing the role of PET in predicting response early in the course of therapy. Patients with newly diagnosed primary breast cancer beginning chemohormonotherapy, underwent a baseline PET and follow-up PET scans during the first three cycles of treatment [34]. Responders demonstrated progressive decreases in FDG uptake by the tumours, to a mean of 52.4% of baseline values at 63 days,while non-responders had no significant change in tumor FDG uptake.Another study has demonstrated that the decrease in FDG uptake is a marker of tumour response and that PET imaging of primary metastatic breast cancer after a single course of chemotherapy may predict treatment response with a sensitivity of 90% and a specificity of 74% [35]. With a threshold defined as a decrease below 55% of the baseline FDG uptake all eventually responded patients were identified after the first course of therapy (sensitivity 100%, specificity 85%) [36]. Increased tracer uptake after the first cycle did not exlude a partial tumor response;only after the second chemotherapy cycle PET was able to distinguish between complete and partial/no response [37]. PET seems to be more accurate than conventional imaging modalities for predicting outcome in breast cancer patients who were reevaluated after primary treatment (accuracy, positive and negative predictive values of 90%, 93% and 84% respectively vs 75%, 85% and 59% respectively) [38]. The advantage of PET/CT compared with PET alone is that it may improve the accuracy in the evaluation of treatment response by directly defining metabolic and morphological changes [11].

FDG-PET BEFORE AND AFTER RADIOTHERAPY

A PET study **before radiotherapy** not only allows evaluation of metabolic tumour activity but also permits treatment planning. The high rate or recurrences within the primary target volume in some tumours necessitates a dose escalation to increase the probability of tumour control. However, radiotoxicity to healthy tissue limits this strategy [39]. The role of PET in determining tumour extension and its relationship with surrounding tissues, is limited but PET/CT is changing this role by integrating the information on tumour morphology provided by CT with that on its metabolism [11]. PET/CT can play a major role by correctly staging the disease and providing an accurate estimate of tumour volumes to be selectively irradiated [11].

An early decrease in FDG uptake does not necessarily indicate a good prognosis.Immediately **after completion of radiation therapy,** PET may demonstrate continued uptake in the periphery of the tumour.This FDG accumulation was found to correlate pathologically with the formation of a fibrous pseudocapsule rather than residual disease [39]. A major problem of post-radiation therapy PET is that normal tissues can manifest radiotherapy induced toxicity to different degrees within a few days or even months.Because of these effects, significantly increased FDG uptake can be seen in selected soft tissue regions that have been irradiated [40]. Some studies suggest that a fair compromise may be to recommend PET imaging 4-6 months after completion of radiation, if possible [39].

Radiotherapy response will, of course, be associated with reduction in tumour size. The definition of complete response can, however, be problematic as complete disappearance of the tumour may occur only rarely, and more commonly residual tissue, whether it be scar or residual tumour, remains [33]. PET can identify changes in glucose uptake after treatment and may prove to be a better indicator of a favourable response to therapy [39].

FDG-PET DURING HORMONE THERAPY

Some researchers have used 18F-labelled oestradiol and other radiolabelled oestrogens and progestins as radio-tracers [40,41]. In a study, fluoro-oestradiol PET and FDG-PET was

performed before and 7-10 days after initiation of tamoxifen therapy [41]. None of the responders developed a clinical flare reaction (i.e.progression of disease), but all demonstrated metabolic flare, with a mean increase in tumour SUVs of 1.4±0.7. No evidence for flare was noted in the non-responders. The findings of a metabolic flare by FDG-PET early after institution of tamoxifen treatment appeared to predict responsiveness to anti-oestrogen therapy in patients with receptor-positive breast cancer. The flare phenomenon has never been observed after chemotherapy but if chemohormonotherapy is performed, this finding should be kept in mind [33].

RESTAGING–DETECTION OF LOCOREGIONAL AND DISTANT RECURRENCES

Recurrence of disease at locoregional and distant sites occurs frequently in women who have undergone primary treatment for breast cancer. Recurrence occurs in up to 35% of patients by 10 years after mastectomy or breast-conserving therapy [42]. Routine follow-up after the completion of initial treatment for breast cancer is standard practice in most countries. Early detection and accurate restaging of recurrent cancer is important in the selection of the most appropriate treatment [14].

The conventional imaging modalities usually performed, such as mammography, CT, MRI and ultrasound, present some limitations in distinguishing between anatomical modifications like scarring and fibrosis, induced by therapy and relapse of disease. In contrast to morphological imaging, assessment of disease with PET is based on functional criteria and since functional changes precede anatomical changes, PET has the potential to detect viable tumour tissue early through its elevated glucose metabolism in comparison with surrounding normal tissues [21,31].

