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Correlation of Nodal and Distant Metastasis with Primary Breast Tumor Size on Pre-Therapy CT Imaging

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ABSTRACT

Introduction: The relationship between the size of the main tumor and the nodal and distant metastases on FDG PET/CT imaging before therapy is not well understood in Pakistan. By offering insight into the early stages of cancer progression, the study's findings will be helpful in creating a treatment plan and enhancing overall patient outcomes. **Methodology:** 470 patients with biopsy-proven breast cancer between the ages of 25 and 80 who were referred for 18FDG PET/CT imaging for initial staging were included. Patients with carcinoma in situ (with or without microinvasion), those who had previously undergone chemotherapy, and those who had previously undergone radiotherapy were not included. 18FDG PET/CT was carried out in accordance with the institutional procedure that was adapted from the EANM standards. Before taking an intravenous dosage, all patients had to fast for four to six hours. They could only drink plain water. Patients were encouraged to lie down comfortably and drink 500 to 1,000 milliliters of ordinary water during the 55.75-minute uptake time. We employed PET scans to find the maximum standardized uptake value (SUV max) of the original tumor, the lymph nodes, and the distant metastases. **Results:** The ipsilateral nodal metastasis had the strongest positive linear connection, followed by the visceral and extra-axillary nodal metastases. There was no significant link between the size of the initial tumor and the skeletal metastases. **Conclusion:** We discovered a linear relationship between the size of the initial tumor and the presence of visceral and nodal metastases, supporting the traditional linear model.

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women globally, accounting for 15% of all cancer-related deaths in women and 30% of all female cancers.[1] Its incidence rate is 43.1/100,000.[2] The death rate for female breast cancer (BC) is the sixth highest. In poor nations, the death rate is much higher than in industrialized ones (15.0 vs. 12.8 per 100,000). It causes one in four cases and one in six fatalities in females.[3] The recent introduction of early detection and multidisciplinary treatment approaches involving customized surgery, chemotherapy, radiotherapy, hormonal therapy, and targeted therapy has resulted in notable reductions in the mortality rate, especially in high-income countries, despite the rising incidence of breast cancer. Low- and middle-income nations (LMICs) have a substantially greater percentage of case fatality rates than high-income countries.[4]

Despite the clinical characteristics and molecular biology of breast cancer, the most significant and dependable prognostic variables are the axillary lymph node (LN) status, the presence and development of distant metastases, and its function in directing adjuvant cancer treatment.[5,6] Although only 5% of patients with BC had distant metastases identified at the time of diagnosis, these metastases that develop over years are the most common cause of death for BC patients. In order to facilitate pretreatment decisions, the preoperative prediction of lymph node and distant metastasis can offer useful information for deciding on adjuvant therapy and creating surgical strategies. Indirect information about the biological characteristics of cancer can be obtained using 18F-FDG-PET/CT. Measured from breast mass, maximum standardized uptake value (SUV max) values are typically linked to the biological aggressiveness of the tumor and may be employed as prognostic indicators.[6]

Based on existing evidence, it is believed that as tumor size increases, the likelihood of nodal and distant metastases increases monotonically because more cells are accessible for metastasis. More and more research shows that the size of breast cancer does not matter as much as its fundamental biology when it comes to the chances of nodal and distant metastases.[1] The size of the initial breast tumor and metastases (distant and nodal) do not correlate linearly, according to a retrospective analysis involving 819,647 participants.[7]

Breast cancer is the most prevalent malignancy in women globally and poses a serious threat to public health. Information about the relationship between the size of the main tumor and distant and nodal metastases on FDG PET/CT imaging before treatment is scarce in Pakistan. By shedding light on the early stages of cancer progression, the study's conclusions will help with treatment strategy development and enhance overall patient outcomes.

METHODOLOGY

470 patients with biopsy-proven breast cancer who presented to the Department of Radiology at Fauji Foundation Hospital, RWP from 6 December 2024 to 6 June 2025, and referred for 18FDG PET/CT imaging for initial staging were included in this descriptive, cross-sectional study. The patients ranged in age from 25 to 80 years. r = 0.132[1], Type I error = 5%, Type II error = 10%, confidence level = 95%, and sample size = 470 are the values from the correlation sample size calculator. Patients were selected using a non-random consecutive sampling technique. Patients with carcinoma in situ (with or without microinvasion), those who had previously undergone chemotherapy, and those who had previously undergone radiotherapy were not included.

