2-(fluorine-18)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography after breast conserving surgery: Correlation with molecular markers of breast cancer

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ABSTRACT

Aim: To investigate the role of 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) early after breast-conserving surgery (BCS) in patients with breast cancer (BC) and whether we can determine which molecular biomarkers of breast carcinoma put the patients at risk. **Materials and Methods:** This retrospective study involved 88 patients with histologically proven T1 or T2 BC, who were treated with BCS and underwent ^{18}F-FDG PET/CT study. The correlation between biological markers (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 [HER2], and Ki-67) of the primary tumor and ^{18}F-FDG PET/CT findings was analyzed. **Results:** ^{18}F-FDG PET/CT demonstrated the presence of BC disease (locoregional disease [LRD], distant metastases, or contralateral BC) in 26 of 88 patients (29.5%). Regarding immunohistochemical profiles, BC expressing high levels of Ki-67 were associated with an increased percentage of LRD, which was the major recurrence pattern on ^{18}F-FDG PET/CT. Although the BC disease was observed more commonly in patients with HER2 positivity compared to those of HER2 negative, the difference did not reach statistical significance. The patients with T2 tumor or a higher histopathological grade had a higher percentage of BC disease. **Conclusions:** This study demonstrated that patients with early stage BC treated with BCS have a remarkable risk of the presence of BC even early after surgery, and there was a clinically important relationship between ^{18}F-FDG PET/CT findings and biological markers of BC. These findings suggest that high-risk molecular biomarkers (Ki-67, HER2) can be taken into account in the decision-making the process for both preoperative imaging and planning of the surgical approach.

Keywords: Breast neoplasms, fluorodeoxyglucose F18, human epidermal growth factor receptor 2, Ki-67 antigen, mastectomy, positron emission tomography, segmental

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women.[1] The widespread screening programs and multimodal therapies have significantly increased the proportion of women with BC eligible for breast conservation.[2] The goal of breast conserving surgery (BCS) is to excise all tumors in patients with invasive and *in situ* cancer and to achieve long-term disease control with a minimum local morbidity and a good cosmetic result.[3] The clinical use of 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been evaluated for diagnosis, staging, restaging, and monitoring response to therapy in BC.[4] Although ^{18}F-FDG PET/CT is recommended for evaluation of

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distant metastasis (DM) and regional lymph node (LN) status in advanced stage BC,[5] routine preoperative systemic staging with 18F-FDG PET/CT is not recommended in patients with Stage 1, Stage 2, and operable Stage 3 BC.[6] There were limited studies on 18F-FDG PET/CT findings early after mastectomy reported in the literature. However, the role of 18F-FDG PET/CT early after breast-conserving therapy has not been specifically discussed yet. The currently available data in the literature regarding BCS makes it necessary to stratify patients according to their relative risk of recurrence or progression.[7]

Therefore, in this retrospective study, we here investigated the role of 18F-FDG PET/CT early after BCS in patients with T1 or T2 breast carcinoma and to determine which molecular biomarkers of breast tumors put the patients at risk.

MATERIALS AND METHODS

Patient population

This retrospective study included 88 BC patients (mostly high risk) (51.5 ± 12.3 years, range: 22–82 years) who were treated with BCS and referred to our clinic between July 2008 and December 2014. In all, primary tumor size was <5 cm (unilateral T1 or T2 tumor) and no signs of distant metastases were detected on conventional diagnostic modalities preoperatively. Breast-conserving surgical treatment was either lumpectomy, quadranectomy or segmental mastectomy accompanied by sentinel LN biopsy (SLNB) (in all clinically eligible patients) or axillary dissection. Patients with a history of neoadjuvant chemotherapy or radiotherapy before 18F-FDG PET/CT were excluded. All patients were performed after an informed consent was obtained.

Histological type of the BC, the pathological size of the tumor, axillary LN status, histological grade, and biological markers of the tumor (expression of estrogen receptor [ER], progesteron receptor [PR], human epidermal growth factor receptor 2 [HER2], and Ki-67 index) were assessed from the pathological records. ER and PR were scored as positive with a cut-off value of at least 10% tumor cell nuclear staining. Tumors with a score of 1+ were classified as HER2 positive. Ki-67 proliferation index were scored as positive with a cut-off of 14%.[8] ER, PR, and HER2 status were available for 76 tumors (86.6%) and Ki-67 index for 68 tumors (77%). Furthermore, only in four patients, T stage, lymph nodal involvement, and histological grade were not obtained from the records. Axillary LN status was determined by the SLNB and/or axillary dissection.

