Original Article

A Study Correlating the Tumor Site and Size with the Level of Axillary Lymph Node Involvement in Breast Cancer

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ABSTRACT

Background: Breast cancer is the leading cancer in women. The most common histologic type of breast cancer is infiltrating ductal carcinoma. The mainstay of the treatment of breast cancer is surgery when the tumor is localized, followed by chemotherapy as well as radiotherapy (when indicated) and in estrogen receptor and progesterone receptor positive tumors, adjuvant hormonal therapy. **Aims and Objectives:** The aim of this study is to correlate tumor site and size with the level of axillary lymph node involvement (ALNI) in early and locally advanced breast cancer. **Materials and Methods:** This prospective and observational study was conducted on fifty female patients of carcinoma breast with early and locally advanced breast cancer. **Results:** The age distribution showed two peaks at 41–50 years and 51–60 years with 42 and 24 patients, respectively, in both the age groups. Preoperative lymph node positivity by ultrasonography matched with postoperative histopathological examination (HPE) report. Preoperative ultrasonographically determined tumor size was similar to the final histopathological T stage. **Conclusion:** As size of tumor increases, there is an increase in ALNI which suggests that nodal metastasis is indicative of tumor chronology. Ultrasonography is a good tool to objectively measure tumor size and lymph node involvement preoperatively. Quadrant of involvement can emerge as a clinically useful prognostic cancer in breast cancer as there is a higher incidence of lymph node positivity with increasing size of the breast tumor and for tumors located at the upper outer quadrant of the breast.

Keywords: *Breast cancer, lymph node, tumor size and site*

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Introduction

Breast cancer is the leading cancer in women, accounting for 25% of all cancer cases worldwide.[1] It is more common in developed countries.[2] Outcomes for breast cancer vary greatly depending on the cancer sub-type, stage of disease, and person's age. The most common histologic type of breast cancer is infiltrating ductal carcinoma.[3] The mainstay of breast cancer treatment is surgery when the tumor is localized, followed by chemotherapy as well as radiotherapy (when indicated) and for estrogen receptor (ER) and progesterone receptor (PR)-positive tumors, adjuvant hormonal therapy.[3,4]

More than two-thirds of breast cancer cases are diagnosed in women aged 50 years and older; the majority of these cases are in developed countries. For women aged 15–49 years, twice as many breast cancer cases are diagnosed in developing countries than in developed countries. In countries where mammography is available and affordable, adherence to recommendations for routine screening is associated with reduced mortality from breast cancer.[5]

The increased use of mammographic screening has led to an increase in the detection of breast tumors

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that measure ≤2.0 cm (American Joint Committee on Cancer [AJCC] classification T1).[6-8]

Axillary node status remains the most important predictor of outcome in breast cancer patients. Data clearly show that women with cancer-free lymph nodes (lymph node-negative) have better survival than women with cancerous nodes (lymph node-positive). As the number of positive nodes increases, survival decreases.[9]

The axillary lymph nodes (ALN) are staged to aid in determining prognosis and therapy. Sentinel lymph node biopsy (SLNB) is the initial standard axillary staging procedure performed in women with invasive breast cancer. Reports demonstrate a 97.5%–100% concordance between SLNB and complete ALN dissection (ALND).[10-15]

Tumors may be measured clinically or pathologically. Axillary nodal involvement is an essential prognostic factor in patients with breast cancer. The presence of positive ALNs implies the need for systemic adjuvant chemotherapy and locoregional irradiation. Hence, ALND contributes to the accurate staging of the disease.[16]

The characteristics of the primary breast cancer closely associated with ALN metastasis are tumor size, tumor grade, and lymphovascular invasion, but only tumor size can be determined preoperatively.[17-19]

The presence of axillary node metastasis and the size of the primary tumor are the two main prognostic factors used clinically for the evaluation of breast cancer patients.[20] "Clinically node-positive" patients will undergo ALND without undergoing SLNB. "Clinically node-negative" patients with T1 or T2 tumors currently undergo SLNB. If the SLNB results are negative, no further axillary dissection is done because there is no survival benefit for performing ALND in this setting.[21-24]

The more lymph nodes that contain cancer cells, the more serious cancer might be. Hence, doctors use the number of involved lymph nodes to help make treatment decisions.[25] After the surgery, a pathologist looks at the cells from breast cancer as well as from the lymph nodes.

