Prospective evaluation of fluorine-18 fluorodeoxyclucose positron emission tomography in breast cancer for staging of the axilla related to surgery and immunocytochemistry

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Abstract. The noninvasive staging of axillary lymph nodes for metastases is investigated in patients with breast cancer prior to surgery by positron emission tomography (PET) with fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG). In 124 patients with newly diagnosed breast cancer, whole-body PET was performed to determine the average differential uptake ratio (DUR) of ^{18}F-FDG in the axillary lymph nodes. Results were correlated with the number of the dissected lymph nodes, size of the primary tumor, tumor type, tumor grade, estrogen and progesterone receptors, DNA ploidy, and the proportion of cells in the synthetic phase of the cell cycle (S-phase). In this prospective study of 124 patients with breast carcinoma, PET correctly categorized all 44 tumor-positive axillary lymph nodes, a sensitivity of 100%. Sixty tumor-negative axillary lymph nodes were negative by PET and 20 tumor-negative axillary lymph nodes were positive by PET. No false-negative PET findings were encountered. A weak correlation was found between DUR and tumor size as well as between DUR and the S-phase of the tumor. In patients with breast carcinoma, ^{18}F-FDG PET can be of value in evaluating axillary lymph nodes for metastatic involvement prior to surgery. It is of particular importance that no false-negative PET findings were encountered, and axillary lymph node dissection might not be necessary in patients without axillary uptake by PET. The DUR of the positive axillary lymph nodes seems to bear a relationship with some of the purported prognostic parameters of the primary tumor.

Key words: Positron emission tomography – Fluorine-18 fluoro-2-deoxy-D-glucose – Breast tumors – Axillary lymph nodes

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Introduction

Breast cancer continues to increase as a worldwide hazard to women, and in the United States alone, 46300 women died from this illness and 183000 were afflicted with it in 1993 [1–3]. Axillary lymph node status remains the single most important prognostic indicator in patients with newly diagnosed breast cancer [4]. As a result, many patients undergo axillary lymph node dissection (ALND) for accurate pathologic staging. Axillary node dissection is not without risks, and its morbidity and costs can be avoided if a noninvasive examination provides similar information.

In 1938, Otto Warburg [5] described a higher rate of glycolysis in malignant cells, which is the underlying mechanism of metabolic imaging. This was first clinically employed in 1953, when Brownell and Sweet [6] used positron emitters to localize brain tumors. In their investigation of CNS tumors with positron emission tomography (PET), Di Chiro and co-workers were the first to use the glucose analog fluorine-18 fluoro-2-deoxy-D-glucose (^{18}F-FDG) [7]. Since then PET has emerged as a noninvasive biochemical imaging technique to identify primary tumors and metastases [8–18]. Recently, the glucose analog ^{18}F-FDG was used to investigate breast tumors with single-photon emission tomography (SPET) [19].

Materials and methods

Prior to any therapeutic intervention, 124 patients with newly diagnosed and histologically proven breast carcinoma were studied by PET. The average age of the patients was 59 years (range 32–94 years), the average weight 73 kg (range 44–132 kg), and the average height 163 cm (range 140–183 cm). Clinical staging revealed lymph nodes in ten patients, while mammography reports mentioned axillary lymph nodes only in four patients. The diagnosis was established by core biopsy in 52 patients, by excisional biopsy (lumpectomy) in 67, and by wide excision (partial mastectomy) in five.

Of the 124 patients, 68 underwent modified radical mastectomy, 28 partial mastectomy and lymph node dissection, ten lump-

ectomy and lymph node dissection, and seven re-excision and lymph node dissection after biopsy. One patient had a bilateral modified radical mastectomy. Ten patients did not undergo additional surgery after biopsy since the tumor was completely excised, but underwent separate nodal dissection. The anatomic levels of the axillary lymph nodes (levels I–III) were determined by their position relative to the pectoralis minor, latissimus dorsi, and chest wall. The written pathology report was the basis for evaluating the number and extent of involved lymph nodes.