Molecular classification of five subgroups were made according to different combinations of ER, PR, HER2, and Ki-67 status and following the recommendations of the 12th International Breast Conference.[9]

SLNB was performed in 36 patients, and LN involvement was found in only 9 of them. Axillary LN dissection was performed in a total of 48 patients.

Statistical analysis

Categorical data are expressed as proportions and were analyzed using Fisher's exact test. Continuous variables were reported as mean ± 1 standard deviation. The correlation among variables was evaluated with Spearman's test. All probability values were two-tailed, and differences were considered as statistically significant when probability values were <0.05.

2-(fluorine-18)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography imaging

18F-FDG PET/CT images were taken during the early postoperative period, ranging between 1 and 5 months (median: 1 month, 1.27 ± 0.7 months). All examinations were performed using a discovery ST-PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin, USA). Although oral hydration with glucose free water was allowed, all patients fasted for 6 h prior to the PET/CT study. Oral contrast was used on a routine basis in all of the cases (Omnipaque 300/50 ml). Patients' blood glucose levels obtained just before injection of 18F-FDG were <200 mg/dl. 18F-FDG (5 MBq/kg) was intravenously injected into the arm opposite to the tumor using a venous line to prevent extravasation. Approximately 1 h later, low-dose CT scan was acquired during shallow breathing and included the areas from the upper thigh to the skull base with a 16-slice multidetector scanner using the following parameters: 80 mA, 140 kV, and 5.0 mm section thickness. A standard whole-body PET scan was taken in a three-dimensional mode with an acquisition time of 4 min per bed position (5–7 bed positions) covering the same field of CT. The acquired data were reconstructed using an iterative algorithm and noncontrast-enhanced CT images were acquired for attenuation correction. After the acquisition, data were transferred to a workstation (Advantage Windows Workstation 4.5, GE Healthcare) for processing and interpretation. The CT, PET, and coregistered PET/CT images were reviewed in transaxial, coronal, and sagittal views.

2-(fluorine-18)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography interpretation

18F-FDG PET/CT images were evaluated by two experienced nuclear medicine physicians. If a consensus was not reached, patients were consulted to a third or fourth reader. For recurrence and metastasis, pattern, 18F-FDG uptake, and CT findings were considered altogether. All foci with pathologic uptake (higher than liver activity) and not corresponding to physiologic uptake sites were reported as positive for malignancy. The expected imaging findings in the postconservation breast was taken into consideration, and breast uptake was carefully evaluated in the early postoperative period to reveal the nonmalignant inflammatory change.[10] The lesions that were thought to possibly have a benign appearance on PET or CT slices, such as those due to trauma or inflammation, also reported as negative on the basis of the pattern.

Disease patterns on 18F-FDG PET/CT were defined as (a) ipsilateral locoregional disease (LRD) that indicates the presence

of tumor in the ipsilateral breast (whether in the same quadrant or not), in the locoregional skin, or in regional LNs (including axillary, the ipsilateral internal mammary, supraclavicular, and infraclavicular nodes) (b) DM and (c) contralateral BC (CBC) was defined as tumor in contralateral breast or in contralateral axillary LN.[11]

The reference standard

All of the ipsilateral/contralateral breast lesions, 11 of 18 regional lymph nodal lesions and 2 of 9 distant metastatic lesions were histopathologically confirmed by needle biopsy and/or surgery. For the remaining lesions, conventional imaging modalities together with clinical follow-up at least 6 months and/or follow-up FDG PET/CT studies used to confirm or exclude suspected positive FDG PET/CT findings.

RESULTS

The characteristics of patients are summarized in Table 1. The ductal histology was the most prevalent type (76 patients, 86.4%). The average tumor size was 2.37 ± 0.95 cm (range from 0.5 cm to 5 cm). BC phenotype was identified in 69 of the 88 breast tumors. Due to the absence of some immunohistochemical parameters, the breast tumors were not classified in the remaining 19 patients.