In several studies in patients with suspicious reccurences [26,27,43-46], the patient-based sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) for PET were 85%-100%, 72%-82%, 84%-90%, 82%-87% and 92% respectively. For comparison, the corresponding values for conventional imaging are 79%-84%, 60%-94%, 74%-88%, 73% and 75% respectively [43,44]. In 15% of patients PET detected metastases outside of the axial field of view of MRI [43]. On a lesion basis the reported sensitivity is lower, due to the low sensitivity in detecting bone metastases (57%) [26]. In contrast in another study [26], PET correctly identified 97% of patients with lymph node metastases,83% with lung metastases and 100% with bone metastases.The majority of studies comparing the diagnostic accuracy of PET and bone scintigraphy for the evaluation of bone metastases in breast cancer patients have found PET to have a similar or higher sensitivity in the detection of osteolytic bone metastases. In contrast, osteoblastic metastases show a lower metabolic activity and are frequently undetectable by PET [42].

The breast cancer metastases in the axilla and the brachial plexopathy are difficult to assess on conventional anatomic imaging. MRI detected 55% of patients with metastatic lesions or recurrence whereas PET identified metastatic lesions in all the patients (100%) [47].

In general, the problem of PET is that exact localisation of an area with increased FDG uptake is often very difficult. PET/CT solves the problem of lesion localisation with the combination of metabolic and morphological imaging in the same patient position following image fusion. PET/CT provides additional information in 78% of patients compared with each modality alone [48]. In 10% of patients the combination of PET/CT led to a change in patient management and was also able to reduce false positive results and pitfalls in 32% of all patients [48,49]. Patient-based sensitivity and specificity of PET/CT in detecting recurrence are 96% and 89%, respectively [26].

Tumour markers whose blood levels seem to correlate with the tumour mass are useful tools in the follow-up of certain cancers. There is general agreement that a progressive increase in a circulating tumour marker can represent an early sign of tumour recurrence [42]. Carcinoembryonic antigen (CEA) and cancer-antigen 15-3 (CA 15-3) are the most frequently used tumour markers for the detection of asymptomatic recurrences of breast cancers [50]. However, they lack specificity and elevation of their levels, although very suggestive, does not always prove the presence or recurrence of cancer and does not predict the number and localization of tumour sites [42,50].

Studies evaluated the impact of PET on the detection of recurrent breast cancer in patients with asymptomatic tumour marker increase (CA 15-3 >32U/ml, CEA >5ng/ml) but negative or equivocal other imaging modality results (bone scan,ultrasonography of breasts,mammography and CT of the chest and abdomen) [50]. Tumour marker-guided PET resulted in a sensitivity, specificity, accuracy, NPV and PPV of 89%-96%, 75%-84%, 87%-90%, 82%-84% and 89%-96.2%, respectively [46,50-52]. All patients with false negative PET results also had negative findings on conventional imaging [10]. In a study, patients with a history of breast cancer underwent a PET/CT examination for restaging after a rise in tumour markers or suspicion of recurrent disease on the basis of clinical follow-up. In 36% of these patients, PET/CT led to a change in the therapeutic management [49].

CONCLUSIONS

During the past decade, the application of PET and PET/CT has remarkably improved the management of cancer pa-

tients and in cases of breast cancer, it is rapidly becoming part of the standard work-up of difficult cases in many centers. PET cannot be recommended as a screening tool for early breast cancer because of its limited spatial resolution and the often only moderate increase in glucose metabolism in breast cancer, which results in a low sensitivity for the detection of small carcinomas, micrometastases and small tumour-infiltrated lymph nodes. However, due to its high positive predictive value in revealing malignancy in metabolically active lesions and its ability to determine loco-regional lymph node status and detect distant metastases, PET or PET/CT using FDG is highly suitable in advanced stages of breast cancer.

Although FDG-PET has been used as a tracer in many tumour entities after radiation and chemotherapy, data in breast cancer are still scarce.The only indication where valid data are obtainable is the monitoring of primary chemotherapy in locally advanced breast cancer.

Several studies have shown that PET and PET/CT scanning are highly accurate methods for whole-body restaging of patients with suspected breast cancer recurrence. PET and PET/CT, as metabolic diagnostic tools can complement the information provided by morphological imaging techniques and thereby increase the sensitivity and specificity in the evaluation of potential disease sites. Recent data indicate a rationale for the use of PET in cases of asymptomatically elevated tumour marker levels in the presence of negative or equivocal results of conventional imaging. The combination of PET and tumour marker assay seems to be usually sufficient for the early detection of breast cancer recurrence.

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