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The role of breast cancer molecular subtypes in axillary lymph node positivity

Mehmet Aslan[1], Abdullah Gunes[2]

[1]Medical Park Kocaeli Hospital, Department of Surgical Oncology, Kocaeli, Türkiye
[2]SBU Derince Training and Research Hospital, Department of General Surgery, Kocaeli, Türkiye

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Abstract

Breast cancer is a complex disease with various histopathological and molecular features. We aimed to investigate the clinicopathological predictor factors, especially molecular sub-types, on axillary involvement in breast cancer patients. Female patients who underwent mastectomy or breast-conserving surgery combined with sentinel lymph node biopsy or axillary dissection were included in this study. Clinicopathological features including age, tumor location, lymphovascular invasion, perineural invasion, grade, tumor size, and hormonal receptor status were recorded. The cohort consisted of 238 patients. The mean age of the participants was 55.24±11.52 years. The most common molecular sub-type was Luminal B HER2- with 30.3%. This sub-type was followed by Triple-Negative (22.7%), Luminal A (18.9%), non-Luminal HER2$^+$ (16.4%), and Luminal B HER2+ (11.8%), respectively. There was a significant relationship between the tumor sub-type and the axillary involvement (p=0.003). Axillary lymph node metastases were less common in Luminal A and Triple-Negative tumors. In luminal A sub-type, axillary involvement was the lowest with a rate of 24.4% (OR=0.260, 95%Cl: 0.124-0.543, p<0.001). In contrast, Luminal B HER2$^+$ and non-Luminal HER2$^+$ sub-types were highly positive in terms of axillary involvement. Luminal B HER2$^+$ sub-type had the highest rate (60.7%). Luminal A, Triple-Negative tumors had a decreased risk of lymph node positivity as compared to other sub-types. Molecular subtypes should be regarded as an important factor affecting the condition of the axilla.

Keywords: Breast cancer, molecular sub-types, hormonal receptor status

Introduction

Breast cancer is a complex disease that displays various histopathological and molecular features [1,2]. Axillary lymph node (LN) positivity and the number of positive lymph nodes are the most important prognostic factor in breast cancer. Sentinel lymph node biopsy (SLNB) is a surgical method applied for the evaluation of axillary lymph nodes [3,4].

The determination of the risk of positive axillary LN is essential for therapeutic decisions. Some clinicopathological predictors have been defined for LN status including age, tumor diameter, grade and molecular sub-types [5-8].

Breast cancer is divided into four main sub-types based on hormone receptor status and biomarkers. Luminal A (LA) and Luminal B (LB) sub-types are positive for estrogen receptors (ER) and progesterone receptors (PR), with different proliferation indexes. Non-Luminal HER2$^+$ sub-type is defined by overexpression of the HER2 gene and Triple-Negative (TN) sub-type is negative for all estrogen or progesterone receptors and HER2 gene [9].

Our aim in this study is to investigate the effects of clinicopathological predictor factors, especially molecular sub-types, on axillary LN positivity.

Material and Methods

The data of patients who undergone breast cancer surgery

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Corresponding Author: Mehmet Aslan, Medical Park Kocaeli Hospital, Department of Surgical Oncology, Kocaeli, Türkiye
Email: ege_mehmetaslan@hotmail.com

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between June 2015 and July 2019 at the SBU Derince Training and Research Hospital were recorded retrospectively.

The cohort consisted of female patients with unilateral invasive breast cancer who were evaluated with SLNB or axillary dissection along with mastectomy or breast-conserving surgery and who did not get neoadjuvant therapy. The study was approved by the local ethics committee, the Unique Identifying Number is 2020-176.

Patient characteristics were obtained from the hospital records. The conditions of ER, PR, and HER2 receptor were determined by immune histochemistry. Estrogen and progesterone receptors were considered positive if stained more than 1%. HER2 receptor positivity was determined by immunohistochemically 3^+ staining and/or with fluorescent in situ hybridization (FISH) method. Molecular sub-types were classified as LA, LB $HER2^-$, LB $HER2^+$, non-Luminal $HER2^+$ and TN by the St. Gallen Consensus Conference performed in 2013 [9]. SLNB was performed following the definition specified in the literature [10].

Clinicopathological features, that are thought to have an impact on axillary lymph node involvement, including age, tumor location, lymphovascular invasion (LVI), perineural invasion (PNI), grade, tumor diameter, and molecular sub-types have been studied in detail.

