Registered and potential indications of FDG PET/CT in breast carcinoma

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Arch Oncol 2012;20(3-4):152-7.
UDC: 618.19-006:616.071:616-052
DOI: 10.2298/AOO1204152B

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Received: 16.08.2012
Accepted: 21.08.2012

SUMMARY

The indication of 18F-fluorodeoxyglucose (FDG) imaging has been more disputed in breast carcinoma than in many other primary cancers (e.g. lung, head and neck, colorectal, lymphoma...) due to a limited sensitivity to detect the primary tumours in case of lobular or in situ forms or small sized tumours detected on systematic mammography, and to identify minimal node invasion in the axilla. Nevertheless dedicated PET machines are now proposed to characterise breast lesions.

For staging locally advanced or restaging recurrent or metastatic breast cancer, FDG PET/CT has a good diagnostic performance. As a functional whole-body imaging modality, it is able to detect extra-axilar metastatic lymph nodes, distant metastases including in the skeleton, where it outperforms bone scintigraphy or SPECT except in case of osteoblastic lesions, or to discover second primary cancers (around 2% of cases). A potential indication is monitoring response to chemotherapy, to early detect disease resistance or progression. To summarise published results and our own experience, the breast tumour SUVmax decreases with the number of cycles in most patients, including those who will show residual disease on pathology. It is therefore best to perform FDG PET/CT at baseline and after 1 cycle of chemotherapy; the criterion for prediction of an incomplete pathologic response would be a SUVmax reduction <50%. In case of adjuvant chemotherapy, the visual interpretation of FDG PET/CT performed after 5 months may be sufficient to predict disease-free survival; the response to chemotherapy evaluated by FDG PET is a better predictor of recurrence-free survival than pathologic response.

Key words: *Breast Neoplasms; Positron-Emission Tomography and Computed Tomography; Fluorodeoxyglucose F18; Mammography; Patient Care Management*

Presented at the 1st Serbian Symposium on Hybrid Imaging and Molecular Therapy, Novi Sad, Serbia, April 23-25, 2012

During the past two decades, the indication of 18F-fluorodeoxyglucose (FDG) imaging has been more disputed in breast carcinoma than in many other primary cancers (e.g. lung, head and neck, colorectal, lymphoma...) due to a limited sensitivity to detect the primary malignant tumours in case of lobular or in situ forms or small sized tumours detected on systematic mammography, and to identify minimal node invasion in the axilla. The good diagnostic performance of FDG PET/CT in precise clinical settings of breast cancer is now well established. Nevertheless, the role of FDG PET/CT for patient management is challenged by other imaging modalities, in particular MRI.

Conversely, dedicated PET machines for positron emission mammography (PEM) allow a better resolution and their utility is currently under evaluation. In a pilot study on FDG PEM published in 2005, 39 of the 44 index lesions were seen on PEM (89%) (1). PEM detected 4 of 5 incidental breast cancers, 3 of which were not seen by any other imaging modalities. Of 19 patients undergoing breast-conserving surgery, PEM correctly predicted 6 of 8 (75%) patients with positive margins and 100% (11/11) with negative margins.

The present article aims to report on the recently published evidence in this domain; since PET/CT has been a major advance for FDG imaging, the period covered by this review will start in 2005 with the large spread of this technique.

FDG FOR DETECTING BREAST CANCER

FDG PET and PET/CT has been widely performed as part of cancer screening in Japan (2). During year 2005, a total of 50 558 healthy subjects underwent such a cancer screening including, among other examinations, FDG PET or PET/CT: 35 cases of breast cancer were discovered. Breast cancer was the fifth more frequent cancer to be detected by FDG screening, after thyroid, colorectal, lung and prostate cancers.

Neither screening for breast cancer nor characterising breast lesions as neoplastic are currently accepted indications for FDG PET/CT.

In contrast, it seems worthwhile to characterise breast incidentalomas found on FDG PET performed for another indication with a frequency of 60/45000=0.13% in the series of Chung (3): 7/24=29% of unexplained foci with persistent imaging findings which were evaluated were malignant. In a similar survey, 9/902 patients =1% had concerning breast findings, and 5 (56%) had subsequent breast cancer diagnoses (4). The positive predictive value (PPV) of PET/CT imaging in these patients was 63%.