In all patients, the pTNM histopathologic classification and grading [20] of the primary tumor was used for citing the stage of the cancer. Of the 124 patients, 65 were classified as pT1N0M0, 22 as pT2N1M0, 17 as pT1N1M0, 13 as pT2N0M0, four as pT3N1M0, and one each as pT1N2M0, pT2N2M0, and pT3N0M0. The histopathologic tumor types comprised 102 invasive ductal, seven invasive lobular, eight invasive mixed ductal and lobular tumors, and seven invasive intraductal tumors with Paget's disease (Table 1). The histopathologic grading was GI in 14 patients, GII in 57, GIII in 47, and GIV in six patients. The average interval between biopsy and node dissection was 7 days (range 0–47 days). The profile of the primary tumor, which was determined in three different laboratories, included the immunocytochemical assay of estrogen (ER) and progesterone receptors (PR), DNA flow cytometry for estimation of DNA content (ploidy), and the fraction of cells in the synthetic phase of the cell cycle (S-phase fraction or SPF). The study was approved by the hospital's institutional review board and all patients gave an informed consent.

The ^{18}F-FDG was produced with an RDS 112 cyclotron (Siemens/CTI, Knoxville, Tenn.), using a standardized technique subsequently approved by the FDA. The scans were obtained with a whole-body PET scanner (ECAT 951-031, Siemens/CTI, Knoxville, Tenn.). The patients fasted at least 4 h prior to the study, with the majority of patients undergoing an overnight fast and having the scan performed the next morning [21]. Serum glucose was monitored prior to injection of ^{18}F-FDG to exclude hyperglycemic patients. All patients underwent a four bed position scan over an axial length of 40 cm, commencing at the lower neck and extending into the abdomen to include the liver. All patients had transmission scans performed (5 min per bed position, approximately 100 million counts), obtained with an integral ring source of germanium-68. Immediately after the transmission scan, a standard dose of 10 mCi of ^{18}F-FDG was injected intravenously through a previously placed catheter. Sixty minutes was allowed for the uptake of the tracer, followed by the emission scan without moving the patient. The emission scan was acquired at 10 min per bed position (average counts 10 million per bed position). The images were reconstructed by filtered back projection with a Hann filter using a cutoff at 0.4 of the sampling frequency. The image resolution was 10.2 mm FWHM. Images were corrected for randoms, detector efficiency, photon attenuation, dead time, and radioactive decay. The pixel values of the reconstructed images were calibrated to radioactivity concentrations expressed in mCi/ml. Differential uptake ratio (DUR) was calculated for axillary nodal uptake, utilizing a previously described methodology [22]. A cutoff point of the DUR values was selected to be 1–3 for metastases and 3 and higher for tumor.

The images were initially reviewed by three experienced nuclear radiologists and the final reading for this study was rendered by an experienced nuclear medicine physician, from a hard copy (8 in.×10 in. film) and a video monitor using a gray-scale display (commercially available software from Siemens/CTI, Knoxville, Tenn.). The observer's knowledge of the patients was limited to biopsy-proven breast carcinoma and blinded to the lymph node status. A scan was read as positive if a discrete focal uptake greater than background was present. Otherwise, the scan was read as negative.

Table 1. Tumor histopathology

1=infiltrating, well-differentiated ductal carcinoma
2=infiltrating, well-differentiated carcinoma and DCIS
3=infiltrating, well-differentiated carcinoma, mucinous type
4=infiltrating ductal carcinoma with scirrhous components
5=infiltrating ductal carcinoma, cribriform type
6=infiltrating ductal carcinoma, apocrine type
7=infiltrating, moderately differentiated carcinoma
8=infiltrating, moderately differentiated carcinoma, comedo type
9=infiltrating, poorly differentiated carcinoma
10=infiltrating, poorly differentiated carcinoma with chondroid and osseous metaplasia
11=infiltrating, poorly differentiated carcinoma, comedo type
12=infiltrating, excessive multifocal carcinoma
13=metaplastic carcinoma, matrix-producing type
14=medullary, circumscribed carcinoma
15=infiltrating, mixed ductal and lobular carcinoma
16=infiltrating lobular carcinoma
17=multifocal lobular carcinoma
18=Paget's disease with intraductal carcinoma

D: Ductal carcinoma
L: Lobular carcinoma
N: Nipple carcinoma

Results

All primary breast tumors were accurately visualized by PET (Fig. 1).

