ORIGINAL ARTICLE

INCIDENCE OF NODAL AND DISTANT METASTASIS AND THEIR CORRELATION WITH PRIMARY BREAST TUMOR SIZE ON PRE-THERAPY FDG PET/CT IMAGING

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ABSTRACT

BACKGROUND: In patients with breast cancer, it is thought that the risk of developing metastases increases monotonically with tumor size, because the larger the cancer at diagnosis, the more cells are available to metastasize with increase disease specific mortality. Purpose of this study was to evaluate relation between primary tumor size and metastases (nodal and non-nodal) using baseline FDG PET/CT. **MATERIAL AND METHODS:** We recruited 214 consecutive breast cancer patients who were referred for FDG PET/CT imaging for initial staging. Patients were categorized in to four groups based on primary tumor size (T1: ≤ 2 cm; T2: >2 cm and ≤ 5 cm; T3: > 5 cm; T4: any size involving chest wall or skin). For each group we determined ipsilateral axillary nodal, extra-axillary (including contralateral axillary) nodal, visceral and skeletal metastases seen on FDG PET/CT imaging. **RESULTS:** 37/214 patients had T1 tumor and found to have 15% axillary, 47% extra-axillary, 11% visceral and 04% skeletal metastases. 104/214 patients had T2 tumor and found to have 21% axillary, 45% extra-axillary, 19% visceral and 11% skeletal metastases. 34/214 patients had T3 tumor and found to have 26% axillary, 47% extra-axillary, 53% visceral and 08% skeletal metastases. 29/214 patients had T4 tumor and found to have 45% axillary, 69% extra-axillary, 55% visceral and 06% skeletal metastases. On regression analysis, highest positive linear correlation was found for ipsilateral nodal metastasis (r = 0.945; significant p-value) followed by visceral (r = 0.941) and extra-axillary nodal (r = 0.772), metastases. No significant correlation was found between primary tumor size and skeletal metastasis (r= 0.129). **CONCLUSIONS:** We found a linear correlation between primary tumor size and presence of metastases to nodes (highest for ipsilateral nodes) and viscera and favoring the conventional linear model. However, no linear correlation was found between presence of skeletal metastases and primary breast tumor size.

Key Words: Breast cancer; tumor size; nodal metastasis; distant metastasis; linear model

Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide and accounts for 30% of all female cancers and 15% of all cancer related deaths among women.[1] Among various prognostic

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factor, tumor size (the largest diameter of the primary breast tumor) is recognized as an important factor with 5 years survival 91% for tumor < 2cm, 80% for 2-5 cm and 63% for > cm.[2] Based on published data it is thought that the risk of developing nodal and distant metastases increases monotonically with tumour size as more cellsare available to metastasize.[3] Most of these studies have categorized the primary tumors into <1 cm (very small tumors), >5 cm (very large tumors) and tumors having size 1-5 cm.[4] A consistent linear relation has been found for tumor size 1-5 cm and metastases and assumed that it can be extrapolated for patients with very small and very large tumors.[3] However, the evidencefor this theory is indirect. Growing body of evidence elucidate that intrinsic biology of breast cancer rather its size to a large extent determines the risk of nodal and distant metastasis.[5,6] A recently published retrospective study including 819,647 patients denies the existence of a linear relation between size of primary breast tumor and metastases (nodal and distant metastasis).[7]
Aim of this retrospective study was to determine the incidence of nodal and distant and their correlation with size of primary breast tumor on pre-therapy FDG PET/CT imaging.

Material & Methods

This was a retrospective study conducted from March 2021 till February 2022 at PET/CT imaging services of Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan. We included 214 consecutive breast cancer patients who were referred for 18-Flourodeoxyglucose positron emission tomography / computerized tomography (18FDG PET/CT) for initial staging. Patients were categorized in to four groups based on primary tumor size determined on CT images (T1: ≤ 2 cm; T2: >2 cm and ≤ 5 cm; T3: > 5 cm; T4: any size involving chest wall or skin). For each group we determined ipsilateral axillary nodal, extra-axillary (including contralateral axillary) nodal, visceral and skeletal metastases seen on 18FDG PET/CT imaging. Findings of histopathology of primary tumor and axillary nodal status were retrieved from hospital data in all patients.

Inclusion Criteria: All patients with biopsy proven breast cancer who were referred for 18FDG PET/CT imaging for initial staging (either preoperatively or after surgical intervention) were considered eligible. Patients with history of prior chemotherapy or radiotherapy were excluded from the study.