^{18}F-FDG PET/CT demonstrated the presence of BC disease (any of LRD, DM, CBC or all) in 26 of 88 patients (29.5%) [Figure 1]. The major recurrence pattern was LRD, which was detected in 20 patients (22.7%). DM was present in nine patients (10.2%) and CBC in two patients (2.3%) [Table 2].
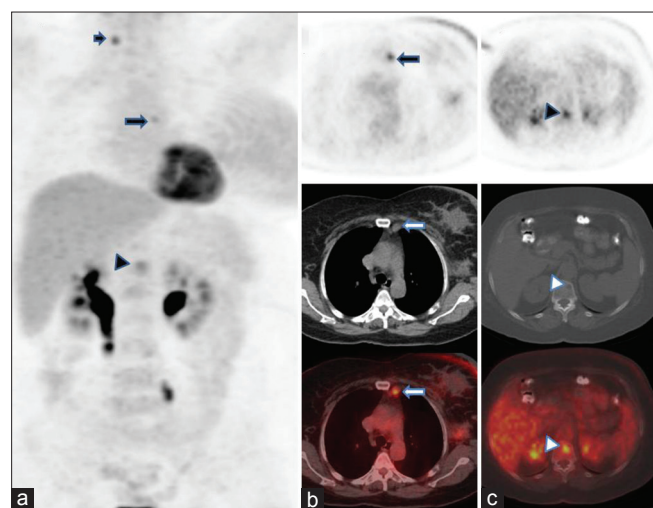

Figure 1: (a) 2-(fluorine-18)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomographyin early postoperative period revealed (b) a mild to moderate hypermetabolic left internal mammarian lymph node (maximum standardized uptake value: 4.7) and (c) the lytic lesion at T12 vertebrae corpus (maximum standardized uptake value: 5.6). Additionally moderate hypermetabolic biopsy verified benign thyroid nodule was also seen (maximum standardized uptake value: 5.9)

Regarding immunohistochemical profiles, BC expressing high levels of Ki-67 were associated with an increased percentage of LRD (14/44: 31.4% vs. 0/22: 0%, $P = 0.003$). There was no statistically significant relationship between hormone receptor status (ER or PR positivity) and BC disease after surgery [Table 3].

The patients with T2 tumor had a higher percentage of BC disease compared to those of T1 tumor (LRD: 16/54: 29.6% vs. 2/30: 6.6%, BC disease: 22/54: 40.7% vs. 3/30: 10%, $P = 0.014$ and $P = 0.003$, respectively). A higher percentage of patients with Grade III tumors (17/40, 42.5%) showed BC disease compared to those of Grade II (8/40, 20%) and Grade I (0/4, 0%) (Spearman's, $r = 0.279$, $P = 0.01$). Although the BC disease was more common in patients with HER2 positivity (40.6% vs. 20.5%) compared to those of HER2 negative, the difference did not reach a statistically significant

Characteristics	n (%)
Histology	
Invasive ductal	76 (86.4)
Invasive lobular	3 (3.4)
Medullary	3 (3.4)
Musinous	3 (3.4)
Mixed (ductal + lobular)	2 (2.3)
Micropapillary	1 (1.2)
Molecular phenotype	
Luminal A	15 (17)
Luminal B-HER2 (−)	18 (20.5)
Luminal B HER2 (+)	26 (29.5)
HER2 (+)	4 (4.5)
Basal	6 (6.8)
T staging	
T1	30 (34.1)
T2	54 (61.4)
Lymph node ınvolvement	
N0	41 (46.6)
N1-3	43 (48.8)
Tumour site	
Right	40 (45.5)
Left	48 (54.5)
Histologic grade	
I	4 (4.5)
II	40 (45.5)
III	40 (45.5)
N/A	4 (4.5)
ER status	
No	10/75
Yes	65/75
PR status	
No	29/76
Yes	47/76
HER2 status	
No	44/76
Yes	32/76
Ki67 index status	
<14%	24/68
>14%	44/68

HER2: Human epidermal growth factor receptor 2, ER: Estrogen receptor, PR: Progesteron receptor, N/A: Not available

(P = 0.057). There was no influence of axillary LN involvement on the presence of BC after surgery.