All 44 patients with surgically confirmed metastatic lymph nodes were correctly categorized as true-positive by ^{18}F-FDG (Fig. 2), corresponding to a sensitivity of 100%. The extension of the axillary nodal involvement was not recorded. The histopathologic type of the 44 tumor-positive axillary lymph nodes was infiltrating ductal carcinoma in 39 patients, infiltrating lobular carcinoma in three, and invasive ductal carcinoma with Paget's disease in two. The size of the primary tumor measured <1 cm in one patient, >1 cm in 11, >2 cm in 15, and >3 cm in 17. The tumor grade was GI in one patient, GII in 23, GIII in 16, and GIV in three. The S-phase was low in 14 tumors, moderate in 11, and high in 16. DNA ploidy was aneuploid in 22 patients, diploid in 12, tetraploid in six, and hypertetraploid in three. It was hypotetraploid in one patient. ERs were found in 33 and PRs in 26 tumors. The average DUR of the tumor-containing axillary lymph nodes was 3.7 (range 1.3–17.7). The relationship of the DUR to size, grade, S-phase, and ploidy of the primary tumor is shown in Table 2.

All 60 patients with surgically tumor-negative axillary lymph nodes were found to be true-negative by ^{18}F-FDG (Fig. 1), corresponding to a negative predictive value of 100%. The histopathologic type of the primary tumor of the 60 tumor-negative axillary lymph nodes was

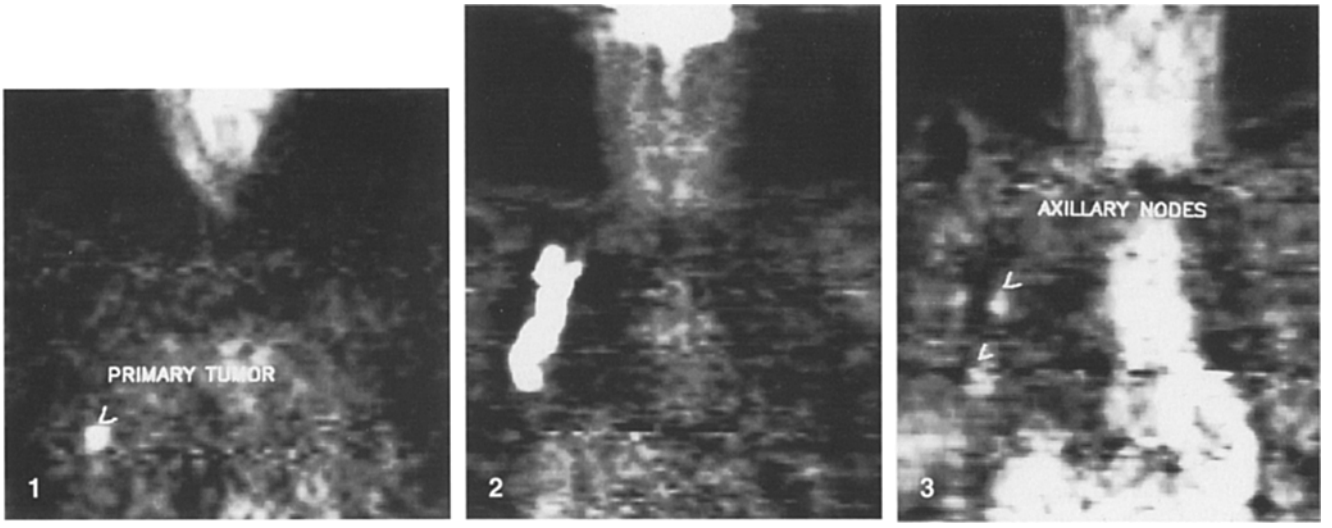

Fig. 1. Anterior ^{18}F-FDG PET images showing uptake in the primary tumor of the right breast and no uptake in the axilla

Fig. 2. Anterior ^{18}F-FDG PET images showing intense uptake in nodal metastases in the right axilla (true-positive finding)

Fig. 3. Anterior ^{18}F-FDG PET images showing focal areas of moderate uptake in the right axilla without evidence of tumor by surgical node dissection (false-positive finding)

infiltrating ductal carcinoma in 56 patients, infiltrating lobular carcinoma in two, and invasive intraductal carcinoma with Paget's disease in two. The tumor size measured <1 cm in 12 patients, >1 cm in 28, >2 cm in 11, and >3 cm in nine. The tumor grade was GI in 12 patients, GII in 24, GIII in 23, and GIV in one. The S-phase was low in 27 tumors, moderate in nine, and high in 14. DNA ploidy was aneuploid in 29 patients, diploid in 24, tetraploid in four, and hypertetraploid in three. ERs were found in 40 tumors and PRs in 33. These findings are summarized in Table 3.