FDG FOR STAGING BREAST CANCER

"Staging locally advanced breast cancer" is part of the sufficiently -documented indications of FDG listed in the European Medicines Agency Core SmPC (5). The recent recommendations of the European Society for Medical Oncology (ESMO) are matched (6). At staging, in case of "*suspicion of metastatic breast cancer, clinical suspicion must be confirmed by imaging including functional imaging such as PET/CT or dynamic contrast-enhanced MRI*".

FDG appears worthwhile only in locally advanced breast cancers that are likely to spread out, i.e. tumour stage T2 and over (Figure 1). Its is also the case of inflammatory breast cancer, as shown by Carkaci (7) in 41 patients: FDG PET/CT showed uptake in the skin, in the affected breast of 40, in the ipislateral axillary nodes in 37, in subpectoral nodes in 18 and in distant metastases in 20, 7 (17%) of whom were not

known before PET/CT. In 45 patients, Ikenaga (8) demonstrated that the SUVmax of the primary tumour was correlated with tumour size, histological grade, expression of oestrogen and progesterone receptors, p53, and number of metastatic axillary lymph nodes. This was confirmed in a series of 275 women with primary breast cancer: multivariable linear regression showed that tumour size, histological grade, Ki-67 expression, oestrogen receptor (ER) status and histological type were significantly related to the SUV (9]. In another recent series of 36 locally invasive breast cancers, the SUVmax was significantly higher in ER-negative cancers than in ER-positive ones (8.5 vs. 4.0, $p<0.001$) (10).

Those correlations were also confirmed when detecting FDG with PEM: ER-negative tumours and progesterone receptor (PR)-negative tumours had significantly higher mean lesion-to-background ratio than did their respective receptor-positive tumours. Triple-negative tumours (i.e., ER-negative, PR-negative, and HER2-negative tumours) had statistically higher mean lesion-to-background ratio than did ER-positive PR-positive HER2-negative tumours. Infiltrating ductal carcinomas had significantly higher PEM FDG uptake values than did infiltrating lobular carcinomas. Breast tumours with higher histologic grade also had significantly higher PEM FDG uptake values than did those with lower grade (11).

Tumour size also influences detection with FDG. In a study comparing PEM and PET, differences in sensitivities between PEM and PET/CT were larger in small tumours <10 mm (73% vs. 60%) and 10-20 mm (96% vs. 84%), than in larger tumours (12). Six lesions of invasive ductal carcinoma 1-13 mm in size were not detected on both PEM and PET. Recently comparative studies have been published between FDG PEM and MRI for locoregional staging of breast cancer. In 472 women with newly diagnosed breast cancer, PEM and MR imaging had comparable breast-level sensitivity, although MR imaging had greater lesion-level sensitivity and more accurately depicted the need for mastectomy (13). Fourteen (3.6%) women had tumours seen only at PEM. PEM had greater specificity at the breast and lesion levels. Eighty-nine (23%) participants required more extensive surgery: 61 (69%) of these women were identified with MR imaging, and 41 (46%) were identified with PEM. The same team also reported the results of search for contralateral cancer in 367 patients (14). MRI had a patient-based sensitivity of 14/15 =93%; 11 contralateral cancers (73%) were visible on PEM, but only 3 (20%) were recognized prospectively as suspicious.

In another series of 67 additional unsuspected ipsilateral lesions or multifocal lesions, PEM had sensitivity of 85% (34/40) vs. 98% (39/40) for MRI, but was more specific 74%, (20/27) compared to 48% (13/27) for MRI (15); differences did not reach statistical significance.

Another approach to detect intramammary malignancy is to fuse FDG PET images acquired in prone position with magnetic resonance mammography (MRM). In the series of Heusner (16), 58 breast lesions were evaluated. The sensitivity, specificity, PPV, negative predictive value (NPV) and accuracy were 93%, 60%, 87%, 75% and 85% for MRM, respectively. For FDG-PET/MRM they were 88%, 73%, 90%, 69% and 92%, respectively. In only 1 patient FDG-PET/MRM would have changed the surgical treatment. FDG can also reveal a second synchronous cancer: 5/275 patients =2% (17) or 3/106 =3% (18).