DISCUSSION

In BC patients staging of the disease plays a crucial role in treatment planning. However, routine systemic staging with ^{18}F-FDG PET/CT is not recommended in the early stage and operable BC patients.[6] ^{18}F-FDG PET/CT is considered as an optional imaging modality not only in early stages but also for advanced stages. Despite this, several authors have found that

Table 2: Overall results of ^{18}F-FDG PET/CT

BC disease	*n* (%)
Locoregional disease	20 (22.7)
Ipsilateral breast tissue	2
Regional Lymph nodes	18
Ipsilateral axillary	12
Ipsilateral internal mammarian	4
Ipsilateral supraclavicular	2
Distant metastasis	9 (10.2)
Cervical lymph nodes	1
Mediastinum	3
Bone	5
Liver	3
Spleen	1
Surrenal gland	1
Abdominal lymph nodes	1
Contralateral BC	2 (2.3)
Contralateral breast tissue	1
Contralateral axillary lymph nodes	1

PET/CT: Positron emission tomography/computed tomography,
^{18}F-FDG: 2-(fluorine-18)-fluoro-2-deoxy-D-glucose, BC: Breast cancer

initial staging ^{18}F-FDG PET/CT may modify the therapeutical approach to the BC patients either by upstaging or downstaging of the disease.[12-16] On the other hand, recent studies suggested an individualized diagnostic workup in BC patients with a higher risk at initial staging.[17] It has been stated that ^{18}F-FDG uptake was the highest in BC's with poor prognostic features such as high grade, hormone receptor negativity, triple negativity, metaplastic tumors, HER2 and Ki-67 positivity and these features could be helpful in the selection of the best candidates for a baseline ^{18}F-FDG PET/CT study.[8,17-19]

In the present study, according to our highly selected patient group who were treated surgically with a less aggressive approach that preserves remnant ipsilateral breast tissue (according to BCS criteria), the major disease pattern was LRD in the early postoperative period, which was detected in 22.7% the patients. In routine oncology practice, ^{18}F-FDG PET/CT is recommended in patients who had clinically palpable axillary LNs. In patients whom had no clinically palpable axillary LNs, as in our group, SLNB is suggested rather than ^{18}F-FDG PET/CT. Nevertheless, our study showed that in 12 of the 88 patients (13.6%) had positive metastatic axillary LN in ^{18}F-FDG PET/CT despite negative SLNB and axillary LN dissection. This relatively high rate of discordance deserves attention and suggests the false-negative SLNB or incomplete axillary dissection.

^{18}F-FDG PET/CT has a limited role in the detection of primary breast tumors. Positron emission mammography even with a higher imaging resolution can be used only as a useful adjuvant to mammography.[20] However, in this study, even though the clear

Table 3: Biological correlates and patterns of BC

	Locoregional disease		Contralateral BC		Distant metastasis		BC metastasis	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
ER								
Negative	7	3	10	0	10	0	7	3
Positive	54	11	63	2	57	8	47	18
PR								
Negative	22	6	27	1	27	1	20	8
Positive	39	8	46	1	40	7	34	13
HER2 status								
Negative	38	6	43	1	23	1	35	9
Positive	23	9	31	1	38	6	19	13
Ki67 index								
Negative	24	0	23	1	23	1	22	2
Positive	30	14[a]	43	1	38	6	25[a]	19
T status								
1	28	2	29	1	28	2	27	3
2	38	16[b]	53	1	47	7	32[b]	22
Histologic grade								
1	4	0	4	0	4	0	4	0
2	24	6	38	2	37	3	32	8
3	28	12	40	0	34	6	23	17[c]
Lymph node involvement								
Negative	31	10	39	2	37	4	28	13
Positive	35	8	43	0	38	5	31	12

[a]$P<0.05$ (Fisher's exact test) compared to those of Ki67 index (−) patients; [b]$P<0.05$ (Fisher's exact test) compared to those T1 patients; [c]$P=0.01$, $r=0.279$ (Spearman's) compared to those of Grade I and Grade II patients. ER: Estrogen receptor, PR: Progesteron receptor, HER2: Human epidermal growth factor receptor 2, BC: Breast cancer, Ki67 (−): Ki67 index <%14, Ki67 (+) Ki67 index >%14

surgical margins, multifocal, and multicentric tumors in remnant breast tissue without axillary involvement was also depicted on ¹⁸F-FDG PET/CT in two cases. It is questionable for these two cases whether preoperative ¹⁸F-FDG PET/CT can shift the surgical procedure from BCS to total mastectomy.