18FDG PET/CT was carried out in accordance with the institutional procedure that was adapted from the EANM standards. Before getting an intravenous dosage of 3 MBq/Kg of 18FDG in the uptake room, all patients had to fast for four to six hours. During the 55.75-minute uptake time, patients were told to lie down comfortably and were allowed to consume 500 to 1,000 milliliters of regular water. Before Celesteion, Toshiba, Japan, called the patient to a PET/CT imaging suite, the bladder was emptied. All patients undergo a low-dose CT scan from head to toe without any contrast through an IV. They also get a PET scan while lying down for three minutes, from toe to head. We measured the size of the tumor in the antero-posterior (AP) and transverse (TV) directions. Two types of nodal metastasis were identified: extra axillary lymph node metastasis (contralateral) and ipsilateral axillary lymph node metastasis. SUV max of extra-axillary or axillary lymph nodes on FDG PET/CT ≥ 2.5. Skeletal metastases (bones) and visceral metastases (abdominal organs and thoracis) were the two categories used to describe distant metastases. Visceral or skeletal lymph node SUV max Z 2.5 on FDG PET/CT.

SPSS Y-25 was used to enter all of the data. Every quantitative measure, including age, BMI, and tumor size, had its mean and standard deviation determined. For every qualitative variable, including diabetes mellitus, breast cancer kind, affected side, axillary, extra-axillary, visceral, and skeletal metastases, frequency and percentage were computed. Calculations were used to determine the Pearson association between tumor size, axillary, extra-axillary, visceral, and skeletal metastases. Stratification was used to adjust for effect modifiers such as age, BMI, and breast cancer type. Following stratification, The Pearson correlation was computed. A P-Value of less than 0.05 was considered significant.

RESULTS

The study comprised 470 women with breast cancer that had been confirmed by a biopsy. Their average age was 61 ± 7.45 years (25–80 years), and their average BMI (kg/m2) was 30.138 ± 5.95. The main tumor was identified in the left breast 45.53% of the time and the right breast 54.47% of the time. Histopathology showed that 47.66% of individuals had invasive ductal cell carcinoma and 52.34% did not (Table 1). In 64.26% of patients, 18FDG PET/CT showed axillary metastasis; in 64.89% of cases, it showed extra-axillary nodal involvement; in 41.49% of cases, it showed visceral metastasis; and in 26.17% of cases, it showed skeletal metastasis. 188 (40.0%) patients had a primary tumor size that fell into the T1 category (≤2 cm), 193 (41.06%) had a size that fell into the T2 category (>2 and <5 cm), 69 (14.68%) had a size that fell into the T3 category (>5 cm), and 20 (4.26%) had a size that fell into the T4 category (any size involving the chest wall). Patients with T1 tumors had 25.32% axillary, 25.11% extra-axillary, 17.23% visceral, and 10.85% skeletal metastases. Patients with T2 tumors had 26.17% of their axillary, 26.81% of their extra-axillary, 15.53% of their visceral, and 9.57% of their skeletal metastases. Patients with T3 tumors had 26% of their metastases in the axillary area, 47% in the extra-axillary area, 53% in the visceral area, and 08% in the skeletal area. The ipsilateral nodal metastasis had the strongest positive linear connection, followed by the visceral and extra-axillary nodal metastases. There was no significant link between the size of the initial tumor and the skeletal metastases (Table 2).

Table 1

Distribution of Patients with Other Confounding Variables (n=470)

Variables		Frequency	%age
Age (years)	25-50	184	39.15
	51-80	286	60.85
BMI (kg/m²)	≤30	330	70.21
	>30	140	29.79
Residence	Rural	252	53.62
	Urban	218	46.38
Type of cancer	Non-invasive	224	47.66
	Invasive	246	52.34
Side affected	Right	256	54.47
	Left	214	45.53

Table 2

Correlation of Nodal and Distant Metastasis with Primary Breast Tumor Size on Pre-Therapy FDG Pet/Ct Imaging

Variables		Tumour	Axillary	Extra	Visceral	Skeletal
Tumour	Pearson's Correlation	1	.025	.050	.014	.016
	P-value		.582	.282	.755	.736
	n	470	470	470	470	470
Axillary	Pearson's Correlation	.025	1	.158**	-.003	-.071
	P-value	.582		.001	.954	.124
	n	470	470	470	470	470
Extra-axillary	Pearson's Correlation	.050	.158**	1	-.014	.063
	P-value	.282	.001		.763	.175
	n	470	470	470	470	470
Visceral	Pearson's Correlation	.014	-.003	-.014	1	.137**
	P-value	.755	.954	.763		.003
	n	470	470	470	470	470

Skeletal	Pearson's Correlation	.016	-.071	.063	.137**	1
	P-value	.736	.124	.175	.003	
	n	470	470	470	470	470

**Correlation is significant at the 0.01 level (2-tailed).

Table 3

Stratification of Correlation between Different Age Groups.