The performances of FDG PET for detecting lymph node extension at initial staging depend on the size of the invaded lymph nodes. FDG PET is unable to detect a microscopic involvement, like any other non-invasive in vivo imaging modality. This could explain differences in sensitivity for metastatic lymph node detection in the axilla observed from one team to another during the past decade. It is now largely accepted that FDG PET cannot replace invasive procedures for detection of metastatic lymph nodes such as sentinel node detection, in particular to rule out axilar lymph node involvement (reported sensitivity was as low as 44% (19) or 49% (20)). Nevertheless, FDG uptake can reveal a more extensive nodal spread than expected, for example to upper axillar (level III of Berg), subclavicular, internal mammary (21/275=8% according to Gil-Rendo (17)) or mediastinal lymph nodes. In those sites, FDG PET is more sensitive than CT. Several authors suggest that a significant FDG uptake in axillary lymph nodes (SUV > 2.3 according to Chung (21)) indicates axillary lymph node dissection instead of sentinel lymph node biopsy (17, 21).

One major interest of FDG PET is the detection of distant metastases (except for brain metastases due to the physiologic FDG uptake by the cerebral cortex) in one single whole-body examination. In the current indication of locally advanced breast cancer, this discovery occurred in 12 of 80 patients (15%) in the series of Port (22). According to this team, FDG PET has a significantly better specificity than conventional imaging and its findings generated less additional tests and biopsies that ultimately had negative results (5% for FDG PET vs. 17% for conventional imaging). The search for bony metastases in invasive or locally advanced breast cancer can also be performed with FDG, best with PET/CT to enhance sensitivity of PET by highlighting the sclerotic bone metastases, which are frequently FDG negative and easy to detect on CT with their high density in Hounsfield Units. A prospective study comparing several imaging modalities in the preoperative staging of 60 patients with large (> 3cm) breast cancer (23) showed that all distant metastases were detected on FDG PET/CT, while bone scintigraphy (BS) localised only 2 of 6 bone metastases, missed 4 osteoclastic lesions, and led to 7 false-positive results, in cases of degenerative joints, rib fractures, fibrous dysplasia, or enchondroma of the femur. A search in the institutional databases of Memorial Sloan-Kettering cancer hospital led to analyse data of 163 women with suspected metastatic breast cancer who underwent FDG PET/CT and BS (24). When the original report was equivocal, the imaging examination was blindly re-read. Results of FDG PET/CT and BS were concordant in 81% of cases, 20% positive and 61% negative. In 12 of the 31 discordant pairs, pathology confirmed bone metastasis: 9 were FDG positive and BS negative, 1 was FDG positive and BS equivocal and 2 were FDG positive and BS negative. Thus, in case of discrepant findings, FDG was more accurate to detect foci which turned to be malignant. In a comparative study of FDG PET/CT and diffusion-weighted MRI (DWI) the sensitivity and specificity of FDG PET/CT, on a per-patient basis, were both 100%; for DWI, the sensitivity was 86% but the specificity was only 8% (25). False-positive results were very frequent with DWI, including 171 bone lesions unremarkable on MRI and/or BS. Some lesions were diagnosed only on DWI,

but, except for the small primary tumour, these true-positive DWI-only findings did not change the overall assessment of any skeletal region or patient. Based on these data, authors conclude that *„DWI seems to be a sensitive but unspecific modality for the detection of metastatic breast cancer. DWI alone may not be recommended as a whole-body staging alternative to FDG PET(/CT)"*.

FDG PET as a staging procedure in 114 patients with newly-diagnosed clinically intermediate or high-risk breast cancer changed the patient management in 32% of cases, with an intermodality therapeutic change in 20% (26). In subsequent series of patients at initial staging, the impact rate of FDG PET/CT was 5/40 =13% (27) and 15/106 =14% (18). In a "region-based" evaluation (regions included the primary tumour itself, chest wall, lymph node basins and lung, liver and bone) in 75 patients with 95 FDG positive regions, PET/CT improved diagnostic confidence, reduced the number of equivocal lesions from 30 to 5 and was significantly more accurate than CT alone (28).

Overall, FDG PET/CT was considered to have additional value to conventional staging in 13/31=42% of high risk breast cancer patients who had no sign of distant metastases (29), including the prevention of additional examinations in 9 cases.