Statistical Analysis

SPSS version 22.0 was used for statistical analyses. Since this is a two-group study, Pearson Chi square and Fischer exact tests were used to evaluate categorical data, Student T test was used for scale parametric data, Mann Whitney U tests were used for non-scale parametric data. In the regression analysis, Binary logistic regression test was performed. P-value<0.05 was considered significant.

Results

The demographic and clinical data of the 238 patients included in the study are shown in detail (Table 1). The cohort consisted of females with a mean age at diagnosis of 55.24±11.51 years (range:30-86).

The surgical intervention applied to the patients were as follows, i) Breast Conserving Surgery (BCS) with SLNB in 89 patients, ii) BCS with Axillary Lymph Node Dissection (ALND) due to LN involvement in SLNB in 112 patients, iii) Simple Mastectomy (SM) with SLNB in 14 patients, iv) Modified Radical Mastectomy (MRM) in 23 patients.

Invasive ductal carcinoma (IDC) was the most common type of breast cancer among the patients (188 patients). 60.9% of patients (145 patients) had stage 2 disease. While there were no LN metastasis in 50% of patients, the average number of metastatic nodes in patients with axillary LN metastasis was 2.55.

In the distribution of molecular sub-types, LB $HER2^-$ was the most common group with 72 patients, while LB $HER2^+$ was the least detected group with 28 patients. The distribution of lymph node metastases according to clinicopathological factors is shown (Table 2).

Table 1. Demographic&clinicopathologic distribution of all patients

Age, year, mean±SD, range	55.24±11.51 (30-86)
Primary Cancer Diagnosis	
IDC	188 (79%)
ILC	17 (7.1%)
Papiller carcinoma	3 (1.3%)
Sarcoma	1 (0.4%)
Spindle cell carcinoma	1 (0.4%)
Mucinous carcinoma	7 (2.9%)
Mix carcinoma	14 (5.9%)
Medullary carcinoma	4 (1.7%)
Paget Disease	1 (0.4%)
Neuroendocrine carcinoma	1 (0.4%)
DCIS	1 (0.4%)
Laterality, n(%)	
Right	113 (47.5%)
Left	122 (51.3%)
Bilateral	3 (1.3%)
Localization, n(%)	
UOQ	121 (50.8%)
UIQ	30 (12.6%)
LOQ	26 (10.9%)
LIQ	8 (3.4%)
Retroareolar	21 (8.8%)
Multicentric	32 (13.4%)
Type of Surgery	
BCS+SLNB	89 (37.4%)
BCS+ALND	112 (47.1%)
MRM	23 (9.6%)
SM	14 (5.9%)
Tumor Size, mm, mean	28.20±16.74 (0-110)
T Invasion Degree, n(%)	
T1	51 (21.4%)
T2	161 (67.6%)
T3	18 (7.6%)
T4	8 (3.4%)
Metastatic Lymph Node Status, n(%)	
Absent	120 (50.4%)
Present	118 (49.6%)
Metastatic Node, number, mean±SD, range	2.55±4.93 (0-42)
N Stage Status, n(%)	
N0	119 (50%)
N1	68 (28.6%)
N2	46 (19.3%)
N3	5 (2.1%)
Stage, n(%)	
Stage 1	29 (12.2%)
Stage 2	145 (60.9%)
Stage 3	64 (26.9%)
Grade, n(%)	
Low	47 (19.7%)
Intermediate	145 (60.9%)
High	46 (19.3%)
PNI Status	
Negative	163 (68.5%)
Positive	75 (31.5%)
LVI Status	
Negative	143 (60.1%)
Positive	95 (39.9%)
Molecular Sub-types	
Luminal A	45 (18.9%)
Luminal B $HER2^-$	72 (30.3%)
Luminal B $HER2^+$	28 (11.8%)
Non-Luminal $HER2^+$	39 (16.4%)
Triple Negative	54 (22.7%)

SD, standard deviation; Min, minimum; Max, maximum; BCS, breast conserving surgery; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; MRM, modified radical mastectomy; SM, simple mastectomy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; UIQ, upper inner quadrant; UOQ, upper outer quadrant; LIQ, lower inner quadrant; LOQ, lower outer quadrant; PNI, perineural invasion; LVI, lymphovascular invasion

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Table 2. Association between lymph node metastases and clinicopathological factors