Age groups (years)			Tumour	Axillary	Extra	Visceral	Skeletal
25-50	Tumor size	Pearson's Correlation	1	.014	-.006	.045	-.111
		p-value		.854	.941	.540	.134
		n	184	184	184	184	184
	axillary	Pearson's Correlation	.014	1	.153*	.058	-.053
		p-value	.854		.039	.435	.474
		n	184	184	184	184	184
	Extra-axillary	Pearson's Correlation	-.006	.153*	1	-.001	.040
		p-value	.941	.039		.992	.594
		n	184	184	184	184	184
	visceral	Pearson's Correlation	.045	.058	-.001	1	.039
		p-value	.540	.435	.992		.599
		n	184	184	184	184	184
	skeletal	Pearson's Correlation	-.111	-.053	.040	.039	1
		p-value	.134	.474	.594	.599	
		n	184	184	184	184	184
51-80	Tumor size	Pearson's Correlation	1	.035	.081	.006	.055
		p-value		.553	.170	.926	.350
		n	286	286	286	286	286
	axillary	Pearson's Correlation	.035	1	.162**	-.043	-.079
		p-value	.553		.006	.466	.184
		n	286	286	286	286	286
	Extra-axillary	Pearson's Correlation	.081	.162**	1	-.022	.076
		p-value	.170	.006		.707	.201
		n	286	286	286	286	286
	visceral	Pearson's Correlation	.006	-.043	-.022	1	.205**
		p-value	.926	.466	.707		.000
		n	286	286	286	286	286
	skeletal	Pearson's Correlation	.055	-.079	.076	.205**	1
		p-value	.350	.184	.201	.000	
		n	286	286	286	286	286

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4

Stratification of Correlation between Different BMI.

BMI			Tumour	Axillary	Extra	Visceral	Skeletal
<31	Tumour size	Pearson's Correlation	1	.073	.018	.020	-.046
		p-value		.185	.739	.716	.402
		n	330	330	330	330	330
	axillary	Pearson's Correlation	.073	1	.137*	-.015	-.034
		p-value	.185		.012	.786	.544
		n	330	330	330	330	330
	extra	Pearson's Correlation	.018	.137*	1	.005	.049
		p-value	.739	.012		.926	.375
		n	330	330	330	330	330
	visceral	Pearson's Correlation	.020	-.015	.005	1	.164**
		p-value	.716	.786	.926		.003
		n	330	330	330	330	330
	skeletal	Pearson's Correlation	-.046	-.034	.049	.164**	1
		p-value	.402	.544	.375	.003	
		n	330	330	330	330	330
31-40	Tumour size	Pearson's Correlation	1	-.053	.127	.038	.157
		p-value		.533	.134	.657	.063
		n	140	140	140	140	140
	axillary	Pearson's Correlation	-.053	1	.205*	.021	-.162
		p-value	.533		.015	.806	.057
		n	140	140	140	140	140
	extra	Pearson's Correlation	.127	.205*	1	-.063	.094
		p-value	.134	.015		.458	.268
		n	140	140	140	140	140
	visceral	Pearson's Correlation	.038	.021	-.063	1	.068
		p-value	.657	.806	.458		.423
		n	140	140	140	140	140
	skeletal	Pearson's Correlation	.157	-.162	.094	.068	1
		p-value	.063	.057	.268	.423	
		n	140	140	140	140	140

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Table 5

Stratification of Correlation between Type of Breast Cancer.

Type			Tumour	Axillary	Extra	Visceral	Skeletal
Non-invasive	tumour	Pearson's Correlation	1	.070	.117	-.034	-.088
		p-value		.295	.082	.615	.189
		n	224	224	224	224	224
	axillary	Pearson's Correlation	.070	1	.212**	.005	-.050
		p-value	.295		.001	.943	.452
		n	224	224	224	224	224
	Extra-axillary	Pearson's Correlation	.117	.212**	1	-.032	.068
		p-value	.082	.001		.634	.309
		n	224	224	224	224	224
	visceral	Pearson's Correlation	-.034	.005	-.032	1	.180**
		p-value	.615	.943	.634		.007
		n	224	224	224	224	224
	skeletal	Pearson's Correlation	-.088	-.050	.068	.180**	1
		p-value	.189	.452	.309	.007	
		n	224	224	224	224	224
Invasive	tumour	Pearson's Correlation	1	-.003	.016	.029	.110
		p-value		.965	.807	.656	.085
		n	246	246	246	246	246
	axillary	Pearson's Correlation	-.003	1	.111	-.007	-.092
		p-value	.965		.083	.918	.152
		n	246	246	246	246	246
	Extra-axillary	Pearson's Correlation	.016	.111	1	.009	.055
		p-value	.807	.083		.893	.393
		n	246	246	246	246	246
	visceral	Pearson's Correlation	.029	-.007	.009	1	.104
		p-value	.656	.918	.893		.105
		n	246	246	246	246	246
	skeletal	Pearson's Correlation	.110	-.092	.055	.104	1
		p-value	.085	.152	.393	.105	
		n	246	246	246	246	246

** Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

This study examined the relationship between the size of the main breast tumor on pre-treatment FDG PET/CT imaging and nodal and distant metastases. We discovered a linear relationship between the size of the main tumor and the metastases to the axillary nodes. Our findings

support a linear association and are consistent with other published research.[8,9] The widely held belief that tumor cells develop the capacity to spread, endure, and proliferate in regional nodal and other distant metastatic destiny as the tumor grows has been used to explain this linear link (traditional model).[10] According to this idea, when more cells are present to spread to distant sites and regional nodes, the probability of developing metastatic sites increases monotonically with the size of the main tumor. However, as patients with breast cancer are not tracked over time to document the change from non-metastatic to metastatic status, a significant drawback of this theory is the indirect evidence. A recent study found that ipsilateral nodal metastases showed the most positive linear correlation (r = 0.945).[1]

A study found that axillary nodal metastasis is more common in tumors that are 2 cm or smaller (23.6% vs. 15%) and between 2 and 5 cm (56.19% vs. 21%).[11] We also looked at our data in relation to one of the biggest retrospective studies ever published. In this study, Victoria et al. examined the relationship between metastases and tumor size in 819647 patients. The outcomes were intriguing.[12]

The rate of axillary nodal metastasis in this study was much greater than in ours (27.2% for ≤ 2 cm vs. 15%; 63% for >2 and < 5 cm vs. 21%). But this study also showed that there is a linear association between the size of the tumor (10 mm to 50 mm) and the spread of cancer to the axillary nodes. However, when the scientists rejected the traditional model, they saw that tumors between 1 and 10 mm and those larger than 60 mm had a non-linear relationship. They called this the parallel model.[13] The parallel model's premise says that a few non-cancerous ductal cells change into cancer stem cells, and their daughter cells move into the blood vessels, lymphatics, and parenchyma to create distant metastases, regional nodules, and invasive ductal carcinoma. These three dynamic processes all start at the same time, progress ahead at the same time but independently, and the size of the tumor and the chance of metastasis depend on the natural features of cancer stem cells. The stem cells' different chances and tendencies to go into lymphatic and artery channels may also help explain the non-linear relationship between very small and very large cancers.[14]

The use of FDG PET/CT as a staging tool in our study, which was unavailable at our institution during the prior study period, could be a tenable reason. In two retrospective investigations based on Surveillance Epidemiology End Results (SEER), the incidence of distant metastasis was less than 5%.[15] We discovered a linear relationship between visceral metastasis and initial tumor size. It has been discovered that there is a non-linear relationship between the size of the initial tumor and skeletal metastases.

The prevalence of distant metastases rose from 3.4% at presentation to 33.7% throughout a 20-year follow-up in a major SEER-based research.[16] Nevertheless, a parallel model supports the non-linear correlation that the same investigation discovered. As described in cases of breast, pancreatic, colon, and melanoma cancer, the parallel model states that the inherent characteristics of cancer stem cells dictate the likelihood of distant metastasis, and that neither the initial tumor nor regional metastatic nodes are the cause of distant metastases.[17] It's important to remember that the study that backed up a parallel model also found a big difference in tumor sizes less than 7 mm and more than 60 mm, as well as a straight line correlation for tumor sizes 7 mm and 60 mm. We put tumors that were less than 20 mm and more than 50 mm into the same group. Because the sample sizes were so little, the curve's resolution at its ends won't be good enough to show correlation. This is the only reason I can think of for this difference.

According to numerous earlier studies, the likelihood of axillary LNM rises in tandem with the size of the breast cancer tumor.[18,19] According to the current study's univariate parameter analysis, axillary LNM grew histopathologically in tandem with tumor size. Tumor size and the cut-off value for FPET axilla lymph node SUVmax, however, did not correlate in the univariate study. While some of the earlier research found no association between histological grade and FPET axilla participation, others did.[20]

CONCLUSION

We discovered a linear relationship between the size of the initial tumor and the presence of visceral and nodal metastases, supporting the traditional linear model. However, there was no discernible relationship between the size of the primary breast tumor and the presence of skeletal metastases.

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