

## Role of FDG PET-CT in evaluation of locoregional nodal disease for initial staging of breast cancer

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Received: November 21, 2014 Revised: March 5, 2014

Accepted: May 16, 2014

Published online: December 10, 2014

### Abstract

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is not indicated or recommended in the initial staging of early breast cancer. Although it is valuable for detecting distant metastasis, providing prognostic information, identifying recurrence and evaluating response to chemotherapy, the role of FDG PET/CT in evaluating locoregional nodal status for initial staging of breast cancer has not yet been well-defined in clinical practice. FDG PET/CT has high specificity but compromised sensitivity for identifying axillary nodal disease in breast cancer. Positive axillary FDG PET/CT is a good predictor of axillary disease and correlates well with sentinel lymph node biopsy (SLNB). FDG PET/CT may help to identify patients with high axillary lymph node burden who could then move directly to axillary lymph node dissection (ALND) and would not require the additional step of SLNB. However, FDG PET/CT cannot replace SLNB or ALND due to unsatisfactory sensitivity. The spatial resolution of PET instruments precludes the detection of small nodal metastases. Although there is still disagreement regarding the management of internal mammary node (IMN) disease in breast cancer, it is known that IMN involvement is of prognostic significance, and IMN metastasis has been associated with higher rates of distant metastasis and lower overall survival rates. Limited clinical observations

suggested that FDG PET/CT has advantages over conventional modalities in detecting and uncovering occult extra-axillary especially IMN lesions with upstaging the disease and an impact on the adjuvant management.

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**Key words:** Breast cancer; Fluorodeoxyglucose positron emission tomography/computed tomography; Locoregional nodal disease; Axillary lymph node; Internal mammary lymph node; Axillary lymph node dissection; Sentinel lymph node biopsy

**Core tip:** The presence and extent of locoregional nodal metastasis at diagnosis is the single most important prognostic factor in breast cancer. The predominant lymphatic drainage pathway from the breast cancer is toward the axilla. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is a good predictor of axillary disease and correlates well with sentinel lymph node biopsy (SLNB). FDG PET/CT may help to identify patients with high axillary lymph node burden who could then move directly to axillary lymph node dissection (ALND) and would not require the additional step of SLNB. However, FDG PET/CT cannot replace SLNB or ALND due to unsatisfactory sensitivity secondary to the limitation of its spatial resolution. The internal mammary node (IMN) involvement is of prognostic significance in breast cancer, and IMN metastasis has been associated with higher rate of distant metastasis and lower overall survival rates. Limited preliminary data indicated that FDG PET/CT plays a role in identification of positive IMN, and it is superior to conventional imaging modalities.

Liu Y. Role of FDG PET-CT in evaluation of locoregional nodal disease for initial staging of breast cancer. *World J Clin Oncol* 2014; 5(5): 982-989 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v5/i5/982.htm> DOI: <http://dx.doi.org/10.5306/wjco.v5.i5.982>

## INTRODUCTION

Breast cancer is the most common solid malignancy in women in the Western world, and a woman's lifetime risk of developing breast cancer exceeds 10%<sup>[1]</sup>. The treatment and prognosis of breast cancer depend on the size of the lesion, pathologic grade, estrogen receptor status, locoregional nodal involvement and metastatic disease. Of these, the presence and extent of locoregional nodal metastasis at diagnosis is the single most important prognostic factor in breast cancer, which is reflected by 5-year survival rates of 99% in the absence of nodal metastasis, and 84% and 23% respectively for locoregional and distant metastatic disease<sup>[2,3]</sup>. An increase in the number of tumor-positive axillary nodes is related to a worsened prognosis irrespective of primary tumor size. Approximately 30% breast cancer with local or locoregional-confined disease eventually relapse<sup>[4,5]</sup>. Therefore, accurate evaluation of locoregional nodal status in breast cancer remains essential because of its implications for treatment and prognosis.