Clinicopathological Factors	No. Of Patients (%)		P Value
	Lymph Node Metastases (-) (120 patients 50.4%)	Lymph Node Metastases (+) (118 patients 49.6%)	
Age, year, mean±SD, range	55.07±11.95(30-86)	55.41±11.10(33-84)	p=0.820†
Primary Cancer Diagnosis			
IDC	88	100	
ILC	11	6	
Papiller carcinoma	2	1	
Sarcoma	0	1	
Spindle cell carcinoma	1	0	p=0.104‡
Mucinous carcinoma	7	0	
Mix carcinoma	6	8	
Medullary carcinoma	3	1	
Paget Disease	1	0	
Neuroendocrine carcinoma	0	1	
DCIS	1	0	
Laterality, n(%)			
Right	55	58	p=0.166‡
Left	65	57	
Bilateral	0	3	
Localization, n(%)			
UOQ	59	62	
UIQ	21	9	
LOQ	17	9	**p=0.032‡**
LIQ	4	4	
Retroareolar	9	12	
Multicentric	10	22	
Tumor Size, mm, range	24.5 (0-70)	25 (0-110)	**p=0.001§**
T Invasion Degree, n(%)			
T1	30	21	
T2	80	81	p=0.131‡
T3	5	13	
T4	5	3	
N Stage Status, n(%)			
N0	119	0	
N1	1	67	**p<0.001‡**
N2	0	46	
N3	0	5	
Stage, n(%)			
Stage 1	29	0	**p<0.001‡**
Stage 2	86	59	
Stage 3	5	59	
Grade, n(%)			
Low	34	13	**p=0.001‡**
Intermediate	70	75	
High	16	30	
PNI Status			
Negative	98	65	**p<0.001‡**
Positive	22	53	
LVI Status			
Negative	104	39	**p<0.001‡**
Positive	16	79	

SD, standard deviation; Min, minimum; Max, maximum; † Student T test; ‡χ2 tests; §Mann Whitney U test
SD, standard deviation; Min, minimum; Max, maximum; IDC, invasive ductal carcinoma; ILC, invasive lobuler carcinoma; UIQ, Upper Inner Quadrant; UOQ, upper outer quadrant; LIQ, lower inner quadrant; LOQ, lower outer quadrant; PNI, perineural invasion; LVI, lymphovascular invasion

Lymph Node Status:

Of the patients who had axillary LN involvement, the mean age at diagnosis was 55.07 years (range: 30-86) and the upper outer quadrant localization was the most common tumor localization. Multicentric and retroareolar tumors were more common (p=0.032). Tumor size, presence of LVI and PNI, were significantly higher (p=0.001).

In patients without axillary LN metastasis, the mean age was 55.41 years (range: 33-84) and upper outer quadrant localization was also the most common tumor localization. Tumor size was significantly lower and low grade tumors were most commonly seen in this group (p=0.001).

Molecular Sub-types:

We found a statistically significant difference in the distribution of axillary LN metastasis according to molecular sub-types (p=0.003) (Table 3).

Of the 45 patients in the LA sub-type, 75.5% had no LN metastases. We also confirmed this result with univariate logistic regression test. There was a significant relationship between LA patients and LN status. This relationship was negatively related and the probability of axillary LN metastases was statistically lower in LA sub-type (OR=0.260, 95%Cl: 0.124-0.543, p<0.001). The accuracy rate of the model is 59.2% (Table 4).

Similarly, there was a statistically significant relationship

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Table 3. Association between lymph node metastases and molecular sub-types

Lymph Node Metastases		Molecular subtype					Total	P Value
		Luminal A	Luminal B HER2$^-$	Luminal B HER2$^+$	Non-Luminal HER2$^+$	Triple Negative		
Negative	Count	34	31	11	16	28	120	**0.003**
	%	28.4%	25.8%	9.1%	13.3%	23.4%	100.0%	
Positive	Count	11	41	17	23	26	118	
	%	9.3%	34.7%	14.4%	19.5%	22.1%	100.0%	
Total Count		45	72	28	39	54	238	

between the LA and other sub-types in terms of the number of LN involvement. Each unit of increase in the number of LN involvement also led to an increase of 1,674 units in the probability that patients were in a sub-type other than the LA sub-type (OR=1.674, 95%Cl: 1.220-2.297, p=0.001).

Table 4. Univariate regression analysis of lymph node metastases for molecular sub-types

Variables	Univariate analysis		
	OR (95% Cl)	Percentage Correct	p value
Luminal A	0.260 (0.124-0.543)	59.2%	<0.001
Luminal B HER2$^-$	1.529 (0.876-2.669)	54.6%	0.136
Luminal B HER2$^+$	1.668 (0.745-3.732)	52.9%	0.213
Non-Luminal HER2$^+$	1.574 (0.785-3.157)	53.4%	0.202
Triple Negative	0.929 (0.506-1.704)	50.4%	0.811

Discussion

Breast cancer tends to spread to axillary lymph nodes and the LN positivity is an independent prognostic factor. The number of axillary LN involvement is similarly associated with overall survival (OS) [11,12].