^{18}FDG PET/CT Imaging: ^{18}FDG PET/CT was performed as per institutional protocol adopted from EANM guidelines. All patients had 4-6 hour fasting (only plain water was allowed) and a fasting blood sugar less than 200 mg% before receiving an intravenous 18FDG dose of 3 MBq/Kg in the uptake room. During uptake period (55 - 75 minute) patients were requested to lie comfortably and allowed to take about 500-1000 ml of plain water. Bladder was emptied prior to call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low dose CT examination (mid brain to mid-thigh) without intravenous contrast from head to toe followed by acquisition of PET imaging using 3 minute/bed position from toe to head in all patients. Tumor size was measured in antero-posterior and transverse (AP and TV) dimension on non-enhanced axial CT images (or pre-operative contrast enhanced CT in patients having post-operative staging). Maximum standardize uptake value (SUV_{max}) of primary tumor, nodal and distant metastases were measured on PET images.

Statistical Analysis: Commercially available packages Microsoft excel 2010, Medcalcfi and statistical package for social sciences (SPSS 19fi, IBM, Armonk, New York, US) was used. Continuous variables were described by mean – standard deviation. Pearson correlation coefficients were analyzed to evaluate linear correlation of primary tumor size with axillary nodal, extra axillary nodal, visceral and bony metastasis respectively. By using Microsoft Excel 2010, bar graphs were plotted for incidence of nodal and distant metastasis in all four groups of BC patients. Statistical significance was defined as $P < 0.05$.

Results

Study included 214 patients (212 women and 02 male) with biopsy proven breast cancer, having a mean age of 56 years (25 - 96 years) and a mean BMI (kg/m^2) of 30.138 – 5.95. Primary tumor was

found in left breast in 107/214 (50%), right breast in 93/214 (43%) while 14/214 (7%) patients had bilateral tumors. Histopathology revealed invasive ductal cell carcinoma in 198/214 (93), invasive lobular carcinoma in 03/214 (3%), ductal carcinoma in-situ in 06/214 (3%) and lobular carcinoma in situ in 04/214 (01%) patients (Tab.1). Axillary nodal sampling revealed N0 in 52/214, N1 in 60/214, N2 in 20/214, N3 in 17/214 while in remaining 65/214 axillary nodal dissection was not done (Nx). ^{18}FDG PET/CT revealed extra-axillary nodal involvement in 105 (49%), visceral metastasis in 59 (28%) and skeletal metastasis in 18 (08%) cases (Tab.2).

Variables	N=214
Age in years	56 ±14
Mean ± SD (range)	(25-96 yrs)
Gender (Male: Female)	02: 212 (01%: 99%)
DM: Non-DM	44: 170 (21: 79%)
BMI (Kg/m2) Mean ± SD	30.138± 5.945
Breast Cancer laterality	93: 107 : 14
Right: Left: Bilateral	(43%: 50%: 07%)
Tumor Type	198: 06 : 06: 04
IDC: ILC : DCIS :LCIS	(93%: 03%: 03%: 01%)
TN classification on Histopathology	
TIS : T1: T2: T3: T4	10: 37: 104: 34: 29
Nx: N0: N1: N2: N3	65: 52 : 60 : 20 : 17
Primary tumorsize on CT Mean ± SD (range)	35 ± 24 mm (10-129)
SUVmax of primary tumor on PET/CT n=94 pre-operative; Mean ± SD(range)	9.02± 6.70 (1.5-33.3)

BMI = Body Mass Index
SD = Standard Deviation
DM = Diabetes Mellitus
IDC : Infiltrating Ductal Carcinoma
ILC : Infiltrating Lobular Carcinoma
DCIS: Ductal Carcinoma in Situ

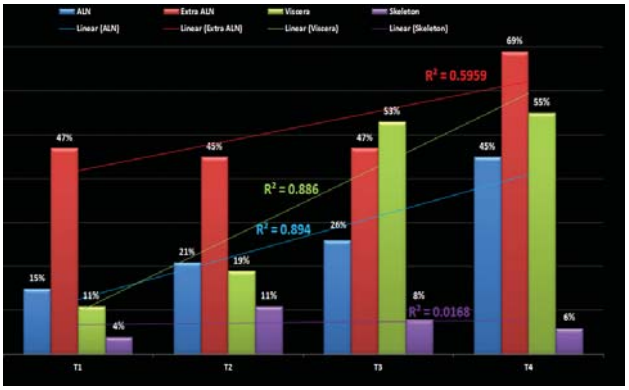
Table 1: Study demographics

Involvement on FDG PET/CT	T1 N=47	T2 N=104	T3 N=34	T4 N=29	Pearson correlation coefficient (r-score)	p-value
Axially Lymph Nodes	07 (15%)	22 (21%)	9 (26%)	13 (45%)	0.945	<0.0001*
Extra Axillary Lymph nodes	22 (47%)	47 (45%)	16 (47%)	20 (69%)	0.772	<0.0001*
Visceral Metastasis	05 (11%)	20 (19%)	18 (53%)	16 (55%)	0.941	<0.0001*
Skeletal Metastasis	02 (04%)	11 (11%)	03 (08%)	02 (06%)	0.129	0.0584

*p<0.05

Table 2: Pattern of nodal and distant metastasis on FDG PET/CT baseline study in correlation with T staging in breast cancer patients.

