COMMENTARY

Is Positron Emission Tomography an Accurate Non-invasive Alternative to Sentinel Lymph Node Biopsy in Breast Cancer Patients?

Ulrich Guller, Egbert Nitzsche, Holger Moch, Markus Zuber

Breast cancer is the most common malignancy among women, leading to approximately 45 000 deaths per annum in the United States *(1)*. The presence of axillary lymph node metastases has major prognostic implications in breast cancer patients *(2,3)*, and it is an important criterion in determining the need for adjuvant chemotherapy *(4)*. Sentinel lymph node (SLN) biopsy has become routine practice in the surgical treatment of patients with breast cancer because the disease status of the SLNs accurately reflects the status of the remaining axillary lymph nodes *(5–7)*. Hence, patients who present with a negative SLN (no metastases) can be spared from having a more traumatic axillary lymph node dissection (ALND), which has been shown to be associated with substantial short- and long-term sequelae *(8,9)*. Despite the enormous advantages of SLN biopsy over ALND in regard to post-operative complications in node-negative patients, it would be of great clinical benefit if a reliable non-invasive method to assess lymph node status in breast cancer patients could be found.

Positron emission tomography (PET) reflects the biochemical and physiologic processes occurring in the tissues being imaged and has been used in diagnosing a variety of malignancies *(10, 11)*. The most frequently used positron emitting radiopharmaceutical is 18-fluor labeled 2-deoxy-D-glucose (^{18}F-FDG), a radioactively labeled glucose analog. The clinical use of ^{18}F-FDG–PET is based on the premise that cancer cells exhibit a higher glycolytic rate than do non-neoplastic cells. Thus, ^{18}F-FDG accumulates predominantly in the tumor tissue and can be visualized by a PET camera. Since the first reported visualization of lymph node metastases with ^{18}F-FDG–PET in a preclinical animal study in 1990 *(12)*, several investigations *(13–19)* have assessed the accuracy of PET in evaluating the nodal status of patients with breast cancer. These investigations have yielded conflicting results, with some investigators doubting that ^{18}F-FDG–PET is capable of accurately assessing the nodal status of breast cancer patients *(13–16)* and others believing that a noninvasive PET scan could replace SLN biopsy at predicting the disease status of the axillary lymph nodes *(17–19)*.

In a recent investigation by an Italian group *(18)*, pre-operative ^{18}F-FDG–PET was compared with the histologic findings of ALND in 167 clinically node-negative T1 (tumor size ≤2cm) and T2 (tumor size >2cm to ≤5cm) breast cancer patients, the largest patient collective published. ^{18}F-FDG–PET detected 68 of 72 patients with axillary metastases, resulting in an overall sensitivity for PET of 94%. In the subset of T2 patients, the sensitivity was even higher (98%; 48/49), with only one false-negative finding. Based on these results, the authors claimed that ^{18}F-FDG–PET can safely predict axillary lymph node status in patients with breast cancer and is a reliable and accurate method to identify patients who can avoid ALND. In the second largest published patient collective *(19)*, pre-operative ^{18}F-FDG–PET was compared with the histologic findings of ALND in 124 pT1–T3 (T3 tumor size >5cm) breast cancer patients. PET scanning correctly identified all 44 patients with axillary lymph node metastases, resulting in an overall sensitivity for PET of 100%. These findings led the investigators of that study to suggest that ^{18}F-FDG–PET should be considered as the initial test in evaluating axillary lymph nodes in breast cancer patients and that those patients without increased axillary ^{18}F-FDG-uptake may not require ALND. Other investigations *(17,20–23)* with smaller patient numbers have reported similar findings, with sensitivities of pre-operative ^{18}F-FDG–PET at detecting axillary lymph-node metastases ranging from 90% to 100%.

In contrast to the above-mentioned investigations, several studies have found that ^{18}F-FDG–PET has a low sensitivity at detecting SLN or axillary lymph node metastases. Indeed, Avril et al. *(14)* suggest that ^{18}F-FDG–PET scanning cannot substitute for histologic analyses of axillary lymph nodes. Their study compared the diagnostic potential of ^{18}F-FDG–PET with ALND in 41 breast cancer patients and reported an overall sensitivity for PET of 79% (19/24). PET sensitivity in the subset of patients with pT1 tumors was, however, only 33%; four of six patients had false-negative results, and the largest metastasis undetected by ^{18}F-FDG–PET measured 12 mm in diameter. Kelemen et al. *(15)* also found low PET sensitivity when they compared ^{18}F-FDG–PET scanning with the histolopathologic findings of SLN biopsies in clinically node-negative T1 and T2 breast cancer patients. If the SLN biopsies were negative by hematoxylin and eosin (H&E) staining, further biopsy sections were obtained for immunohistochemical (IHC) analyses using polyclonal anti-cytokeratin (CK) antibodies. Four of five patients with SLN metastases had false-negative ^{18}F-FDG–PET scans (i.e., ^{18}F-FDG–PET sensitivity was only 20%), and the missed metastases ranged from a micro-metastasis (defined as a cohesive cluster of malignant cells >0.2 mm to ≤2.0 mm in diameter), which was identified by IHC only, to macro-metastases up to 11 mm in