The ability to predict axillary LN metastasis may be useful for surgeons so that they can modify the axillary treatment plan. In conjunction with The American College of Surgeons Oncology Group Z0011 trial, axillary LN treatment approach has been updated in patients with limited nodal metastasis. Based on the study, patient selection criteria and treatment options for limited axillary surgery were revealed [13].

Studies have been reported to determine the factors that can predict the risk of LN positivity to guide axillary treatment options [14-17].

With the discovery of molecular subtyping by Pereu [18], the opinion that breast cancer is actually a complex disorder rather than a homogeneous has prevailed. The fact that patients with same grade, t stage, or similar nodal status have different early recurrence rate or long-term survival outcomes supported this view. For this reason, we examined the axillary nodal status according to molecular sub-types to find out the effect of hormonal status on axillary LN metastasis.

The present study demonstrated the incidence of nodal metastasis differed according to hormonal receptor status (molecular sub-type) of tumor. Moreover, the presence of PNI or LVI and tumor size were also significantly different between molecular sub-types.

We found LA and TN tumors had a decreased risk of nodal metastasis as compared to other sub-types. LA type had the lowest rate of axillary LN positivity (25%). Howland et al reported a study classifying the factors affecting nodal involvement in breast cancer patients. LA tumors had minimum risk of lymph node involvement, while age, increased tumor grade, tumor diameter and HER2$^+$ sub-type were associated with increased risk of nodal involvement [19]. In a recent study tumor diameter, increased grade, and LVI have been reported as independent factors for LN metastasis in LA sub-type [20]. Moreover, it has been reported that the risk of nodal positivity decreases as patient age increases in LA tumors [21]. Axillary treatment approach may vary depending on the involvement of sentinel or non-sentinel lymph nodes. In a predictive model to evaluate sentinel LN positivity in early breast cancer, sentinel LN metastasis was reported less frequently in HER2$^-$ tumors [22]. In a study evaluating the risk of non-sentinel nodal involvement, it was shown that HER2$^+$ tumors had increased risk than LA tumors [23].

Based on the results of present study, TN breast cancers tended to have lower risk of nodal metastasis as compared to HER2$^+$ sub-types. PNI or LVI was detected in 30% of TN tumors. Most of the TN tumors were having grade 2 disease with 48.1% lymph node positivity and the tumor diameter was greater than LA type. A study that included 20.09 patients demonstrated that TN tumors had a lower risk of nodal involvement than other molecular sub-types [24]. A study that consisted of 3.198 patients revealed that the probability of nodal positivity in TN tumors was significantly lower as compared with other sub-types (28.2% vs 4.-44.8%), although without multivariate analysis [25]. TN breast cancer had a relatively lower rate of axillary LN metastasis as these tumors tend to spread hematologically.

Nodal involvement is more common in HER2$^+$ tumors. Furthermore, PNI or LVI, and grade 3 tumor were more frequently reported in HER2$^+$ sub-type. In LB HER2$^-$, LB HER2$^+$ and non-Luminal HER2+ sub-types, positive axillary LN metastasis ratio was similar and about 60%. Buglioni et al reported that nodal metastasis was significantly associated with HER2$^+$ sub-type and LVI [3].

In contrast, some studies has found no association between nodal metastasis and hormonal receptor status [26,27].

We believe that the above-mentioned effects of the molecular sub-type of the tumor on Axillary LN metastasis can contribute in the treatment of axilla and may find a place in clinical practice. We believe that the hormonal status of the tumor may also be a potential patient selection criterion for determining the axillary treatment approach, and less invasive axillary surgical options

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may be preferred in sub-types with a low nodal involvement rate, such as LA or TN breast cancer. However, randomized-controlled trials are needed to elucidate this hypothesis.

The limitations of this study are that the study was planned retrospectively and the non-sentinel lymph nodes were not examined. Thus, it has the potential to introduce significant bias into our analyses.

Conclusion

Hormonal receptor status can predict axillary LN metastasis. Nodal involvement varies widely among molecular sub-types of breast cancer. LA and TN tumors have decreased incidence of LN metastasis than LB and $HER2^+$ tumors. Molecular sub-types may contribute to the selection of axillary treatment modalities.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
Ethics Board aproval was obtaine from SBU Derince Training and Research Hospital Ethical Board (No: 2020-176).