The impact of FDG PET/CT at initial staging is actually dependent on the disease stage. In the series of Groheux (30), it modified staging for 6% of stage IIA patients, for 15% of stage IIB patients, and for 28% of stage IIIA patients. However, within stage IIIA, the yield was specifically high among the 18 patients with N2 disease (56% stage modification). When considering stage IIB and primary operable IIIA (T3N1) together, the yield of FDG PET/CT was 13% (10/77); extraaxillary regional lymph nodes were detected in 5 and distant metastases in 7 patients. In this series as in most previous studies, FDG PET/CT outperformed BS, with only 1 misclassification vs. 8 for BS.

FDG FOR MONITORING CHEMOTHERAPY OF BREAST CANCER

As mentioned in the ESMO guideline (6), *"the role of PET-CT in response assessment is still under investigation, but it may be used to determine disease progression"*.

Monitoring response to chemotherapy to early detect disease resistance or progression is an important indication since an ineffective regimen of chemotherapy means futile costs and unbalanced toxicity. Many chemotherapy regimens are now in use and the efficacy of FDG to early identify the non-responders should be demonstrated for all types of anticancer agents not just cytotoxics; also, the timing of FDG imaging has to be optimised to obtain the most accurate but also most "operational" prediction of efficacy.

Several studies have been published about the prediction of clinical or pathologic complete response (pCR) after completing the neoadjuvant treatment, based on the evolution of FDG uptake by the tumour between pre-treatment and after few cycles of treatment. This evolution was usually appreciated on SUV (most recently SUVmax) variation, after a variable number of cycles (mostly 1 or 2) using variable threshold for response.

In 2009, a review article by Avril summarized the available data (31). Since then Schwartz-Dose confirmed in 104 patients a relation between pCR and early metabolic response measured with FDG (32). A drop of SUV < 45% or its rise after the 1st cycle had a NPV of 90%, a drop < 55% or a rise after 2 cycles had a NPV of 89%. NPV was similar for combined or sequential association epirubicine + paclitaxel. One group of patients (24/104 = 23%) mostly ER-positive with initial SUV < 3 did not respond to chemotherapy. This finding was confirmed by Martoni (33): 8/34 patients = 24% were ER-positive, their SUV dropped <50% at 2 cycles of anthracycline and taxane-based chemotherapy, and all 8 were non-responders at pathology. Concordantly, Keam (34) observed that ER-negative patients have greater initial FDG SUV but a larger drop during chemotherapy with docetaxel/doxorubicin. Another study on 63 patients reported concordant results (35). To summarise available data, the SUVmax of the breast tumour is decreasing with the number of cycles in most patients, including those who will show residual disease on pathology. It is therefore best to perform FDG PET/CT at baseline and after 1 cycle of chemotherapy only; the criterion for prediction of a lack of complete response at the end of neoadjuvant chemotherapy would be a reduction of less than 50% in the SUVmax of the breast tumour after the 1st cycle.

In our own prospective study (P020907), post-surgical pathology showed in 15 of 22 patients persisting cancer in the primary tumour after sequential neoadjuvant chemotherapy with anthracyclins and then taxanes. Of them, 12 had a reduction of SUVmax of less than 50% (even an increase in 2 cases) after one cycle of anthracyclin. An informative NPV (12/17= 71%) of FDG PET after only one cycle of a sequential regimen was confirmed; however, the PPV was still low after one cycle (2/5= 40% in our study), as it is difficult to rule out the persistence of a small cluster of neoplastic cells. Rousseau addressed the early prediction of response of FDG-positive lymph nodes to neoadjuvant chemotherapy; very similarly to the primary tumour, the best NPV was observed after one cycle, considering a drop in SUVmax <50% (36).

FDG imaging at the end of neoadjuvant chemotherapy has also been proposed, to detect residual tumour. In this setting, FDG PET had lower sensitivity than MRI, mammography and ultrasonography while its specificity was better in a series of 99 patients (37). These results could have been expected: after chemotherapy the mass reduction and the reduction of metabolism of the tumour, even if still viable tissue is present, play against a functional modality with a limited resolution. In contrast, it is clear from the low specificity of anatomical imaging (57% for mammography and less than 40% for the others) that those modalities cannot characterise a residual mass.