Imaging plays a critical role in the initial evaluation of breast cancer and serves as an important adjunct to surgical, pathologic and clinical staging. Several imaging modalities are used in the diagnosis and staging of breast cancer, including mammography, ultrasonography, computed tomography (CT), magnetic resonance imaging and positron emission tomography/computed tomography (PET/CT). For initial assessment of primary breast cancer, mammography is still the most used modality usually complemented with ultrasonography for the evaluation of axillary nodal involvement. Today metabolic imaging PET/CT with F18-fluoro-2-deoxy-D-glucose (FDG) has gained widespread clinical applications in oncology, and is accepted as a standard care in many malignancies. FDG is an analog of glucose and is used as a tracer of glycolysis. Malignant tissue and cells often demonstrate increased rate of glycolysis for rapid proliferation, due to increased numbers of glucose transporter protein and increased intracellular hexokinase and phosphofruktokinase levels<sup>[6]</sup>. The intensity of FDG is proportional to the rate of glycolysis, therefore is potentially semi-quantitative with standardized uptake value (SUV). It is well known that FDG PET/CT is valuable for detecting distant metastasis, providing prognostic information, identifying recurrence, and evaluating response to chemotherapy<sup>[7]</sup>. However, knowledge of the value of FDG PET-CT for locoregional nodal staging is limited and somehow controversial. This review aims to present the role of FDG PET/CT in evaluating locoregional nodal status of breast cancer.

## FDG PET/CT FOR AXILLARY LYMPH NODES

The most important prognostic factor in breast cancer is the axillary lymph node status. However, management of the axilla in patients with operable breast cancer is

still one of most controversial areas in clinical oncology. The best procedure to examine the axillary lymph nodes is still axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB). SLNB remains the gold standard for axillary nodal evaluation. Lymphoscintigraphy is a radionuclide imaging method to localize sentinel node in the axilla for biopsy. However, SLNB and ALNB carry significant surgical complications<sup>[8]</sup>.

The accuracy of FDG PET-CT for detecting axillary nodal lesion has been studied primarily in early-stage disease. Veronesi *et al*<sup>[9]</sup> compared SLNB and FDG PET/CT in detecting occult axillary metastases in 236 consecutive patients. All patients with pathological confirmed cancer and negative axillae on clinical examinations underwent FDG PET/CT and SLNB. PET/CT identified positive axillary nodes in 43 patients (18.2%), 38 of these were confirmed true-positive on ALND (34) and SLNB (4). The results indicated a high positive predictive value of FDG PET/CT, and those with FDG PET positive axillae preoperatively should proceed directly to ALND without the need for SLNB. But SLNB identified 65 axillary positive cases, which was greater than the number of positive cases identified by FDG PET/CT. FDG PET/CT was unable to detect occult axillary metastases in one third of cases.

In a prospective multicenter trial, FDG PET-CT was performed in 360 women with newly diagnosed invasive breast cancer, and the PET results were compared to pathologic findings<sup>[10]</sup>. Overall, FDG PET was 61% sensitivity and 80% specificity for axillary metastases, with a positive predictive value of 62% and a negative predictive value of 79%. Patients with false negative PET had significantly smaller and fewer tumor-positive lymph nodes than true-positive cases. The results indicated the limitation of FDG PET in detection of micrometastases and small, tumor-infiltrated axillary lymph nodes.

Another prospective study was obtained by Ueda *et al*<sup>[11]</sup>, which evaluated the utility of FDG PET/CT in combination with ultrasound for axillary staging in breast cancer. 183 patients underwent both FDG PET/CT and ultrasound within 5 wk of surgery. All patients had SLNB and/or ALND. FDG PET/CT was positive in the axillary lymph nodes in 40 (22%) patients, 34 (85%) of those were true-positive on correlation with surgical pathology. Of 143 negative PET/CTs, 25 (17%) were false-negative. The sensitivity and specificity of FDG PET/CT were 58% and 95%, respectively. The authors concluded that FDG PET/CT added incremental diagnostic confidence to axillary ultrasonography.

