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Impact of Molecular Subtypes of Breast Cancer on Axillary Lymph Node Metastasis: A Tertiary Center Experience

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ABSTRACT

Background: Axillary lymph node metastasis (ALNM) is one of the important prognostic factors of breast cancer. The objective of this study was to assess the risk of ALNM in different molecular subtypes determined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2Neu) of breast cancer.

Methods: This retrospective study was conducted on patients who had undergone upfront breast conserving surgery (BCS) or modified radical mastectomy (MRM). Patients were classified as HR (hormone receptor)+/ HER2Neu- (ER or PR positive and HER2Neu negative), HR+/HER2Neu+ (ER or PR positive and HER2Neu positive), HR-/HER2Neu- (ER, PR and HER2Neu negative or triple negative or basal type), and HR-/HER2Neu+ (ER or PR negative and HER2Neu positive). The association between clinicopathological variables and ALNM was evaluated in logistic regression analyses.

Results: In this study, 476 patients met the inclusion criteria, and had 67.2% ALNM at diagnosis. ALNM was statistically significantly correlated with age ≤ 40 years (P=0.026), tumor grade (P=0.007), pathological tumor size (P<0.001), estrogen receptor (P=0.045), molecular subtypes (P=0.021), LVI (P<0.001), and PNI (P<0.001). Post Hoc test revealed that HR-/HER2Neu+ subtypes of breast cancer had the highest and HR+/HER2Neu- had the lowest risk of ALNM.

Conclusion: ALNM may be predicted by molecular subtypes of breast cancer. The risk of ALNM is less in TNBC although it is clinically more aggressive. These findings may play an important role in gauging the individualized axillary management in breast cancer.

INTRODUCTION

Breast cancer ranks top in cancer incidence in 2020 surpassing the lung cancer, estimating 11.7% of all cancer cases.[1] The incidence of breast cancer in India is 13.5%, ranking first in cancer incidence and cancer related death.[2] Breast cancer is one of the most heterogeneous diseases considering its origin, pathology, tumor biology, molecular subtypes, gene mutations, disease progression, therapeutic response, and clinical outcome.[3] Axillary lymph node metastasis is one of the important factors in determining staging, treatment, and outcome in breast cancer patients.[4] Several factors including age, tumor location, tumor size, tumor grade, and lymphovascular invasion (LVI) predict the axillary lymph nodes metastasis (ALNM).[5] Breast cancers are classified into different molecular subtypes based on the expression of estrogen receptor (ER), progesterone

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receptor (PR), and human epidermal growth factor receptor 2 (HER2Neu) on immunohistochemical analyses. These subtypes may be used to guide the treatment, predict the response and outcome of breast cancer.[6, 7] However, the role of breast cancer molecular subtypes (BCMS) in predicting the axillary lymph node metastasis is not well established.[8, 9] In this study, we retrospectively analyzed clinicopathological data to predict the risk of axillary lymph node metastasis according to breast cancer molecular subtypes.

METHODS

A retrospective single institutional observational study was conducted at the department of radiotherapy, Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata. All cases of registered nonmetastatic breast carcinoma from January 2013 to September 2018 were retrieved from medical records files and analyzed. The patients included were females who had histopathologically confirmed diagnosis of unilateral breast carcinoma and underwent either breast conservative surgery (BCS) or modified radical mastectomy (MRM) with axillary lymph node dissection (ALND). Patients treated with neoadjuvant chemotherapy or recurrent breast carcinomas were excluded from the study. Four hundred and seventy six (476) patients meeting the inclusion criteria were included in this study. Clinicopathological features including age at presentation, age group≤ 40 years,[10, 11] post-menopausal, pathological tumor size (pT), pathological lymph node (pN), molecular subtypes of nonmetastatic breast carcinoma were studied with respect to axillary lymph node metastasis. Tumors with immunohistochemistry (IHC) of estrogen receptor (ER), progesterone receptor (PR) having expression≥1% were considered positive. Immunohistochemistry (IHC) for HER2Neu was done on formalin-fixed paraffin-embedded sections by polymer horseradish peroxide technique. A score of +3 for human epidermal growth factor receptor 2 (HER2Neu) was considered as HER2Neu positive, a score of 0 or +1 was considered as HER2Neu negative while a score of +2 was considered as equivocal. A histopathological specimen having an IHC score of +2 for HER2Neu was considered for fluorescence in situ hybridization (FISH) study to find out whether the tissue specimen was HER2Neu negative or positive. FISH negative for HER2Neu was considered as HER2Neu negative and FISH positive for HER2Neu was considered as HER2Neu positive. The IHC result of Ki-67 was not available for all patients; therefore, molecular subtypes were not classified as per criteria provided at St. Gallen International Breast Cancer Conference.[12]