Patients were found to have primary tumor size falling in category of T1 in 37 (17%), T2 in 104 (48%), T3 in 34 (16%), T4 in 29 (14%) while tumor in-situ in 10 (5%) patients. Patients with T1 tumor were found to have 15% axillary, 47% extra-axillary, 11% visceral and 04% skeletal metastases. Patients with T2 tumors had 21% axillary, 45% extra-axillary, 19% visceral and 11% skeletal metastases. Patients with T3 tumor were found to have 26%axillary, 47% extra-axillary, 53% visceral and 08% skeletal metastases. Patients with T4 tumor had 45% axillary, 69% extra-axillary, 55% visceral and 06% skeletal metastases (Table 2). On regression analysis, highest positive linear correlation was found for ipsilateral nodal metastasis ($r = 0.945$; $p<0.0001$) followed by visceral ($r = 0.941$; $p<0.0001$) and extra-axillary nodal metastases ($r = 0.772$; $p<0.0001$). No significant correlation was found between primary tumor size and skeletal metastasis ($r= 0.129$; $p=0.0584$) (Fig.1).



R-score; 0.945=axillary nodes, 0.772=extra axillary nodes, 0.941=visceral and 0.129=bony metastasis.

Figure 1: Correlation of primary tumor size with axillary nodal, extra axillary nodal, visceral and skeletal metastasis on baseline FDG-PET/CT in staging of breast cancer patients.

Discussion

In this retrospective study we have studied the correlation between size of primary breast tumor and nodal and distant metastases in patients who had ^{18}FDG PET/CT studies for staging purpose. We have

found a linear relation between primary tumor size and axillary nodal metastasis. Our results are in concordance with previously published studies favoring a linear correlation.[3,9] This linear correlation has been explained by a commonly accepted notion that as tumor grow, its cells acquire the capability to metastasize, survive and grow in regional nodal and other distant metastatic destinies (conventional model).[10] This theory favors that risk of producing metastatic sites has a monotonic relation with size of primary tumor as more number of cells are present to spread to regional nodes and distant sites. However, major limitation of this theory is the indirect evidence as patients with breast cancers are not followed temporally to record transition from non-metastatic to metastatic status.A study published from our region (Tehran, Iran)has reported a higher incidence of axillary nodal metastasis in tumor ≤ 2 cm (23.6% Vs 15%) and >2 and ≤ 5cm (56.19 Vs 21%).[11] The plausible explanations could be larger sample size (Total: 789 Vs 214; ≤ 2 cm -76 Vs 47; >2cm and ≤ 5 cm 248 Vs 138) and genetically more aggressive or high grade invasive ductal carcinomas in Iranian women. We have also compared our results with one of the largest retrospective studies published by Victoria et al., examining the relation between tumor size and metastases in 819647 patients with interesting results.[7] This study also reported a linear correlation between tumor size 10 mm - 50 mm and axillary nodal metastasis although a significantly higher incidence than our study (≤ 2 cm 27.2 Vs 15%; >2 and ≤ 5cm 63% Vs 21%). However, authors reported a non-linear relation for tumor 1-10 mm and >60 mm and have called it parallel model[7] by rejecting the conventional model.[10] The hypothesis supporting the parallel model is that few non-cancerous ductal cells acquire features of cancer stem cell and their daughter cells enter into parenchyma, lymphatics and blood vessels to give invasive ductal carcinoma, regional nodal and distant metastases.[7] These three dynamic processes start simultaneously, proceed synchronously but independently and correlation between tumor size and metastatic potential is a function of inherent characteristic of cancer stem cells. Other potential explanation for non-linear correlation for very small and very large tumors could be variable tendency and chance of stem cells to get access to vascular and lymphatic pathways.[7]