Better performance of FDG has been subsequently reported in this context (38, 39), but earlier evaluation in the course of chemotherapy should be recommended.

The response to chemotherapy evaluated by FDG PET either after 1 cycle (35) or at the end of neoadjuvant chemotherapy (40) is a better predictor of recurrence-free survival than pathologic response.

In case of adjuvant chemotherapy for metastatic cancer, the visual interpretation of FDG PET/CT performed after 3 courses (Figures 1, 2) was the best predictor of survival in 47 patients (41).

FDG FOR DETECTING AND RESTAGING RECURRENT BREAST CANCER

"Reasonable suspicion of recurrence of breast cancer" is part of the sufficiently-documented indications of FDG listed in the European Medicines Agency Core SmPC (5). ESMO recommendations for using FDG PET/CT after initial treatment are concordant, and give more details (6): "*PET/CT may be useful for identifying the site of relapse, particularly when traditional imaging methods are equivocal or conflicting. It may also be helpful to identify or confirm the situation of an isolated locoregional relapse or metastatic lesion, since this subset of patients may benefit from a more aggressive multidisciplinary approach*".

Recurrent malignant breast lesions were detected in a more sensitive way by dedicated breast MRI, but PET/CT was more specific; it was also able to detect metastatic spread and changed the management by detection of distant lesions in 6 of 21 patients = 29% (42). In a comparative study of MRI and PET/CT, Schmidt (43) showed that sensitivity (93% and 91%) and specificity (86 and 90%) were similar for both imaging modalities but this was a preliminary study including 23 patients with suspicion of recurrent breast cancer.

FDG PET/CT had higher diagnostic performances (both sensitivity and specificity) than contrast enhanced CT, in 47 women with rising tumours markers 1-21 years after their initial diagnosis (44) (Figure 2), and in 53 patients referred for restaging (45). Similar results were reported more recently in 52 patients with suspicion of recurrence based on elevated levels of tumour markers in 32 cases: patient based accuracy was 96% for PET/CT vs. 73% for contrast-enhanced CT, lesion based sensitivity was 93% vs. 66% and lesion-based specificity 100% vs. 92% (46). Of 89 patients with occult biochemical recurrence (serum Ca 15-3 levels=64.8±16.3 U/mL), cancer lesions were detected in 40 cases (45%), which is a good result in this setting where all other diagnostic modalities have failed (47). In 23/40 patients solitary small lesions were amenable to radical therapy. In 7 out of these 23 patients a complete disease remission lasting more than 1 year was observed. Authors conclude that their findings *„agree with other studies in promoting regular investigations such as tumour markers and FDG-PET/CT rather than awaiting the developments of physical symptoms as suggested by current guidelines, since the timely detection of early recurrence may have a major impact on therapy and survival"*.

In the study of Du (48), bone metastases were found in 67 of 408 consecutive patients with known or suspected recurrent breast cancer on FDG PET/CT; 25 patients had sequential FDG PET/CT examinations identifying bone lesions. FDG was taken-up by the majority of the osteolytic (94%) and mixed pattern (82%) lesions but by fewer osteoblastic lesions (61%). After treatment, 81% of the osteolytic lesions became FDG-negative and osteoblastic on CT and only 19% relatively large lesions remained FDG avid; 52% of the FDG avid osteoblastic lesions became FDG-negative but 48% remained FDG avid and increased in size on CT. The initial FDG uptake appears thus more predictive for the evolution than the radiologic aspect.

With PET/CT, an impact rate on patient management of 24/47 =51% has been reported (44), and more recently, a change in therapeutic management in 29/70 patients =41% (49). In another series, FDG PET changed the management by detection of distant lesions in 6/21 patients =29%