In this study, patients were classified as HR (hormone receptor)+/HER2Neu- (ER or PR positive and HER2Neu negative), HR+/HER2Neu+ (ER or PR positive and HER2Neu positive), HR-/HER2Neu- (ER, PR and HER2Neu negative or triple negative or basal type), and HR-/HER2Neu+ (ER or PR negative and HER2Neu positive). The histological grades of tumor were determined using modified Scarff-Bloom Richardson scale.[13] All the patients were staged according to American Joint Committee on Cancer (AJCC TNM), seventh edition.[14] The patients received their adjuvant treatment including systemic chemotherapy, radiotherapy, hormonal therapy, and trastuzumab according to stage, risk factors, hormonal receptor (HR), and HER2Neu status. Those patients who had undergone BCS were advised for whole breast radiotherapy and lumpectomy cavity boosts were given according to their indication.[15] Following completion of the treatment, the patients were followed up once every month for the first three months, every three months for one year, every six months for the next five years. The information was entered into predesigned proforma (data capture sheet) followed by analysis of different clinicopathological characteristics and their correlations.

Ethical approval

The Ethics Committee of Institute of Post Graduate Medical Education and Research, Kolkata waived ethical approval in view of retrospective nature of the study and all the procedures being performed were part of the routine care.

Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS for Windows, version 25.0) was used for statistical analysis. Descriptive statistics were used to characterize the study population using frequencies, mean, and median. Continuous variables were analyzed using the student's t-test. Univariate analysis of factors associated with axillary lymph node metastasis was conducted using logistic regression analysis and factors found to be significant were included in multivariate logistic regression analysis to find out the independent factors associated with axillary lymph node metastasis. Analysis of variance (ANOVA) was used to compare the means of the different groups with regard to a variable. A $P<0.05$ was considered statistically significant in all performed analyses.

RESULTS

In this study, 476 nonmetastatic breast cancer patients were registered at our institute from January 2013 to September 2018 and underwent upfront BCS or MRM. The median age at diagnosis was 46 years. Axillary lymph nodes showed 67.2% nodes positive and 32.8% nodes negative for metastasis. The median number of retrieved axillary lymph nodes in the pathological specimen was 10 (1-51) and the median number of metastatic axillary lymph nodes was 2 (0–32). Estrogen and progesterone receptors were found

positive in 46, and 32.8%, respectively. IHC results for HER2Neu showed a score of 1 (294), a score of 2 (23), and a score of 3 (159) in 61.8, 4.8, and 33.4% of the patients. The tissue specimen of patients showing an IHC score of 2 for HER2Neu underwent FISH study (23), which showed 52.1% (12) of them were FISH positive and 47.8% (11) FISH negative for HER2Neu gene amplification. During the median follow-up of 38 months (14–59), 25% showed recurrence. The different clinicopathological features are depicted in Table 1. Association between molecular subtypes, axillary lymph node metastasis, and tumor size is depicted in Table 2.

Table 1. Clinicopathological characteristics of patients

Variables		N	%
Presenting Symptom	Pain	59	12.4
	Lump	279	58.6
	Lump with pain	80	16.8
	Nipple discharge	10	2.1
	Lump with ulcer	48	10.1
Side	Right	225	47.3
	Left	251	52.7
Histopathological Subtype	Cribriform	24	5.0
	ILC	5	1.1
	Medullary	12	2.5
	NOS	435	91.4
Grade	Grade I	9	1.9
	Grade II	210	44.1
	Grade III	257	54.0
Type of Surgery	BCS	54	11.3
	MRM	422	88.7
Pathological T	pT1	24	5.0
	pT2	193	40.5
	pT3	173	36.3
	pT4	86	18.1
Pathological N	pN0	156	32.8
	pN1	143	30.0
	pN2	144	30.3
	pN3	33	6.9
Stage	Stage IA	18	3.8
	Stage IIA	74	15.5
	Stage IIB	107	22.5
	Stage IIIA	170	35.7
	Stage IIIB	72	15.1
	Stage IIIC	35	7.4
LVI	Negative	80	16.8
	Positive	396	83.2
PNI	Negative	199	41.8
	Positive	277	58.2
Axillary lymph node metastasis	Negative	156	32.8
	Positive	320	67.2
Molecular subtypes	HR+/HER2Neu-	150	31.5
	HR+/HER2Neu+	91	19.1
	HR-/HER2Neu-	155	32.6
	HR-/HER2Neu+	80	16.8
Recurrence	Yes	177	37.2
	No	299	62.8