Kim *et al*<sup>[12]</sup> tried to determine whether pre-surgical FDG PET/CT could be used as a guide for ALND or SLNB. 137 patients with biopsy-proven breast cancer underwent preoperative FDG PET/CTs, those who were positive in the axillae went to ALND directly, and those who were negative in the axillae proceeded to SLNB. There were 8 false negative and no false positive scans. The overall sensitivity and specificity of FDG PET/CT in predicting axillary metastases were 77% and 100%. 27

patients were spared unnecessary SLNB by using FDG PET/CT.

A study by Choi *et al*<sup>[13]</sup> suggested that FDG PET/CT has similar sensitivity and specificity to breast ultrasonography in detecting axillary nodal lesions. One hundred and fifty-four consecutive biopsy-proven invasive breast cancer patients were enrolled in this study. All patients had preoperative FDG PET/CT and conventional image studies. Postoperative histopathologic results were used as the final standard. The sensitivity and specificity of FDG PET/CT to detect metastatic axilla were 37.3% and 95.8%, respectively; whereas the corresponding estimates of breast ultrasonography were 41.2% and 93.7%, respectively.

A meta-analysis by Cooper *et al*<sup>[14]</sup> examined 7 studies with a combined 862 patients who underwent PET-CT for breast cancer staging. The mean sensitivity for detecting nodal metastasis was 56%. However, although the overall sensitivity of nodal evaluation in early-stage breast cancer is low, PET-CT still outperformed traditional imaging modalities.

The sensitivity of FDG PET-CT for axillary nodal metastasis depends on both axillary tumor burden and FDG avidity of primary tumor<sup>[15,16]</sup>. A significantly higher proportion of metastases are detected in patients with aggressive histologic features.

In a study of 61 consecutive breast cancer patients by Heusner *et al*<sup>[17]</sup>, FDG PET/CT was obtained and compared to either SLNB or ALND, or both. Of 24 histologically positive axillae, FDG PET/CT predicted lymph node involvement in 17. In 14 true positive PET/CT cases, the mean diameter of the nodal lesions was 9 mm (range 4-22 mm). In 10 false negative PET/CT cases, the mean diameter of the axillary nodes was 3 mm (range 0.8-6 mm). The overall sensitivity was 58%, and specificity was 92%.

In a more recently published Ontario Clinical Oncology Group Study with 325 patient enrollments and ALND or SLNB as the gold standard following FDG PET/CT, the sensitivity, specificity, positive predictive value and negative predictive value were 23.7%, 99.6%, 95.8% and 75.4%<sup>[18]</sup>. Using logistic regression, primary tumor size was predictive for prevalence of the nodal lesion and for PET sensitivity.

Table 1 outlines the major studies about the role of FDG PET/CT in evaluation of axillary nodal disease in breast cancer.

In conclusion, the data above indicate that positive axillary FDG PET/CT is a good predictor of axillary disease and correlates well with SLNB. FDG PET/CT may help to identify patients with high axillary lymph node burden who could then move directly to ALND and would not require the additional step of SLNB<sup>[1]</sup>. However, FDG PET/CT cannot replace SLNB or ALND due to unsatisfactory sensitivity. False-negative FDG PET/CT in the evaluation of the axillary disease is mainly secondary to small size of the lymph nodes. A negative scan cannot exclude micrometastasis in the axilla. The spatial resolution (approximately 5-6 mm) of PET instruments

precludes the detection of small nodal metastases.

## FDG PET/CT FOR INTERNAL MAMMARY LYMPH NODES

Although the predominant lymphatic drainage pathway from the breast cancer is toward the axilla, nodal metastases outside the axilla may be present in up to 56% of breast cancer<sup>[1]</sup>. The sites of extra-axillary nodes include the internal mammary chain, interpectoral space, supraclavicular/infraclavicular region<sup>[19,20]</sup>. In which, breast cancer drainage to internal mammary node (IMN) happens in as many as 30% of patients<sup>[21,22]</sup>. Most of IMN metastases have concomitant axillary metastases, but 8%-10% patients with breast cancer may have IMN metastases only<sup>[23]</sup>.