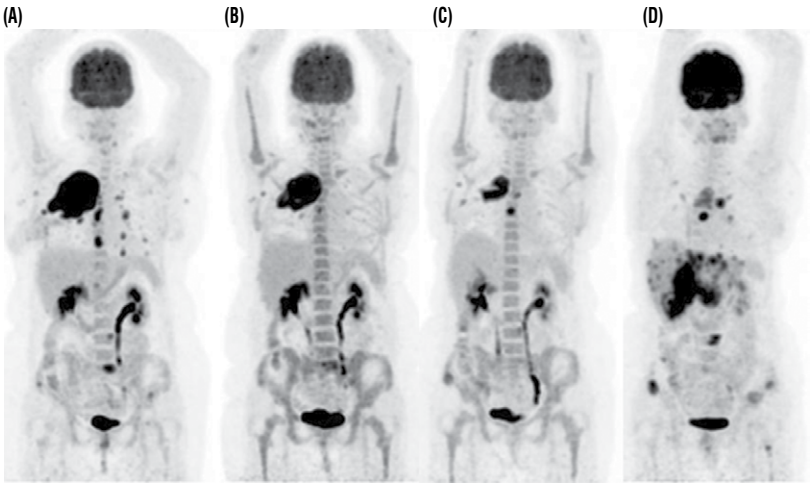

Figure 1. Invasive ductal breast carcinoma grade III, ER+, PR+; Her2-, initially T4cN3M1 (IV) (A). Four months later, partial metabolic response after 4 courses of chemotherapy and activation of bone marrow due to treatment by colony stimulating factors (B). Dissociated metabolic response after 3rd line of chemotherapy: response of the primary tumour, but increased FDG uptake in distant metastases (C). Due to toxicity, the chemotherapy was switched to radiotherapy + tamoxifen which led to partial response of the primary tumour but continuing progression of distant lesions and appearance of new lesions (D).

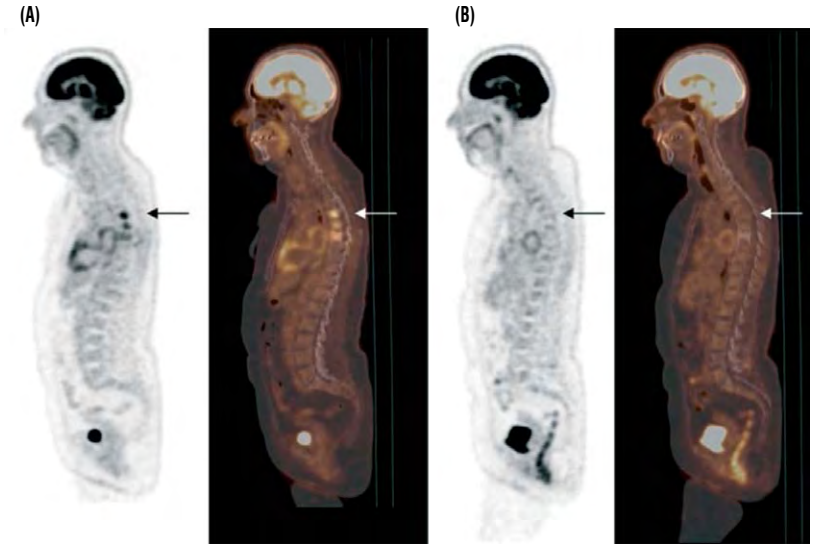

Figure 2. Rising CA 15-3 level (50 U/mL) in patient treated for breast carcinoma 18 years ago. FDG PET/CT revealed foci in thoracic spine (arrow) (A - left image: sagittal FDG PET, right image: PET/CT fusion). Eight months later, complete metabolic response after treatment by letrozole (B).

(42). An impact on therapy was observed with PET/CT in 2/44 patients as compared with the decision based on PET and CT read site by site, or 4/44 = 9% as compared with the decision based on PET alone, and 5/44 = 11% with reference to the decision based on CT alone (50). FDG PET/CT demonstrated hypermetabolic supraclavicular lymph nodes in 33 of the patients referred during year 2005 for radiotherapy of a recurrent breast cancer (51), thus prompting coverage of specific regions of the supraclavicular fossa in radiation field.

A recent systematic review of the performance of FDG PET and PET/CT for the diagnosis of breast cancer recurrence analysed the results of 28 studies and concluded that *"PET/CT appears to show a clear advantage over CT for the diagnosis of BC recurrence and that current recommendations for its use for diagnosing metastatic BC following equivocal findings on conventional imaging techniques appear to be justified"* (52).

Acknowledgement

Part of the results of the clinical research project P00907 has been summarised in this article. This study was funded by the French Ministry of health and the sponsor was AP-HP.

Conflict of interest

We declare no conflicts of interest.

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