Axillary lymph node involvement is statistically significantly associated with age ≤ 40 years (χ^2-4.925; P=0.026), tumor grade (χ^2- 9.846; P=0.007), pathological tumor size (χ^2- 24.645; P<0.001), estrogen receptor (χ^2- 4.015; *P*=0.045), molecular subtypes (χ^2- 9.711; P=0.021), LVI (χ^2- 26.686; P<0.001), and PNI (χ^2- 37.136; P<0.001). Axillary lymph node involvement is statistically significantly not associated with HER2Neu status (χ^2- 2.972; P=0.226), progesterone receptor (χ^2- 0.196; P=0.658), and post-menopausal status (χ^2- 0.058; P=0.809).

The univariate logistic regression analysis showed that the age group ≤ 40 years (Odds ratio-0.604; P=0.027), tumor grade (Odds ratio-1.498; 0.026), tumor size (Odds ratio-1.724; P<0.001), LVI (Odds ratio-3.518; P<0.001), PNI (Odds ratio-3.371; P<0.001), and molecular subtypes (Odds ratio-1.286; P=0.006) are statistically significantly associated with axillary lymph node metastasis (Table 3). The multivariate logistic regression analysis of factors associated with axillary lymph node involvement showed that tumor size (Odds ratio-1.460; P=0.005), LVI (Odds ratio-2.261; P=0.004), PNI (Odds ratio-2.592; P<0.001), and molecular subtypes (Odds ratio-1.442; P<0.001) are the independent factors affecting the axillary lymph nodes metastasis (Table 4).

The results of analysis of variance (ANOVA) with post hoc test of least significant differences (LSD) between axillary nodal metastasis and molecular subtypes of breast cancer are presented in Table 5 and Figure 1. It is clear from Figure 3 that HR-/HER2Neu+ subtypes of breast cancer had the highest risk of axillary lymph node involvement and HR+/HER2Neu– had the lowest risk of axillary lymph node involvement.

Table 2. Association between tumor size, axillary lymph node metastasis and molecular subtypes of breast cancer.

		Molecular subtypes								P
		HR+/HER2Neu-		HR+/HER2Neu+		HR-/HER2Neu-		HR-/HER2Neu+		
		Count	N %	Count	N %	Count	N %	Count	N %	
Pathological T	pT1	8	1.7	3	0.6	9	1.9	4	0.8	0.902
	pT2	56	11.8	40	8.4	67	14.1	30	6.3	
	pT3	55	11.6	30	6.3	55	11.6	33	6.9	
	pT4	31	6.5	18	3.8	24	5.0	13	2.7	
Pathological N	pN0	63	13.2	26	5.5	48	10.1	19	4.0	0.032
	pN1	35	7.4	31	6.5	48	10.1	29	6.1	
	pN2	37	7.8	27	5.7	54	11.3	26	5.5	
	pN3	15	3.2	7	1.5	5	1.1	6	1.3	

Table 3. Univariate logistic regression analysis of factors associated with axillary lymph node metastasis.

Characteristics	Odds ratio	95% Confidence Interval	P
Age ≤ 40 years*	0.604	0.386 – 0.945	0.027
Post-menopausal[#]	1.049	0.711 – 1.547	0.809
Tumor grade[@]	1.498	1.050 – 2.137	0.026
Tumor size[$]	1.724	1.346 – 2.207	< 0.001
LVI**	3.518	2.145 – 5.770	< 0.001
PNI[##]	3.371	2.262 – 5.023	< 0.001
Molecular subtypes[$$]	1.286	1.076 – 1.538	0.006

*age ≤ 40 vs > 40 years; [#] Yes vs No; [@] grade I vs Grade II and III; [$] T1 vs T2, T3, T4; ** Positive vs Negative; [##] Positive vs Negative; [$$]HR+/HER2Neu- vs HR+/HER2Neu+, HR-/HER2Neu-, HR-/HER2Neu+

Table 4. Multivariate logistic regression analysis of factors associated with axillary lymph node metastasis.