The presence of IMN metastasis is classified as stage N3. IMN involvement is of prognostic significance in breast cancer, and IMN metastasis has been associated with higher rate of distant metastasis and lower overall survival rates<sup>[24-28]</sup>. Yao *et al*<sup>[24]</sup> examined the relationship between lymphoscintigraphic evidence of IMN drainage and survival in early stage breast cancer patients. The results show a near 3-fold increase mortality in IMN positive patients. Prognosis of patients with both axillary and IMN metastases is poor when compared with axillary nodal metastasis only<sup>[29]</sup>. IMN involvement might predict treatment failure, early recurrence or distant metastasis in breast cancer<sup>[30]</sup>. Multiple studies have consistently found that medial breast cancers carry a worse prognosis compared with lateral cancer, even after adjusting for other known prognostic factors. Because there is no plausible evidence that medial tumors are more biologically aggressive, it is likely that the worse outcome is a result of the un-treatment of IMN metastases, which is more common in medial cancer<sup>[31,32]</sup>.

The assessment of IMN remains a challenge. IMN metastasis is often clinically occult. Visualization of IMN drainage by lymphoscintigraphy depends on the use of peritumoral injection<sup>[24]</sup>, and drainage to IMN varies by locations of tumors<sup>[24]</sup>. The peritumoral, or intratumoral injection of radiotracer was a useful method for identifying a significant portion of tumors that have primary IMN drainage because anatomic studies have shown that IMN is supplied primarily by retro-mammary lymphatic<sup>[33,34]</sup>. With peritumoral or intratumoral injection technique, up to 25% IMN drainage could be identified by lymphoscintigraphy<sup>[21,34]</sup>. However, subareolar injection, which improves axillary lymph node detection, rarely shows IMN uptake due to the superficial lymphatic channels. Although the gold standard for establishing the status of IMN metastasis is surgical, most surgeons do not routinely perform IMN sampling or dissection due to the relative inaccessibility and lack of convincing data for established survival benefit<sup>[26,33]</sup>. In studies where biopsy was performed for hot internal mammary sentinel node on lymphoscintigraphy, tumor was detected patho-

**Table 1** The studies evaluating the role of fluorodeoxyglucose positron emission tomography/computed tomography in axillary lymph nodes in breast cancer

Author	Year	Patient No.	Ref.	PET/CT Sensitivity (%)	PET/CT Specificity (%)	PET/CT PPV (%)	PET/CT NPV (%)	Conclusions
Wahl <i>et al</i> <sup>[10]</sup>	2004	360	ALND	61	80	62	79	FDG PET was limited in detection of micrometastasis
Veronesi <i>et al</i> <sup>[9]</sup>	2007	236	SLNB	37	96	88	66	High specificity of FDG PET/CT indicated that patients with positive PET should have ALND directly
Ueda <i>et al</i> <sup>[11]</sup>	2008	183	SLNB and/or ALND	58	95	85	83	Diagnostic accuracy of PET/CT was nearly equal to ultrasound
Kim <i>et al</i> <sup>[12]</sup>	2009	137	ALND or SLNB	77	100	100	94	FDG PET/CT could help to select patients for either ALND or SLNB
Heusner <i>et al</i> <sup>[17]</sup>	2009	61	SLNB	58	92	82	77	FDG PET/CT could not replace invasive approaches for axillary staging
Choi <i>et al</i> <sup>[13]</sup>	2012	154	Biopsy or additional imaging and follow-ups	37	96	83	74	FDG PET/CT could not be recommended as a primary diagnostic procedure
Groheux <i>et al</i> <sup>[16]</sup>	2011	70	SLNB or US-FNA	63	91	63	91	FDG PET/CT might impact cancer management in small portions of patients
Koolen <i>et al</i> <sup>[3]</sup>	2012	290	SLNB or US-FNA	82	92	98	53	FDG PET/CT could be recommended as a standard staging procedure
Pritchard <i>et al</i> <sup>[18]</sup>	2012	325	SLNB or ALND	24	100	96	75	FDG PET/CT was not sufficiently sensitive to detect positive axillary nodes

FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography; PPV: Positive predictive value; NPV: Negative predictive value; ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy.