Our data also demonstrated that the patients with BC expressing high levels of Ki-67, T2 tumors, Grade III histopathology and HER2 positivity had a higher risk for progression of BC disease early after BCS.

The nuclear-associated antigen Ki-67 protein is a nuclear protein that expressed during cellular proliferation. Overexpression of Ki-67 corresponds to the high proliferation rate of tumor cells and is an independent factor for worse prognosis in BC patients.[21] Ki-67 index was also used as the main marker to distinguish between luminal A and luminal B BC subtypes.[8] In line with previous studies, a high level of Ki-67 is an unfavorable predictor of LRD and DM similar to our study, in which clinically important relationship was found.[22,23]

The HER2 regulates cell growth, survival, and differentiation. HER-2 amplification and overexpression have been reported in 15–30% of all BC cases and are associated with more aggressive disease, as in our study.[24]

Although there were reports on ¹⁸F-FDG PET/CT findings early after surgery or at initial staging preoperatively, the analyze of the biological correlates of ¹⁸F-FDG PET/CT findings early after breast-conserving therapy has not been reported yet. BC is a heterogenous class of tumors with distinct subtypes and molecular characteristics with different responses to systemic and local therapies.[25] There is growing interest on the identification of predictive surrogate markers for stratifying BC patients into distinct subgroups after therapy.[26] The St. Gallen International Expert Consensus Panel strongly recommended the clinicopathological determination of ER, PR, HER2, and Ki-67 when planning targeted therapies in patients with early BC.[9] Likewise individualized therapeutic strategy, the recent data, and our study suggests an individual determination of the diagnostic strategy in breast carcinoma.

Molecular markers of BC were obtained from the postoperative material in our study. It raises the question whether we identify the high-risk BC patients according to their status of the molecular markers with tru-cut biopsy, can we reduce the risk of undertreatment by directing them to ¹⁸F-FDG PET/CT before surgery. Further studies are needed to investigate the role of ¹⁸F-FDG PET/CT in BC patients with high-risk molecular markers identified by tru-cut biopsy before surgical intervention.

Limitations of the study

The percentage of the presence of BC disease was surprisingly high. This can be explained by a referral bias that caused by the surgeons who ordered ¹⁸F-FDG PET/CT scans mostly to the high-risk patients after BCS. Although there were retrospective

studies close to this ratio in the literature,[15] prospective studies are needed to overcome this problem. In addition, most of these lesions might exist in the preoperative period. Since it could not be evaluated by the conventional methods, ¹⁸F-FDG PET/CT have found such a relatively high rate. If ¹⁸F-FDG PET/CT was performed before surgery, clinical stage and the surgical decision might be changed approximately in 30% of the cases.

The reference standard in this study included a variety of follow-up type. The lack of availability of histopathological data for all of the metastatic sites appears to be a disadvantage, but it was not possible to obtain histopathological confirmation of all lesions in routine practice due to practical, ethical and technical reasons. On the other hand, physiological or inflammatory uptake sites can be easily defined on coregistered ¹⁸F-FDG PET/CT images. This study was a retrospective analyze of the patients after BCS, and the maximum standardized uptake values of primary BC were not available. The patient population was relatively small in accordance to the inclusion criteria for the study, and our data will need confirmation in larger studies.

CONCLUSIONS

This study demonstrated that patients with early stage BC treated with BCS have a remarkable risk of the presence of BC even early after surgery. Considering the heterogeneous patterns of BC, high-risk molecular predictors should be taken into account at the initial diagnostic workup due to the presence of a clinically important relationship between ¹⁸F-FDG PET/CT findings and biological markers of BC.

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Conflicts of interest

There are no conflicts of interest.

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