In the remaining 20 patients, ^{18}F-FDG detected metabolically active, but tumor-free axillary lymph nodes (Fig. 3). The average DUR of these lymph nodes was 2.6 (range 1.2–14.2). In these patients with false-positive axillary lymph nodes, the histopathology of the primary tumor was infiltrating ductal carcinoma in 19 patients and lobular carcinoma in one. The S-phase was low in 11 tumors, moderate in five, and high in two. DNA ploidy was aneuploid in six patients, diploid in 12, and tetraploid and hypoploid in one each. ERs were found in 13 tumors and PRs in 12. A summary of these findings is shown in Table 4. Of these 20 patients with false-positive results, 16 had axillary lymph node dissection of level I and four of level I–II. Except for two patients, who were found to have reactive changes in the lymph nodes, there was no mention of inflammatory findings in the histopathology reports of the dissected lymph nodes. With the exception of one patient, the intravenous injection of ^{18}F-FDG was given on the side contralateral to the primary breast tumor.

The average number of dissected lymph nodes was 20 (range 7–39) for the true-positive, 16 (range 7–36) for the true-negative, and 20 (range 9–46) for the false-positive group. The distribution of the histopathologic subtypes, comprising poorly and moderately differentiated tumors, was the same in the dissected true-positive, true-negative, and false-positive axillary lymph nodes, and did not depend on the number of lymph nodes removed.

The clinical follow-up of the 20 patients with false-positive axillary lymph nodes after 1–2 years showed no recurrence of the disease. Four patients received radiotherapy alone, four patients radiotherapy in combination with hormone therapy, and two patients radiotherapy in combination with chemotherapy. Five patients only received hormone therapy and one only chemotherapy. Four patients did not undergo any supplemental therapy after surgery.

Discussion

The visualization of ^{18}F-FDG uptake even in small tumors confirms the high sensitivity of PET [23] and the superiority of PET over SPET [19]. The low sensitivity in visualizing tumors smaller than 1.4 cm with ^{18}F-FDG SPET found in a prospective study of breast tumors [19] can be attributed to the inferior resolution of SPET in comparison to PET.

More importantly, this study showed that ^{18}F-FDG PET can correctly predict the pathologic stage of the level I axillary lymph nodes in patients with breast carcinoma prior to surgery. It is of particular importance that no false-negative PET findings were encountered. This study further suggests, but cannot prove, accurate ^{18}F-FDG PET staging of the axillary lymph nodes at the levels II and III since level II dissection was not performed in every case and level III dissection was not performed at all.

Table 2. Relation of tumor specification and DUR in true-positive axillary lymph nodes

	No. of patients (%) (n=44)	Differential uptake ratio (%)	
		1–3[d]	>3[d]
Tumor size (cm)			
<1	1 (2)	0	1 (2)
>1	11 (25)	8 (18)	3 (7)
>2	15 (34)	9 (21)	6 (14)
>3	17 (39)	8 (18)	9 (20)
Tumor grade[a]			
Grade 1	1 (2)	1 (2)	0
Grade 2	23 (52)	15 (34)	8 (18)
Grade 3	16 (36)	9 (20)	7 (16)
Grade 4	3 (7)	1 (2)	2 (4)
Tumor histopathology[b]			
D 9	12 (27)	5 (11)	7 (16)
D 7	10 (23)	6 (14)	4 (9)
D 8	4 (9)	3 (7)	1 (2)
D 15	4 (9)	3 (7)	1 (2)
D 6	3 (7)	2 (5)	1 (2)
D 12	3 (7)	1 (2)	2 (5)
L 16	3 (7)	2 (5)	1 (2)
D 5	2 (5)	1 (2)	1 (2)
N 18	2 (5)	2 (5)	0
D 2	1 (2)	0	1 (2)
S-phase[c]			
Low	14 (32)	10 (23)	4 (9)
Moderate	11 (25)	7 (16)	4 (9)
High	16 (36)	7 (16)	9 (20)
Ploidy			
aneuploid	22 (50)	14 (31)	8 (18)
Diploid	12 (27)	7 (16)	5 (11)
Tetraploid	6 (14)	2 (4)	4 (9)
Hypertetraploid	3 (7)	2 (4)	1 (2)
Hypotetraploid	1 (2)	1 (2)	0
Estrogen receptor	33 (75)	21 (48)	12 (27)
Progesterone receptor	26 (59)	16 (36)	10 (23)