References

1. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the st. gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol. 2011;22:1736-47.
2. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. Mol Oncol. 2011;5:5-23.
3. Buglioni S, Di Filippo F, Terrenato I, et al. Quantitative molecular analysis of sentinel lymph node may be predictive of axillary node status in breast cancer classified by molecular subtypes. PLoS One. 2013;8:e58823.
4. Voduc KD, Cheang MC, Tyldesley S, et al. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol. 2010;28:1684-91.
5. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol. 2011;29:3885.
6. Fragomeni SM, Sciallis A, Jeruss JS. Molecular subtypes and local-regional control of breast cancer. Surg Oncol Clin N Am. 2018;27:95-120.
7. Sawaki M, Idota A, Ichikawa M, et al. Impact of intrinsic subtype on predicting axillary lymph node metastasis in breast cancer. Oncol Lett. 2014;8:1707-12.
8. Al-Thoubaity FK. Molecular classification of breast cancer: a retrospective cohort study. Ann Med Surg (Lond). 2019;49:44-8.
9. Goldhirsch A, Winer EP, Coates A, et al. Personalizing the treatment of women with early breast cancer: highlights of the st gallen international expert consensus on the primary therapy of early breast cancer 2013. Ann Oncol. 2013;24:2206-23.
10. Keshtgar MR, Ell PJ. Clinical role of sentinel-lymph-node biopsy in breast cancer. Lancet Oncol. 2002;3:105-10.
11. Fisher ER, Anderson S, Redmond C, et al. Pathologic findings from the national surgical adjuvant breast project protocol b-06 10-year pathologic and clinical prognostic discriminants. Cancer. 1993;71:2507-14.
12. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989;63:181-7.
13. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of surgeons oncology group z0011 randomized trial. Ann Surg Sep 2010;252:426-32.
14. Wang NN, Yang ZJ, Wang X, et al. A mathematical prediction model incorporating molecular subtype for risk of non-sentinel lymph node metastasis in sentinel lymph node-positive breast cancer patients: a retrospective analysis and nomogram development. Breast Cancer. 2018;25:629-38.
15. Si C, Jin Y, Wang H, Zou Q. Association between molecular subtypes and lymph node status in invasive breast cancer. Int J Clin Exp Pathol. 2014;7:6800-6.
16. Zhang J, Li X, Huang R, et al. A nomogram to predict the probability of axillary lymph node metastasis in female patients with breast cancer in China: a nationwide, multicenter, 10-year epidemiological study. Oncotarget. 2017;8:35311.
17. Dihge L, Bendahl P, Rydén L. Nomograms for preoperative prediction of axillary nodal status in breast cancer. Br J Surg. 2017;104:1494-505.
18. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406:747-52.
19. Howland NK, Driver TD, Sedrak MP, et al. Lymph node involvement in immunohistochemistry-based molecular classifications of breast cancer. J Surg Res. 2013;185:697-703.
20. Chas M, Boivin L, Arbion F, et al. Clinicopathologic predictors of lymph node metastasis in breast cancer patients according to molecular subtype. J Gynecol Obstet Hum Reprod. 2018;47:9-15.
21. Oliveira Filho HRd, Dória MT, Piato JRM, et al. Criteria for prediction of metastatic axillary lymph nodes in early-stage breast cancer. Rev Bras Ginecol Obstet. 2015;37:308-13.
22. Houvenaeghel G, Lambaudie E, Classe JM, et al. Lymph node positivity in different early breast carcinoma phenotypes: a predictive model. BMC Cancer. 2019;19:1-10.
23. Gülben K, Berberoğlu U, Aydoğan O, et al. Subtype is a predictive factor of nonsentinel lymph node involvement in sentinel node-positive breast cancer patients. J Breast Cancer. 2014;17:370-5.
24. Holm-Rasmussen EV, Jensen MB, Balslev E, et al. Reduced risk of axillary lymphatic spread in triple-negative breast cancer. Breast Cancer Res Treat. 2015;149:229-36.
25. Zhu X, Ying J, Wang F, et al. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status in invasive breast cancer: a 3,198 cases study at National Cancer Center, China. Breast Cancer Res Treat. 2014;147:551-5.
26. Gangi A, Mirocha J, Leong T, et al. Triple-negative breast cancer is not associated with increased likelihood of nodal metastases. Ann Surg Oncol. 2014;21:4098-103.
27. Capdet J, Martel P, Charitansky H, et al. Factors predicting the sentinel node metastases in T1 breast cancer tumor: an analysis of 1416 cases. Eur J Surg Oncol. 2009;35:1245-9.