Influence of tumor location on breast cancer prognosis

The risk of dying increased significantly (up to 21%) with increasing distance of tumor location from the axilla. Survival is significantly better for women with a tumor in the upper lateral quadrant than tumors located elsewhere in the breast.[26-28]

Axillary node involvement is the most significant and durable prognostic factor for women with breast cancer. The use of systemic adjuvant chemotherapy is often determined by the presence or absence of axillary lymph node metastasis.[29,30]

Aims and Objectives

To correlate tumor site and size with the level of ALN involvement (ALNI) (lymph node-positive) in early and locally advanced breast cancer.

Materials and Methods

This prospective and observational study was conducted on fifty female patients of carcinoma breast in a tertiary level center on 50 females with a confirmed diagnosis of carcinoma breast.

Inclusion criteria

1. Early (Stage IIB) and locally advanced breast cancer (Stage IIB till IIIB).

Exclusion criteria

1. Metastatic disease
2. Tx, Nx patients as per AJCC tumor, node, and metastasis (TNM) staging
3. To, N1 patients as per AJCC TNM staging.

Procedure

Assessment of tumor size

Tumor size was assessed clinically as well as ultrasonographically for all the patients and the longest dimension in length, width, or depth was taken for size consideration. The final size as described by histopathologists on grossing for all the patients was taken into correlation and this parameter was taken finally for all the patients.

Assessment of tumor site

The breast was divided into five regions with the x- and y-axis centered on the nipple which included 4 quadrants and the central nipple-areola complex.

The tumor was assigned to the quadrant where the bulk of it lay, as assessed ultrasonographically.

If tumor site was equivocal and involved more than one quadrant then tumor site was described as diffuse.

Lymph node status of the axilla

The axilla was assessed clinically, ultrasonographically, and intra-operatively for lymph nodes and statistically compared with each other.

Intraoperatively, lymph nodes up to level III of the axilla were dissected with the axillary fat.

The axillary fat was then dissected for visible ALNs.

These nodes were counted and sent for histopathological assessment, and the final status of axilla was taken to be provided by the histopathological assessment.

The patients were then staged according to the TNM staging by AJCC.[31]

Classifying as early or locally advanced

This was a preoperative classification:

- Early Breast Cancer: Node-negative cancer (up to Stage IIB)
- Locally Advanced Breast Cancer: Node-positive cancer (stage IIB till IIIB).

Site, size, and axillary involvement descriptors for patients who receive neoadjuvant chemotherapy

- T: Done by clinical examination and ultrasonography for evidence of size
- N: Done by clinical examination and ultrasonography for evidence of nodal status.

(For Internal Mammary lymph nodes, chest X-ray PA view was done, if it showed widened mediastinum, then contrast enhanced computed tomography chest was done).

Locally advanced cancer was described before starting neoadjuvant chemotherapy.

Results

The present study was undertaken between September 2015 and April 2017. A total of 50 cases of early and locally advanced breast cancer were included in the study to develop a correlation between site and size of tumor with lymph node involvement based on clinical examination, ultrasound findings, intraoperative findings, and postoperative histopathological reports. The Chi-square test was applied for statistical analysis.

The study for clinical examination for nodes was found to be nonsignificant whereas that for ultrasonography for nodes was found to be highly significant indicating that preoperative ultrasonography is a significant predictor of lymph node positivity.

In this study, it was observed that out of the two patients with tumor size <2 cm, none had the involvement of lymph nodes. While among 45 cases with size between 2 cm and 5 cm, 7 cases had no lymph nodes involved, 6 had 1–3, 22 had 3–9, and 10 cases had more than 10 lymph nodes involved. Of 3 patients with tumor size more than 5 cm, all had more than 10 lymph nodes involved. The study was found to be highly significant. Thus, predicting that with an increase in tumor size, number of lymph nodes involved increases.

As per our study, patients with tumor present in the upper outer quadrant had more number of lymph nodes involved. On analyzing the data, our study was found to be significant with $P = 0.042$.