[a] Tumor grade: G 1=well differentiated, G 2=moderately differentiated, G 3=poorly differentiated, G 4=undifferentiated
[b] Tumor histopathology: see Table 1
[c] Three patients not quantifiable
[d] 1–3, cut-off point for metastases; 3, cut-off point for tumor

Table 3. Tumor specification in true-negative axillary lymph nodes

	No. of patients (%) (n=60)
Tumor size (cm)	
<1	12 (20)
>1	28 (47)
>2	11 (18)
>3	9 (15)
Tumor grade[a]	
Grade 1	12 (20)
Grade 2	24 (40)
Grade 3	23 (38)
Grade 4	1 (2)
Tumor histopathology[b]	
D 7	13 (22)
D 9	13 (22)
D 3	6 (10)
D 11	5 (8)
D 12	5 (8)
D 15	4 (7)
D 2	3 (5)
D 1	2 (3)
D 13	2 (3)
N 18	2 (3)
L 16	2 (3)
D5, D 8, D 14 each	1 (2)
S-phase	
Low	27 (45)
Moderate	9 (15)
High	14 (23)
Ploidy	
Aneuploid	29 (48)
Diploid	24 (40)
Tetraploid	4 (6)
Hypertetraploid	3 (5)
Estrogen receptor	40 (66)
Progesterone receptor	33 (55)

[a] Tumor grade: G 1=well differentated, G 2= moderately differentiated, G 3=poorly differentiated, G 4=undifferentiated
[b] Tumor histopathology: see Table 1

Only a weak correlation between DUR of the metastatic axillary lymph nodes and tumor size as well as between DUR and S-phase of the primary tumor was found, with no correlation detected between DUR and other tumor parameters. The relationship between DUR and hormone receptors was not determined. The weak correlation between DUR of the metastatic axillary lymph nodes and size and S-phase of the primary tumor supports the predictability of the patient's outcome from parameters derived from the primary tumor [24–27]. This needs further research outside the scope of our investigation.

The status of the axillary lymph nodes has been repeatedly shown to be the most important prognostic factor, and the finding of the axillary lymph node dissection remains the gold standard for the patient's prognosis [28]. PET with ^{18}F-FDG is a noninvasive method for the evaluation of the axillary lymph nodes. Why 20 of 80 patients with tumor-free lymph nodes had increased uptake, with reactive changes found only in two patients, is undetermined. These false positive findings might benefit from the complementary use of lymphoscintigraphy. Because of its sensitivity of 100% (no false-negative findings) found in our series, PET should be considered

Table 4. Relation of tumor specification and DUR in false-positive axillary lymph nodes

	No. of patients (%) (n=20)	Differential uptake ratio (%)	
		1–3[c]	>[c]
Tumor size (cm)			
<1	3 (15)	3 (15)	0
>1	10 (50)	10 (50)	0
>2	4 (20)	1 (5)	3 (15)
>3	3 (15)	2 (10)	1 (5)
Tumor grade[a]			
Grade 1	1 (5)	1 (5)	0
Grade 2	10 (50)	8 (40)	2 (10)
Grade 3	8 (40)	6 (30)	2 (10)
Grade 4	1 (5)	1 (5)	0
Tumor histopathology[b]			
D 7	7 (35)	5 (25)	2 (10)
D 9	6 (30)	6 (30)	0
L 16	1 (5)	0	1 (5)
D 1	1 (5)	0	1 (5)
D 2, 3, 5, 8, 17 each	1 (5)	1 (5)	0

[a] Tumor grade: G 1=well differentiated, G 2=moderately differentiated, G 3=poorly differentiated, G 4=undifferentiated
[b] Tumor histopathology: see Table 1
[c] 1–3, cut-off point for metastases; 3, cut-off point for tumor

the initial test in evaluating the axillary lymph nodes. If our findings can be confirmed, patients without increased axillary uptake need not undergo an axillary node dissection, avoiding the morbidity and costs of this procedure.

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