



Breast Cancer: Comparison Study between Early Stage and Locally Advanced Disease



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Abstract

Aim: Initial staging in breast cancer is considered as locoregional and systemic disease. Distant metastases is rarely expected in early stage breast cancer patients. Although, we observed that, stage is not as clinically expected after staging with FDG PET-CT both in early and advanced stage breast cancer. Our main objective was to test the hypothesis by comparing the distant metastases rate on initial FDG PET-CT in a group of early stage to advanced stage breast cancer patients. Assessment of associations between distant metastases and tumor T stage was a second objective of the present retrospective study.

Materials and methods: A total of 114 patients with breast cancer (age range: 25-77, mean: 51.1) who underwent PET-CT for initial staging were enrolled. All patients were diagnosed by tru-cut, core or FNAB before imaging and had confirmed breast malignancy.

Results: The mean SUVmax of primary breast lesions in a total of 114 patients was found to be 7.64 (range: 1.45-20.94). PET-CT detected distant metastasis in 24 of the 114 patients. Of the total 34 metastatic regions, 41.1% (14/34) was bone/bone marrow metastasis, 5.9 % (2/34) was lung metastasis, 14.7 % (5/34) was mediastinal lymph node metastasis, 5.9 % (2/34) was liver metastasis, 5.9 % (2/34) had other organ/system metastasis, and 26.5 % (9/34) had other lymphadenopathies. According to T staging, the percentages of distant metastasis were as follows: 6.5 % of the 46 T1 stage patients, 23.6 % of the 55 T2 stage patients, and 88.8 % of the 9 T4 stage patients.

Conclusion: FDG PET-CT led to a change in the stage of disease and the treatment approach in newly diagnosed breast cancer in both early stage or advanced stage patients. PET-CT imaging in patients with T1c to T4 breast lesions are suggested to underwent PET-CT examinations for cancer initial staging before any treatment.

Keywords: FDG PET-CT; breast cancer; Initial staging; Distant metastasis

Introduction

Initial staging in breast cancer is considered as locoregional and systemic disease. Regional disease includes axillary and internal mammary lymph node metastases and important in early stage breast cancer. In patients with locally advanced breast cancer (LABC), the risk of infra and supraclavicular lymph node metastases is high, as well as axillary and internal mammary lymph nodes. The status of metastatic lymph nodes is very important in terms of changing the treatment process. Distant metastases is rarely expected in early stage breast cancer patients. Although, we observed that, stage is not as clinically expected after staging with 18-Fluorodeoxyglucose Positron emission tomography-Computed tomography (FDG PET-CT) both in early and advanced stage breast cancer. Currently, FDG PET-CT is not a part of the conventional work-up among newly diagnosed breast cancer patients. Nevertheless, in certain

clinical situations PET-CT may be of great significance, especially as treatment algorithm. Criteria for selection of patients who would benefit most from a PET-CT scan is still not clear for breast cancer patients. Our main objective was to test the hypothesis by comparing the distant metastases rate (DMR) on initial FDG PET-CT in a group of early stage to advanced stage breast cancer patients. Assessment of associations between distant metastases and tumor T stage was a second objective of the present retrospective study.

Materials and Methods

Patients

A total of 114 female patients (age range: 25-77, mean: 51.1) with primary breast malignancies (64 left and 50 right breast) underwent PET-CT examinations for cancer initial staging.

Informed consent was obtained from all individual participants included in the study. All patients were diagnosed by tru-cut, core or FNAB before imaging and had confirmed breast malignancy. Patients who were diagnosed by excisional biopsy, mastectomy-axillary lymph node dissection history or axillary lymph node metastasis diagnosed by excisional biopsy were excluded from study.