Table 1: Age of patient and number of lymph nodes

Age groups (years)	Total cases	Number of lymph nodes present			
		0, *n* (%)	1-3 (N1), *n* (%)	3-9 (N2), *n* (%)	≥10 (N3), *n* (%)
40-50	21	5 (10.0)	3 (6.0)	6 (12.0)	7 (14.0)
51-60	23	3 (6.0)	3 (6.0)	13 (26.0)	4 (8.0)
>60	6	1 (2.0)	0 (0.0)	3 (6.0)	2 (4.0)
Total	50	9 (18.0)	6 (12.0)	22 (44.0)	13 (26.0)

Table 2: Correlation between size of tumor and lymph node involvement determined by clinical examination and sonomammography

Size (cm)	Clinical examination for lymph nodes		Sonomammography for lymph nodes	
	Present	Absent	Present	Absent
<2	2	0	2	0
2-5	25	20	41	4
>5	0	3	3	0
χ^2	5.269		13.086	
P	0.072		0.001	
Significance	NS		HS	

NS: Not significant, HS: Highly significant

Table 3: Correlation of preoperative tumor size (ultrasonography) with lymph node involvement determined on postoperative HPE

Size (cm)	Total cases	Number of lymph nodes			
		0, *n* (%)	1-3 (N1), *n* (%)	3-9 (N2), *n* (%)	≥10 (N3), *n* (%)
<2	2	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
2-5	45	7 (14.0)	6 (12.0)	22 (44.0)	10 (20.0)
>5	3	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)
Total	50	9 (18.0)	6 (12.0)	22 (44.0)	13 (26.0)
χ^2			18.357		
P			0.005		
Significance			HS		

HS: Highly significant, HPE: Histopathological examination

Table 4: Correlation of preoperative tumor site (ultrasonography) with lymph node involvement determined on postoperative HPE

Site of tumour	Total cases	Number of lymph nodes			
		0, *n* (%)	1-3 (N1), *n* (%)	3-9 (N2), *n* (%)	≥10 (N3), *n* (%)
Upper outer	28	2 (4.0)	1 (2.0)	13 (26.0)	12 (24.0)
Lower outer	13	4 (8.0)	3 (6.0)	6 (12.0)	0 (0.0)
Central	2	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)
Upper inner	6	1 (2.0)	2 (4.0)	2 (4.0)	1 (2.0)
Lower inner	1	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	50	9 (18.0)	6 (12.0)	22 (44.0)	13 (26.0)
χ^2			21.597		
P			0.042		
Significance			S		

S: Significant, HPE: Histopathological examination

Table 5: Luminal type versus number of lymph nodes

Luminal type	Total cases	Number of lymph nodes			
		0, *n* (%)	1-3 (N1), *n* (%)	3-9 (N2), *n* (%)	≥10 (N3), *n* (%)
A	30	7 (14.0)	4 (8.0)	16 (32.0)	3 (6.0)
B	10	1 (2.0)	1 (2.0)	3 (6.0)	5 (10.0)
Basal	6	0 (0.0)	0 (2.0)	1 (2.0)	5 (10.0)
Her2neu	4	1 (2.0)	1 (2.0)	2 (4.0)	0 (0.0)
Total	50	9 (18.0)	6 (12.0)	22 (44.0)	13 (26.0)
χ^2			19.265		
P			0.023		
Significance			S		

S: Significant

Using the Pearson Correlation test, we found that preoperative ultrasonographic-determined tumor size had a positive correlation of 0.890 to the final histopathological Tumor size ($P < 0.001$), which implies that ultrasound was a good tool to objectively measure tumor size before the surgery.

Discussion

The present study of breast carcinoma showed that 46% of cases belonged to 51–60 years of age group, 42% to 40–50 years age group and 12% to > 60 years age group. These findings showed that most of the breast cancer in our study was of the age group 40–60 years (88%) and locally advanced type. In a study by Chopra *et al*.[32] conducted in 100 patients of histopathologically confirmed breast cancer, the mean age of patients was 51 years (standard deviation = 10.48). The age distribution showed two peaks at 41–50 years and 51–60 years with 42 and 24 patients, respectively, in both the age groups [Table 1].

The ALNI increased significantly ($P = 0.008$) as the tumor size increased as shown by our study [Table 2].

In a study by Kumar and Mukherjee[33] when lymph node status and size of the tumor were correlated, it was found that 26 out of 50 (52%) patients were of N1. T2, T3, and T4 showed an increase in lymph node positivity as three out of five (60%) in the T3 were of N2 lymph node status, whereas all of T4 were of N3 lymph node status.

Legha *et al*.[34] found that as the average size of the breast tumor increases, so does the average number of lymph nodes, both clinically as well as histopathologically positive for metastasis. It was also seen that as the number of lymph nodes increased, so did the size of the tumor by both clinical and histopathological examination.