Characteristics	Odds ratio	95% Confidence Interval	P
Age ≤ 40 yrs*	0.662	0.407 – 1.074	0.95
Tumor grade[@]	1.280	0.865 – 1.893	0.218
Tumor size[$]	1.460	1.120 – 1.903	0.005
LVI**	2.261	1.308 – 3.909	0.004
PNI[##]	2.592	1.676 – 4.010	< 0.001
Molecular subtypes[$$]	1.442	1.181 – 1.759	< 0.001

*age ≤ 40 vs > 40 years; [@] grade I vs Grade II and III; [$] T1 vs T2, T3, T4; ** Positive vs Negative; [##] Positive vs Negative; [$$]HR+/HER2Neu- vs HR+/HER2Neu+, HR-/HER2Neu-, HR-/HER2Neu+

Table 5. Analysis of variance showing post hoc test with least significant differences (LSD) between axillary lymph node metastasis and molecular subtypes of breast cancer.

(I) Molecular subtypes	(J) molecular subtypes	Mean Difference (I-J)	P	95% Confidence Interval	
				Lower Bound	Upper Bound
HR+/HER2Neu-	HR+/HER2Neu+	-0.13*	0.031	-0.26	-0.01
	HR-/HER2Neu-	-0.11*	0.040	-0.22	-0.01
	HR-/HER2Neu+	-0.18*	0.005	-0.31	-0.06
HR+/HER2Neu+	HR+/HER2Neu-	0.13*	0.031	0.01	0.26
	HR-/HER2Neu-	0.02	0.698	-0.10	0.15
	HR-/HER2Neu+	-0.05	0.500	-0.19	0.09
HR-/HER2Neu-	HR+/HER2Neu-	0.11*	0.040	0.01	0.22
	HR+/HER2Neu+	-0.02	0.698	-0.15	0.10
	HR-/HER2Neu+	-0.07	0.262	-0.20	0.05
HR-/HER2Neu+	HR+/HER2Neu-	0.18*	0.005	0.06	0.31
	HR+/HER2Neu+	0.05	0.500	-0.09	0.19
	HR-/HER2Neu-	0.07	0.262	-0.05	0.20

*The mean difference is significant at the 0.05 level

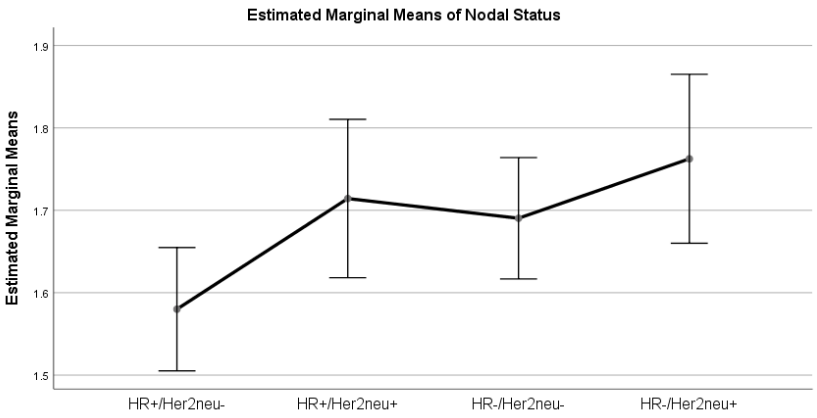

Figure 1. Axillary lymph node metastasis according to molecular subtypes of breast cancer.

DISCUSSION

This study aimed to assess the impact of molecular subtypes of breast cancer on axillary lymph nodal involvement. The median age at presentation in this study was 46 years, which was similar to other Indian studies, which reported median age at diagnosis between 45 and 49 years.[11, 16-18] The median age at diagnosis of our patients is similar to that for Korean and Taiwanese population but lower than that for