logically in 8% to 27% of patients<sup>[33]</sup>. Usually, if there is drainage to IMN, there is concomitant drainage to axillary node. In such case, general practice is surgical excision of only axillary sentinel node<sup>[22]</sup>. Systemic treatment strategy is rarely influenced by IMN metastasis, due to concurrent axillary nodal metastasis and unfavorable primary tumor characteristics. Most of these patients would need adjuvant therapy such as chemotherapy and/or radiation and/or hormonal therapy. However, two recent European studies showed that IMN dissection improved accuracy of breast cancer staging and survival<sup>[35,36]</sup>. The patients with IMN metastases had a better 5-year survival after IMN radiotherapy and chemotherapy<sup>[34]</sup>. Heuts *et al*<sup>[36]</sup> also suggested that tailored adjuvant systemic therapy and additional parasternal radiotherapy have a beneficial effect on the prognosis of these patients. However, the value of IMN radiation is uncertain and subject of debate partially due to a concern about the risk of cardiac toxicity associated with IMN radiotherapy<sup>[36]</sup>.

Although data are limited regarding the role of FDG PET/CT for IMN metastasis in breast cancer, some studies had demonstrated that FDG PET is superior to conventional diagnostic techniques in the detection of extra-axillary nodal metastases, particular to the IMN. Eubank *et al*<sup>[37]</sup> compared the detection rates of CT and FDG PET/CT in 73 patients with recurrent or metastatic breast cancer. All patients had CT and PET/CT within 30 d of each other. The prevalence of abnormal FDG uptake in the IMN or mediastinum doubles that of abnormal CT findings in the extra-axillary nodal regions. FDG PET/CT could uncover disease in these nodal regions not detected by conventional staging methods. In

another prospective study with 154 preoperative patients with breast cancer by Choi *et al*<sup>[13]</sup>, 7 extra-axillary nodal lesions were detected by FDG PET/CT only although all patients had additional conventional imaging studies. Aukema *et al*<sup>[38]</sup> found that in 60 breast cancer patients with tumor size greater than 3 cm and/or proven axillary nodal metastasis, pre-chemotherapy FDG PET/CT detected abnormal IMN in 8 patients. In 4 of the 8 patients, treatment planning was changed and radiotherapy was added. Koolen *et al*<sup>[3]</sup> reported that in 310 patients with breast cancer and scheduled for neoadjuvant chemotherapy, FDG PET-CT detected 26 (8%) abnormal IMN. PET/CT findings helped selecting patients for postoperative internal mammary chain radiotherapy. Bernsdorf *et al*<sup>[39]</sup> analyzed FDG PET/CT data of 103 consecutive patients with newly diagnosed operable breast cancer and tumors greater than 2 cm. Extra-axillary lymph node involvement was detected in the internal mammary chain by PET/CT in 10 patients, 5 of them had adjuvant treatment modifications. Recently, Wang *et al*<sup>[40]</sup> reported the role of FDG PET/CT in the detection of IMN metastases with pathologic correlation in a large series of patients. One hundred and ten of 1259 patient had FDG avid IMNs on PET/CT. Twenty-five patients underwent ultrasound-guided fine needle aspiration of suspicious IMN based on PET/CT, and 20 IMNs (80%) were cytologically proven metastases from the primary breast malignancies. The results indicated a very high likelihood of malignant involvement of FDG avid IMNs. In another recently reported study by Koolen *et al*<sup>[41]</sup>, pre-chemotherapy FDG PET/CT scans identified IMN nodal lesions in 17 of 278 patients with breast cancer. The results show