diameter. Furthermore, a Canadian study *(24)* also found low PET sensitivity when evaluating the accuracy of ^{18}F-FDG–PET at detecting axillary lymph node metastases in 41 T1–3 breast cancer patients. All patients underwent pre-operative ^{18}F-FDG–PET scan, SLN biopsy, and ALND. The SLN was examined using serial sectioning and IHC using a monoclonal anti-CK antibody (CAM 5.2 clone) in addition to standard H&E staining. They reported that ^{18}F-FDG–PET was unable to identify SLNs that were found to be node positive by IHC only and that PET had a sensitivity of 27% at detecting axillary lymph node metastases.

We found similar PET sensitivity results in our own investigation *(13)*, in which we compared pre-operative ^{18}F-FDG–PET with the histopathologic analysis of SLN biopsies in 31 clinically node-negative pT1 and pT2 breast cancer patients. SLNs were analyzed by standard H&E staining, IHC (anti-CK antibody cocktail CK22 and monoclonal anti-CK antibody Lu-5), and step sectioning. The step sectioning technique examines adjacent serial sections of the SLN, which are cut at different intervals, making them different thicknesses. Each SLN was analyzed intra-operatively, and lymph nodes that were more than or equal to 5 mm in diameter were bisected along their longitudinal axis into sections of 3–4 mm and snap frozen. The SLNs were intra-operatively examined at three levels with H&E stained sections (cutting interval of 150 μm). If no metastases were diagnosed in the frozen sections, the remaining tissue of the lymph node was formalin-fixed and embedded in paraffin for histologic analysis. This residual tissue was then examined using serial sectioning (cutting interval of 150 μm; at least six levels), and the permanent H&E stained slides were screened for tumor cells. Of the 14 patients with SLN metastases, eight had false-negative results by ^{18}F-FDG–PET scan, including three patients with macro-metastases (4 mm, 4 mm, and 13 mm, respectively), two patients with micro-metastases (0.8 mm and 1 mm, respectively), and three patients with sub-micro-metastases that remained unidentified. Hence, ^{18}F-FDG–PET had an overall sensitivity of detecting SLN metastases of 43% (6/14).

A study from The Netherlands *(16)* that evaluated 70 patients with predominantly early-stage breast cancer who underwent ^{18}F-FDG–PET followed by SLN biopsy and/or ALND has confirmed our finding of low PET sensitivity in detecting axillary lymph node metastases. If the first slice of the SLN was negative for the presence of metastases, an additional four to six sections were examined by H&E staining and IHC (using monoclonal anti-CK antibody CAM5.2). For patients undergoing ALND, up to two slices per lymph node were examined by IHC. The overall sensitivity of ^{18}F-FDG–PET at detecting lymph node metastases was 25% (8/32), and sensitivity was dependent on the tumor load in the axilla and the ^{18}F-FDG avidity of the primary tumor. The authors also found that ^{18}F-FDG–PET was unreliable in the detection of axillary lymph node micro-metastases, regardless of the ^{18}F-FDG avidity of the primary tumor.

Our investigation *(13)* as well as other studies *(2,16,25–27)* indicate that the percentage of detected metastases in lymph nodes increases when using step sectioning and IHC as compared with standard pathology protocols. Most institutions make only one H&E-stained slice from each node obtained from an ALND, or they divide the node in half along its longitudinal axis and make one section from each tissue slice. In addition, serial or step sectioning of lymph nodes is usually not required as a standard procedure. In response to the false-negative rates associated with the SLN biopsy procedure, new pathology protocols

have emerged, including intra-operative serial frozen sections, cytokeratin IHC, and molecular biology techniques such as reverse transcription polymerase chain reaction. IHC and step sectioning techniques are particularly useful in the detection of small tumor infiltrates (i.e., micro-metastases), which often remain undetected using standard histopathologic analyses. Although large retrospective studies *(2)* have shown disease-free and overall survival disadvantages for breast cancer patients with micro-metastases, therapeutic consequences and the prognostic importance of micro-metastases remain a matter of scientific debate. It should be emphasized, however, that both micro- and small macro-metastases cannot be identified by PET scanning, because their diameters (i.e., <3 mm) are below the current spatial resolution of PET imaging, which is currently reported to be between 3 mm and 10 mm *(28–30)*. Hence, investigations comparing pre-operative ^{18}F-FDG–PET with standard histologic analyses of ALND could miss micro-metastases and small macro-metastases by both histologic analysis and PET scanning. Thus, patients with small tumor infiltrates that are undetectable by PET scan (i.e., false-negatives) might be wrongly classified as "true-negatives" by histologic analysis, resulting in incorrectly high sensitivities for PET scanning.