Our study shows an overall incidence of visceral metastasis in (59/214) 28% of cases which is significantly higher than another study published from our own institute (70/370 patients; 18.9%).[12] The plausible explanation could be use of FDG PET/CT in our study as staging tool which was not available in our institute during previous study period. Similarly, incidence of distant metastasis in two Surveillance Epidemiology End Result (SEER) based retrospective studies were <5%.[7,13] The most plausible explanation is the use of FDG PET/CT in our study for staging having better diagnostic accuracy for visceral and marrow metastasis than conventional imaging modalities. We have also found a linear correlation between primary tumor size and visceral metastasis. However, skeletal metastasis has been found to have a non-linear correlation with primary tumor size. In a large SEER based study, prevalence of distant metastasis has increased from 3.4% at presentation to 33.7% during 20-year follow-up.[7] However, same study has found a non-linear correlation and supported by a parallel model. According to parallel model, inherent property of cancer stem cell determines the potential for distant metastasis and neither primary tumor nor regional metastatic nodes are source of distant metastasis as reported in cancer of breast,[14] pancreas,[15] colon[16] and melanoma.[17] It is important to understand that study supporting a parallel model also had linear correlation for tumor size 7 mm and 60 mm and notable departure for tumor <7 mm and >60 mm. Sentinel explanation for this discordance is that we grouped tumors <20 mm and >50 mm as one category and due to low sample sizes, resolution of curve at its extremes will be too low to depict correlation adequately.

We found a linear correlation between primary tumor size and presence of metastases to nodes (highest for ipsilateral nodes) and viscera and favoring the conventional linear model. However, no linear correlation was found between presence of skeletal metastases and primary breast tumor size.

Conflict of Interest: Declared none by authors

References

1. Jemal A, Bray F, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; **61:** 69-90.

2. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989; **63:** 181.

3. Michaelson JS, Silverstein M, Wyatt J, Weber G, Moore R, Halpern E, et al.Predicting thesurvival of patients with breast carcinoma using tumor size. Cancer 2002; **95:** 713-23.

4. Laura S, Coombs N, Ung O, Boyages J. Tumour size asa predictor of axillary node metastases in patients with breastcancer. ANZ J Surg 2006; **76:** 1002-06.

5. Yu KD, Jiang YZ, Chen S, Cao Z, Wu J, Shen Z, et al. Effect of large tumorsize on cancer-specific mortality in node-negative breast cancer.Mayo Clin Proc 2012; **87:** 1171-80.

6. Zheng YZ, Wang L, Hu X, Shao ZM. Effect of tumor sizeon breast cancer-specific survival stratified by joint hormonereceptor status in a SEER population-based study. Oncotarget 2015; **6:** 22985-95.

7. Victoria Sopik, Steven A. Narod. The relationship between tumour size, nodal status and distant metastases: on the origins of breast cancer. Breast Cancer Research and Treatment 2018; **170:** 647-56.

8. Boellaard R, Bolton RD, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; **42:** 328-54.

9. Yu KD, Jiang YZ, Shao ZM. Difference between observed and expected number of involved lymph nodes reflectsthe metastatic potential of breast cancer independent to intrinsicsubtype. Oncotarget 2015; **6:** 16686-97.

10. Weigelt B, Peterse JL, van t Veer LJ. Breast cancer metastasis:markers and models. Nat Rev Cancer 2005; **5:** 591-602.

11. Orang E, Marzony ET, Afsharfard A. Predictive Role of Tumor Size in Breast Cancer with Axillary Lymph Node Involvement - Can Size of Primary Tumor be used to Omit an Unnecessary Axillary Lymph Node Dissection? Asian Pac J Cancer Prev 2013; **14(2):** 717-22.

12. Ali B, Mubarik F, Zahid N, Sattar AK. Clinicopathologic Features Predictive of Distant Metastasis in Patients Diagnosed With Invasive Breast Cancer. JCO Global Oncol 2020; **6:** 1346-51.

13. Xiao W, Zheng S, Yang A, Zhang X, Zou Y, Tang H, et al. Breast cancer subtypes and the risk of distant metastasis at initial diagnosis: a population-based study. Cancer Manag Res. Nov 2018; **10:** 5329-5338.

14. Hosseini H, Obradovic MM, Hoffmann M, Kathryn LH, Soledad MS, Werner-Klein M, et al. Early dissemination seeds metastasis in breast cancer. Nature2016; **540(7634):** 552-8.

15. Rhim AD, Mirek ET, Aiello NM et al (2012) EMT and dissemination precede pancreatic tumor formation. Cell **148:** 349-61.

16. Sottoriva A, Kang H, Ma Z, Graham TA, Salomon M, ZhaoJ, et al. A big bang model ofhuman colorectal tumor growth. Nat Genet 2015; **47:** 209-16.

17. Werner-Klein M, Scheitler S, Hoffmann M, Isabelle Hodak, Klaus Dietz, Petra Lehnert et al. Geneticalterations driving metastatic colony formation are acquired outsideof the primary tumour in melanoma. Nat Commun 2018; **9:** 595.