Imaging protocol

All patients fasted for at least 6 h before an FDG injection of 370MBq (10mCi). PET-CT scans were obtained 60 min after injection using an integrated scanner (GE Discovery PET-CT 610, US). A whole-body CT scan was performed without intravenous contrast administration with 130 kV, 50 mAs, a pitch of 1.5, a section thickness of 5mm and a field of view of 70cm. A PET scan was performed immediately after an unenhanced CT scan and acquired from the skull base to the upper thigh with a 3-min acquisition per bed position using a three-dimensional acquisition mode.

Diagnostic criteria for benign and malignant lesions

Histopathology and follow-up information after PET-CT scanning served as the standard of reference. For final assessment standards of references for breast lesions was based on biopsy in all patients. Standards of references for metastatic lesions were biopsy, interval growth, reduction after chemotherapy, clinical and imaging follow-up.

Image analysis

PET-CT images were qualitatively evaluated and assessed in consensus by two nuclear medicine physicians (readers A and B with more than 10 years of experience) on PET-CT. PET-CT images were viewed in the coronal, axial, and sagittal sections. SUVmax (Standardized uptake value maximum) of lesions were calculated on images by using region of interest (ROI) included at least two-thirds of the lesions. The quantitative uptake values of FDG (SUVmax) in the lesion ROIs were semiautomatically calculated using workstation (GE).

Statistical analysis

Statistical analysis was carried out with SPSS software (SPSS Inc., Chicago, Illinois,

USA). A P value of less than 0.05 was considered statistically significant.

Table 1: Illustrates all 24 metastatic patients.

Age (Year)	Lesion Size	Primary lesion SUVmax	Multicentricity	Axillary LN Status	Axillary LN SUVmax
46	20	5.2	+	+	7.96
48	25	12.44	-	-	-
63	23	5.26	-	-	-
41	36	7.83	+	+	5.09
54	47	14.17	-	+	10.3
62	98	18.53	-	+	5.13

Result

A total of 114 female patients (age range: 25-77, mean: 51.1) with primary breast malignancies (64 left and 50 right breast) underwent PET-CT examinations for cancer initial staging. In total 114 patients, 35 patients (30.7%) had multi-centric breast ca, whereas 79 patients (69.3%) had single focus. In 35 multi-centric patients, 24 were positive for axillary LN (68.6%) and 11 were negative (31.4%). Ten of the multi-centric 35 patients were positive for metastases (28.6%) and 25 were negative (71.4%). A total of 5 patients (14.3%) had a positive internal mammary lymph node.

The mean SUVmax of primary breast lesions in a total of 114 patients was found to be 7.64 (range: 1.45-20.94). Axilla was positive in 53 patients (46.5%) and negative in 61 patients (53.5%). The average axillary lymph node (LN) SUVmax value was 6.6 (range: 1.5-25.08) in patients with positive axillary LN.

PET-CT detected distant metastasis (DM) in 24 of the 114 patients. Of the total 34 metastatic regions in 24 metastatic patients, 41.1% (14/34) was bone/bone marrow metastasis, 5.9% (2/34) was lung metastasis, 14.7% (5/34) was mediastinal lymph node metastasis, 5.9% (2/34) was liver metastasis, 5.9% (2/34) had other organ/system metastasis, and 26.5% (9/34) had other lymphadenopathies. The mean age of 24 patients with DM was 49.75 (range: 25-75 years). The mean size of the primary malignancy of the 24 patients with distant metastases was found to be 37.4 (range: 13-100mm). The mean primary lesion SUVmax of patients with distant metastases was calculated as 9.37 (range: 2.04-24.52) which was higher significantly ($p < 0.05$) than that of total patients' breast lesion SUVmax value. Table 1 illustrates all 24 metastatic patients. Primary lesion region were left breast in 17 of 24 DM patients and right in 7 of total DM patients. In ninety patients without DM, 47 patients had left, 43 had right breast primary lesion. DM positive 3 patients had negative axillary lymph node (LN), 9 patients had multi-centricity, 3 patients had positive internal mammary (IM) LN. According to T staging, the percentages of distant metastasis were as follows: 6.5% of the 46 T1 stage patients, 23.6 % of the 55 T2 stage patients, and 88.8 % of the 9 T4 stage patients. T stage numbers in all 114 patients were illustrated in Table 2 and T stage in metastatic 24 patients were shown in Table 3.