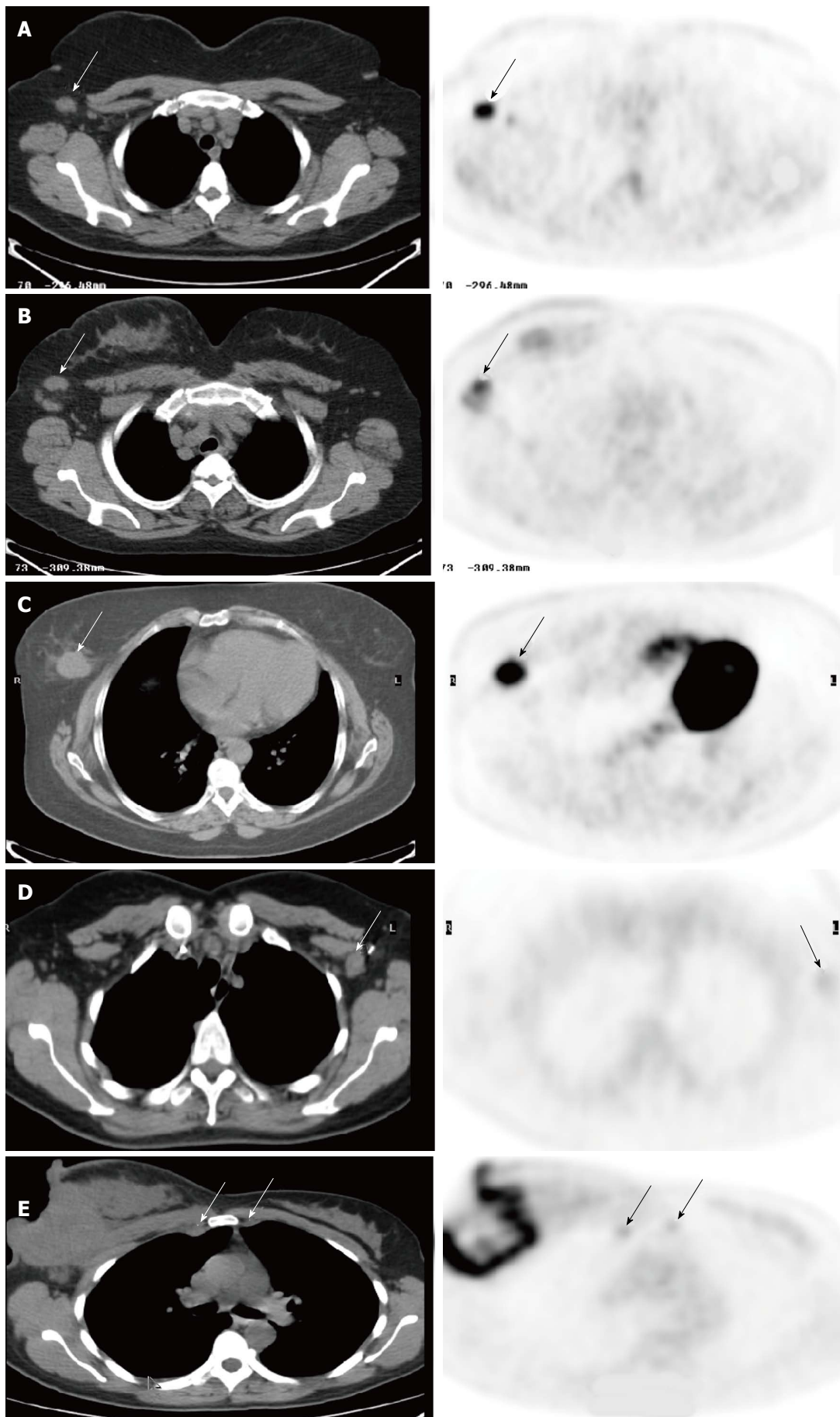


Figure 1 Fluorodeoxyglucose positron emission tomography/computed tomography. A: In a 61-year-old woman with newly diagnosed breast cancer. There was