western population.[19, 20] Majority of the patients (58.2%) were postmenopausal. Raina *et al.* reported in their study an equal distribution of pre- and post-menopausal women, 49% vs. 48%, respectively.[21] Pathologically pT1, pT2 and pT3 were observed in 5.1%, 40.5%, and 36.3% patients, respectively. A similar finding was observed by Kumar *et al.* in their study on 56 patients with breast cancer and reported pT1, pT2, and pT3 were 14.2%, 55.4%, and 30.4%, respectively.[22] Nene *et al.* in reported almost 60% patients having a tumor size of 5cm or less.[23] A study of 186 patients by Harish *et al.* reported almost 30% of patients presented with pT3.[16] These studies corroborate the findings of our study. In this study, we found stage IA in 3.8%, stage IIA in 15.5%, stage IIB in 22.5%, stage IIIA in 35.7%, stage IIIB in 15.1%, and stage IIIC in 7.4% of the patients. A large Indian multicentric study by Doval *et al.* reported stage I in 11.8%, stage IIA in 40.9%, stage IIB in 25.9%, stage IIIA in 12.6%, and stage IIIC in 8.8% of the participants in their study.[24] In this study, 67.2% of the patients had axillary lymph node metastasis. Gogoi *et al.* reported 80% of axillary lymph node metastasis.[25] A large Indian study reported about 48% of patients with pathologically involved axillary lymph nodes.[24] A larger percentage of patients in our cohort presented with tumors of size>5cm and axillary lymph node positivity compared to the participants in other Indian or Western studies, possibly due to inclusion of patients who had undergone upfront surgical intervention in this study.[26] This may also reflect the late presentation of the disease in association with the natural course of tumor biology, treatment seeking behavior of patients towards cancer or lack of public awareness.

Axillary lymph node metastasis was associated with age, grade of the tumor, tumor size, LVI, PNI, and molecular subtypes as reported by most of the studies in the literature, a finding which is also supported by findings of this study.[16, 21, 23-25] The distribution of molecular subtypes of breast cancer in this study was HR+/HER2Neu- in 31.5%, HR+/HER2Neu+ in 19.1%, HR-/HER2Neu- (TNBC) in 32.6%, and HR-/HER2Neu+ in 16.8% of their subjects, respectively. Indian studies reported HR+/HER2Neu- in 19.5 - 55.2%, HR+/HER2Neu+ in 21.3 - 30%, TNBC in 14.7 - 38.2%, and HR-/HER2Neu+ in 17.7 - 21%.[25, 27-29] A large retrospective study including 1945 patients by Dawood *et al.* reported Luminal A in 65.8%, Luminal B in 14.3%, TNBC in 10.4%, HER2Neu enriched in 4.9% of their participants, respectively.[30] Studies from China, Korea and Malaysia reported Luminal A in 34 - 53.1%, Luminal B in 21.7- 59.2%, TNBC in 13.6 – 20%, and her2enriched in 9 – 27.2% of their participants.[31-33]

HR-/HER2Neu+ and HR+/HER2Neu- had the highest and lowest risk of axillary lymph node metastasis found in our study. Vaidyanathan *et al.* in their study on 368 patients reported HER2Neu over-expression was more significantly associated with axillary lymph node metastasis compared to hormone receptor positive cases.[34] There is paucity of data on molecular subtypes and risk of axillary lymph node metastasis. There are very few Indian studies directly analyzing the risk of lymph node metastasis with molecular subtypes of breast cancer. Si *et al.* reported HR-/HER2Neu- and HR+/HER2Neu+ having the lowest and highest risk of axillary lymph node metastasis.[35] He *et al.* reported in their study on more than 3000 patients that HR-/HER2Neu- had the lowest risk of axillary lymph node metastasis compared to other molecular subtypes of breast cancer.[36] Rossing *et al.* also reported that TNBC or basal like tumor had the least risk of axillary lymph node metastasis.[37] Several studies suggest the association between molecular subtypes and axillary lymph node metastasis[38-42], while Jones *et al.* and Gangi *et al.* reported no association between molecular subtypes and axillary lymph node metastasis.[43, 44] There is also an interesting finding in the Korean study, which reported higher risk of axillary lymph node metastasis in patients with TNBC.[44] However, the role of molecular subtypes of breast cancer in predicting the axillary lymph node metastasis is controversial due to heterogeneous findings in the literature.[45, 46]

There are some limitations in our study. It is a single center retrospective study. The classification of molecular subtypes was not done according to criteria laid down at St. Gallen International Breast Cancer Conference.

CONCLUSION

In conclusion, our results show that axillary lymph node metastasis may be predicted by molecular subtypes of breast cancer. HR-/HER2Neu+ subtypes of breast cancer had the highest and HR+/HER2Neu- had the lowest risk of axillary lymph node metastasis. The risk of axillary lymph node metastasis is less in TNBC although it is clinically more aggressive. These finding may play an important role in gauging the individualized axillary management in breast cancer. However, a larger study needs to confirm our findings.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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