We have seen a close relationship between tumor size and ALNI. The risk of ALN metastasis increases as tumor size increases which suggests that nodal metastasis is indicative of tumor chronology.[35] T stage was significantly associated with nodal positivity. Larger tumor size was found to be an independent predictor of node positive disease in our study, concurring with data from several other centers.[36,37]

It was also observed that the majority of cases 45 fell into T2 stage, 11 (24.44%) out of these were of N3 nodal status which is quite high in relation to the T stage. This shows that there may be high nodal involvement even in smaller-sized tumors. Hence, there is a need for early screening programs as even small-sized tumors may have already metastasized at the time of presentation.

Similar to the findings of Chan *et al.,*[38] we also found that preoperative ultrasonographically determined tumor size was similar to the final histopathological T stage which implies that ultrasound was a good tool to objectively measure tumor size before thesurgery and this is particularly useful in hospitals without radio nuclear medicine expertise for SLN imaging. Furthermore, the preoperative determination of tumor size with ultrasound correlates well with the actual level of ALNI. Therefore, tumor size can be used to guide the surgeon to more limited axillary dissection as an alternative to SLNB for T1-node negative breast cancers [Table 3].

From our study, it was also seen that preoperative lymph node positivity by ultrasonography matched with postoperative HPE report, indicating that ultrasonography was a significant predictor of lymph node involvement.

In this study, the site of tumor and lymph node status were correlated. It was observed that out of the majority of cases had tumor involving upper outer quadrant of the breast, among which 14 cases had N2 lymph node status and 11 had N3 lymph node status [Table 4].

Legha *et al.*[34] also found that the upper and outer quadrant of the breast was involved in 62% cases. The second most common site was upper and inner (16%) followed by lower outer in 6% and diffuse, i.e., more than 2 quadrants involved in 12% cases. This may be attributed to a greater amount of breast tissue in the upper outer quadrant than other sectors of the breast.

We have observed that ALN positivity correlates with the location of the primary tumor. The presence or absence of ALNI is the most important prognostic indicator for patients with breast cancer. Increase in the number of involved ALNs is associated with an increased probability of recurrence and mortality.[39] Hence, quadrant of involvement can emerge as a clinically useful prognostic factor in breast cancer.

Although women with tumors in the upper outer quadrant are likely to have more number of ALNs and predictably poorer outcome, but they are also likely to have the most complete surgical management of the tumor burden where axillary Level I and II dissection is a standard procedure. Compared to these patients, women with tumor in the inner quadrant, which may have drainage also to other lymph nodes outside Level I and II of the axilla (mostly internal mammary chain), may have a higher likelihood of having regional undiscovered metastatic spread after standard surgical treatment.[40,41-44] Thus, incomplete removal of tumor tissue among women with tumors located away from the axilla may explain why survival disadvantage is observed in them.

Similar to a study by Kumar and Mukherjee,[33] our results also showed that lymph node involvement is more in hormone receptor negative tumors as compared to other subtypes. Although Luminal A was the most common subtype but 5 out of a total of 6 patients in Triple negative type had N3 lymph node status. Some studies contradict this finding[34,45,46] as they found that triple-negative subtype was associated with a lower risk of lymph node metastasis as compared to other subtypes. Hence, it can be assumed that other factors might also play a role in determining the relation between receptor status and lymph node status and further research may be required to determine them. In future, molecular classification of early-stage breast cancer using immunohistochemistry may help in predicting the probability of developing ALN metastasis [Table 5].

Limiting factor in our study was nonavailability of SLNB at our institute. Hence, all the cases of doubtful lymph nodes had to undergo ALND to decrease the risk of missed nodal metastasis.

This study was designed to develop a correlation between site and size of carcinoma breast with ALNI based on clinical examination, ultrasound findings, intra-operative findings, and post-operative histopathological reports.

As the size of tumor increases, there is an increase in ALNI which suggests that there may be high nodal involvement even in T2 tumors, so there is a need for early screening. Tumor size can be used as a guide for more limited axillary dissection as an alternative to SLNB for T1 node negative tumors. Quadrant of involvement can emerge as a clinically useful prognostic cancer in breast cancer. The increasing use of SLNB may reduce the complications of ALND at the expense of increasing the risk of missed nodal metastasis. The decision of doing SLNB or ALND in early node-negative tumors should be based on individual patient needs. Molecular classification of early-stage breast cancer using IHC may help in predicting the probability of developing ALN metastasis. It provides a survival advantage for patients with ER + PR + tumors as a treatment in the form of adjuvant hormonal therapy is available easily and is cost-effective.

Conclusion

This study concludes that there is a higher incidence of lymph node positivity with increasing size of the breast tumor as well as for tumors located at the upper outer quadrant of the breast.

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Conflicts of interest

There are no conflicts of interest.

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