Although step sectioning and IHC would increase the rate of detection of small tumor infiltrates in axillary lymph nodes, the systematic use of these techniques is not feasible in the assessment of ALND specimens because these procedures are prohibitively time consuming and costly *(2)*. In contrast, SLN biopsy offers the advantage that these techniques can be applied on a small number of lymph nodes. Interestingly, all four reported studies *(13,15,16,24)* that compared ^{18}F-FDG–PET with histopathologic analyses of axillary lymph nodes yielded poor sensitivities for PET at detecting metastases (20%–43%, Table 1). The use of step sectioning and IHC in our investigation *(13)* allowed the detection of sub-micro-metastases, all micro-metastases, and one macro-metastasis, all of which were undetected in the intra-operative frozen section analysis and in the initial H&E staining. The failure to detect tiny metastatic foci in large lymph nodes represents a limitation of the frozen section technique used in standard pathology protocols. Indeed, in our study *(13)*, the sensitivity of ^{18}F-FDG–PET at detecting sentinel lymph node metastases, which was initially 88% using standard H&E staining only, dropped to 43% after step sectioning and IHC were also used. It should be emphasized that none of the studies *(17–19)* that suggest that ^{18}F-FDG–PET is a reliable and non-invasive alternative to ALND/SLN biopsy used techniques that would allow the detection of small metastases. Therefore, it is reasonable to assume that the reported values for sensitivities of ^{18}F-FDG–PET in those studies—most of them close to 100%—are overly optimistic and do not accurately reflect the limitations of this diagnostic tool. Therefore, it might be misleading to report the diagnostic potential of ^{18}F-FDG–PET without systematically performing histologic analyses that allow the detection of small tumor infiltrates.

In contrast to the limited sensitivity of PET scanning in the detection of small axillary lymph node metastases, most studies report high specificity *(13,16,20–22,24,32)* (Table 1). Although inflammatory processes, such as abscesses and sarcoidosis, can result in increased ^{18}F-FDG uptake *(33,34)*, the rate of false-positive results is usually low (0–6%) *(13,16,20–22,24,32)*. Due to high accuracy, pre-operative PET scanning has been suggested as a tool for tumor staging of patients with suspected

Table 1. Sensitivity and specificity of ^{18}F-FDG-PET scanning at detecting sentinel lymph node (SLN) and axillary lymph node metastases in patients with breast cancer*

Author, year	No. of patients	Sensitivity, %	Specificity, %	Use of immunohistochemistry (IHC)/step/serial sectioning
Van der Hoeven et al., 2002 (16)	70	25	97	Sentinel lymph node (SLN): Step sections and IHC analyses (monoclonal anti-cytokeratin [CK] antibody CAM 5.2); axillary lymph node dissection specimens: 1–2 additional sections for IHC/node.
Kelemen et al., 2002 (15)	15	20	90	If SLN was negative by hematoxylin and eosin staining, further sections were made for IHC analyses (polyclonal anti-CK antibodies).
Guller et al., 2002 (13)	31	43	94	If SLN was negative by hematoxylin and eosin staining, further step sections and IHC analyses (anti-CK antibody cocktail CK22 and monoclonal anti-CK antibody Lu-5) were performed.
Lovrics et al., 2001 (24)	41	27	98	SLNs: Serial sectioning and IHC analyses (monoclonal anti-CK antibody CAM 5.2).
Greco et al., 2001 (18)	167	94	86	No
Schirrmeister et al., 2001 (31)	85	79	92	No
Yutani et al., 2000 (32)	38	50	100	No
Noh et al., 1998 (21)	27	93	100	No
Smith et al., 1998 (22)	50	90	97	No
Adler et al., 1997 (17)	50	95	66	No
Avril et al., 1996 (14)	41	79	100	No
Scheidhauer et al., 1996 (23)	18	100	89	No
Utech et al., 1996 (19)	124	100	75	No
Crowe et al., 1994 (20)	20	90	100	No

*^{18}F-FDG-PET = 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography.

breast cancer (14,23). Previous studies (14,22) have found that PET scanning is able to provide additional and useful information about the extent of the disease. For example, the identification of distant metastases or tumor involvement of level III axillary lymph nodes, supra-clavicular, or internal mammary lymph nodes might have important implications in regard to the choice of local radiotherapy and systemic chemotherapy (14). However, it is currently premature to recommend a pre-operative PET scan for all patients with suspicious breast masses because the diagnostic, quality of life, and economic implications of this diagnostic tool need further elucidation.

In summary, based on the present literature (14–16) and on own experience (13), we suggest that PET scanning does not currently have the adequate spatial resolution to detect both micro- and small macro-metastatic disease in axillary lymph nodes of patients with breast cancer. Therefore, PET scanning cannot serve at this time as a non-invasive alternative to SLN biopsy. It is possible, however, that with the advent of new detector materials in clinical practice (e.g., lithium, silicon, curved crystals), the sensitivity of ^{18}F-FDG–PET will further improve (35) and could eventually replace invasive procedures in the evaluation of the nodal status of patients with breast cancer.

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