54	17	5.95	-	+	6.27
73	28	4.49	+	+	6.87
50	14	5.13	-	+	6.6
75	20	6.22	-	+	12.03
48	26	10.15	-	+	4.03
28	15	15.58	-	+	2.62
62	33	10.28	-	+	11.4
54	13	2.04	-	+	5.75
27	34	24.52	+	+	25.08
43	15	5.44	-	-	-
52	70	12.38	-	+	13.75
39	30	7.35	+	+	10.28
57	40	5.6	+	+	2.93
41	35	4.9	+	+	4.58
64	37	5.06	-	+	2.33
25	100	16.4	+	+	4.5
38	100	11.71	+	+	12.2
50	21	8.14	+	+	11.85

Table 2: T stage numbers in all 114 patients.

Tumour T Stage	Total Patient N	Metastatic Patient N
T1a	0	0
T1b	6	0
T1c	33	3
T2	55	13
T3	4	0
T4a	0	0
T4b	6	5
T4c	3	3
T4d	0	0

Table 3: T stage in metastatic 24 patients.

Primary Tumour T Stage		Patient Number
	T1a	0
	T1b	0
	T1c	3
	T2	13
	T3	0
	T4a	0
	T4b	5
	T4c	3
	T4d	0

IM lymph nodes were positive in 8 of 114 patients. The mean SUVmax of the IM lymph nodes was 4.95 (range: 2.45-7.54). The mean age of patients with positive IM lymph node was 43.3 (range: 25-63 years). A total of 5 of 8 IM-positive patients were

multi-centric, 5 had axillary LN positivity, and 3 had distant metastases. 3 of 8 IM patients had both axillary LN positivity and multicentricity. 3 of 8 IM patients had axillary negative LN. These 3 axillary LN negative patients were found to have distant metastases. One of the IM-positive patients had multicentricity as well as positive axillary LN and distant metastasis.

Discussion

Breast cancer is the second most common cancer all over the world. It is most frequent cancer in women. Breast cancer may manifest as local advanced, metastatic or early stage at the time of initial diagnosis. Although, locally advanced breast cancer (LABC) definition is not uniform across centers. LABC may be described as AJCC stage III breast cancer. Tumor with regional lymphadenopathy (N1-N3) of more than 5cm or direct extension to chest wall and/or skin irrespective of regional lymphadenopathy and size or infraklavikular, supraklavikular, fixed axillar or internal mammary lymph nodes with any stage tumor [1,2]. Clinically stage III patients have a risk of distant metastases in 15 to 20%. Initial accurate breast cancer staging is critical for deciding optimal therapy management and predicting the prognosis of the disease. Conventional staging work-up is recommended for LABC traditionally including chest CT and abdominal CT, bone scintigraphy, and/or abdominal ultrasound (US) and chest X-ray. NCCN recommended chest X-ray, abdomen US and bone scintigraphy for the detection of distant metastasis and the recommendation has been updated to include CT chest and CT abdomen considering the low sensitivity of US abdomen and chest X-ray to detect lung and liver metastasis [3]. Breast cancer staging includes assessment of primary tumor, regional lymph nodes and distant sites. PET is a functional imaging technique that measure and visualize various biochemical and metabolic