a single palpable axillary lymph node on physical examination. The images demonstrated a 1.5 cm axillary node with intense uptake (SUV 10, arrows), consistent with metastasis. There were also additional smaller axillary nodes with abnormal uptake. The patient underwent axillary lymph node dissection (ALND), and surgical pathology revealed that two axillary nodes were positive; B: In a 51-year-old woman with newly diagnosed right breast cancer. There were palpable right axillary lymph nodes on physical examination. The images demonstrated a few enlarged right axillary nodes with intense uptake (SUV 6.5, arrows). The patient had ALND, which showed three metastatic lymph nodes; C: In a 54-year-old woman with newly diagnosed right breast cancer. The images showed a 3.0 cm fluorodeoxyglucose (FDG) avid tumor in the right breast (arrows), but were negative in the right axilla. The patient had lymphoscintigraphy for sentinel lymph node biopsy, which was negative for axillary metastasis; D: In a 40-year-old woman with history of left breast cancer and post lumpectomy. On physical examination, there was a palpable lymph node in the left axilla. Positron emission tomography/computed tomography (PET/CT) showed a 1.5 cm left axillary lymph node with very mild uptake (SUV 1.4, arrows), consistent with a benign etiology. Subsequent SLNB confirmed lymphadenitis; E: FDG PET/CT in a 41-year-old woman with newly diagnosed inflammatory carcinoma of the right breast. In addition to large right breast necrotic mass and axillary nodal lesions, there are a 1.2 cm right internal mammary node (IMN) and a 1.0 cm left IMN, and both are mildly FDG avid (SUV 3.2) and suspicious for IMN metastases (arrows). The patient was excluded as a surgical candidate based on FDG PET/CT findings. She received chemotherapy and radiation. SUV: Standardized uptake value.

that FDG PET/CT contributes to pretreatment staging and therapy planning, upstaging substantial proportion of patients to the high risk group, thereby potentially changing prognosis and possibly implicating postoperative irradiation.

In conclusion, there is a significant disagreement in the oncologic community regarding the management of IMNs in breast cancer, most likely due to the difficulties in assessment of IMN and conflicting evidence of significance of IMN treatment. Lymphoscintigraphy may help to identify the IMN drainage, but the IMN sampling or dissection is much more difficult than for axillary nodes, and only a small portion of hot sentinel IMNs are positive for metastases on pathological studies. As a non-invasive imaging modality, FDG PET/CT plays a role in identification of positive IMN, which may renew the oncologists' interest in IMN management. But to date, the data regarding FDG PET/CT for IMN in breast cancer are very limited, and more clinical studies are warranted.

## CASE EXAMPLES

Figure 1 illustrate the role of FDG PET/CT in locoregional nodal staging of breast cancer. In the case 1 and 2 (Figure 1A and B), FDG PET/CT was positive in the axillae. The patients avoided SLNB and directly had ALND. Pathology confirmed true-positive PET/CT findings.

FDG PET/CT was negative in the axilla in the case 3 (Figure 1C), and suggested a benign axillary lymph node in the case 4 (Figure 1D). In spite of negative PET/CT results, both patients had SLNB due to large primary tumor (the case 3) or palpable axillary lymph node (the case 4). SLNB demonstrated negative axillary disease consistent with PET/CT findings.

In the Case 5 (Figure 1E), FDG PET/CT identified positive IMNs, which updated staging, and subsequently changed the patients' managements.

## CONCLUSION

Although FDG PET/CT is valuable for detecting distant metastasis, identifying recurrence and evaluating response to chemotherapy, the role of FDG PET/CT in evaluating locoregional nodal status for initial staging of breast cancer has not yet been well-defined in clinical practice. FDG PET/CT is not recommended as a routine imaging modality for initial staging of early breast cancer<sup>[42]</sup>,

although the direct scientific evidence to support this recommendation is limited. FDG PET/CT has high specificity but compromised sensitivity for identifying axillary nodal disease in breast cancer. Positive axillary FDG PET/CT is a good predictor of axillary disease and correlates well with SLNB. FDG PET/CT may help to identify patients with high axillary lymph node burden who could then move directly to ALND and would not require the additional step of SLNB. However, FDG PET/CT cannot replace SLNB or ALND due to unsatisfactory sensitivity. The spatial resolution of PET instruments precludes the detection of small nodal metastases.

There are substantial disparities in regard to the significance of IMN in breast cancer, and evaluation of IMN status is difficult in practice. Limited Data suggested that FDG PET/CT has advantages over conventional modalities in detecting and uncovering occult extra-axillary especially IMN lesions with upstaging the disease and an impact on the adjuvant management.

Positive FDG PET/CT is highly predictive for locoregional nodal disease in locally advanced breast cancer. Although the indications and role in initial staging of breast cancer remain to be validated, FDG PET/CT can be used in concert with other imaging modalities especially for patients with high risk.

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