phenomenon by using positron-emitting radionucleotides. Integrated PET-CT devices provide in a single examination both metabolic information by use of FDG PET and anatomical information using CT. Being a wholebody procedure, PET-CT is able to provide metabolic activity of the disease and assessment of primary tumor, regional lymph nodes and distant sites, in a single test. Currently, PET-CT is not used in breast cancer initial screening or diagnosing primary breast cancer. This is primarily due to the high prevalence of false negative results, particularly for tumors with a diameter smaller than 1cm. PET-CT has good sensitivity of identifying large tumors of more than 2cm in size (90%). However, PET-CT tends to miss additional small foci of breast cancer due to its limited spatial resolution and the low FDG avidity of well differentiated tumors [4,5]. Axillary lymph nodal status is the most important prognostic variable in breast cancer. Cooper et al. in a meta-analysis, evaluated diagnostic accuracy of PET or PET-CT for the assessment of axilla; they reported that mean sensitivity was 63% (95% CI: 52-74%; range 20-100%) and mean specificity 94% (95% CI: 91-96%; range 75-100%). The authors concluded that present literature does not support the routine use of PET-CT to assess clinically N0 axilla [6]. However, the specificity of PET-CT was high (94%) in evaluating axilla. PET-CT has been shown to perform better in demonstrating extra-axillary regional lymphadenopathy including supraclavicular and IM nodes in comparison to conventional imaging [7,8]. PET-CT also helps in identifying non-regional distant lymphadenopathy, such as cervical, mediastinal, hilar and/or contralateral axillary and para-aortic, pelvic and/or inguinal. Current evidence suggests that FDG PET-CT is more accurate than conventional imaging in upstaging both lymph nodal disease and distant metastasis in LABC. In addition being a wholebody procedure, PET-CT is able to provide metabolic activity of the disease, assessment of primary tumor, regional lymph nodes and distant sites, in a single test. IM lymph nodes were positive in 8 of 114 patients in the current study. A total of 5 of 8 IM-positive patients were multi-centric, 5 had axillary LN positivity, and 3 had distant metastases. 3 of 8 IM patients had both axillary LN positivity and multicentricity. Positive IM lymph nodes were rarely found and it seems associated with distant metastases, multicentricity and axillary nodal status. Skeleton is the most common site of metastasis in breast cancer. In the current study, bone/bone marrow metastasis, was found as the most common metastatic region (41.1%). Breast cancer related skeletal metastasis can be best evaluated with PET-CT. Groheux et al. [8] reported low sensitivity of bone scintigraphy (76.7%) in comparison to PET-CT (100 %). In the current study, of the total 114 patients, 35 patients (30.7%) had multi-centric breast ca, whereas 79 patients (69.3%) had single focus. In 35 multi-centric patients, 24 were positive for axillary LN (68.6%) and 11 were negative (31.4%). Ten of the multi-centric 35 patients were positive for metastases (28.6%) and 25 were negative (71.4%).

A total of 5 patients (14.3%) had a positive internal mammary lymph node. Multi-centric breast ca patients had more axillary node, IM node and distant metastases. In initial staging on PET/CT imaging, multicentricity was one of the most important finding that predicts metastases. PET-CT detected distant metastasis (DM) in 24 of the 114 patients. The mean primary lesion SUVmax of patients with distant metastases was calculated as 9.37 (range: 2.04-24.52) which was higher significantly ($p < 0.05$) than that of total patients' breast lesion SUVmax value. We observed that the higher the SUVmax value of the primary lesion, the greater the metastasis rate. In the current study, according to T staging, the percentages of distant metastasis were found as follows: 6.5% of the 46 T1 stage patients, 23.6% of the 55 T2 stage patients, and 88.8% of the 9 T4 stage patients. In our patient group we observed metastases not only in higher T stages (88.8%) but also in early T stage (30.1%) patients.

Conclusion

FDG PET-CT led to a change in the stage of disease and the treatment approach in newly diagnosed breast cancer in both early stage or advanced stage patients. PET-CT imaging in patients with T1c to T4 breast lesions are suggested to underwent PET-CT examinations for cancer initial staging before any treatment. More prospective studies with larger sample size are needed in future to define the role of PET-CT in the management of both early and LABC.

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