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Comparison of lymph node metastasis rates in breast cancer molecular subtypes; A retrospective clinical study

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Abstract

Breast cancer is the most common cancer in women. Axillary lymph node metastasis in breast cancer is the most important determinant of long-term prognosis, but isn't an independent risk factor for overall survival. Invasive breast cancer is divided into molecular subtypes according to the presence of estrogen, progesterone and Her2 receptors: these subtypes can guide systemic therapy. Our aim in the study is to compare the axillary lymph node metastasis rates statistically in breast cancer subtypes. Patients treated for breast cancer were retrospectively evaluated in Group1(LuminalA-likeERand/orPR+,Her2 -), Group2 (LuminalB-likeER and/or PR+,Her2-), Group3 (Her2+,ER and/or PR+), Group4 (Her2+,ER and/or PR-) and Group5 (Her2-,ER and PR-) analyzed for tumor type, pathological stage, lymph node metastasis.208 patients were included in the study, and the mean age of the patients was 57.3±12.8. Although the age distribution of the groups was similar, no significant difference was found between the groups in terms of menopausal status. While the lymph node distribution was highly proliferative in Group 2. Demonstrating metastasis organotropisms in the effect of molecular subtypes of breast cancer is necessary to understand tumor mechanisms. ER and PR positive tumors usually metastasize to bones, while Her2+ or triple-negative breast cancers usually tend to metastasize to the visceral system, including the central nervous system. As with distant metastasis habits, lymph node metastasis rates of molecular subtypes of breast cancer can also vary. Being aware of these metastasis possibilities is also helpful in understanding the clinical behavior of the disease. It is important to know the molecular subtypes and susceptibility of lymphatic metastases as well as trying to avoid unnecessary complications of axillary dissection using the sentinel lymph node sampling technique.

Keywords: Breast cancer, molecular subtypes, luminal, er status, pr status, Her2 status

Introduction

Breast cancer is the most common cancer in women and one of the three most seen cancers together with lung and colon cancer worldwide [1]. There are numerous publications in the literature on prognosis, overall survival, early-stage diagnosis, and various subjects about breast cancer due to having seen enormously. To date, axillary nodal involvement at diagnosis has been considered the most critical determinant of long-term prognosis of breast cancer patients. Although other clinicopathologic characteristics have also become increasingly evident in determining the long-term outcome of breast cancer patients [2]. However, it has been reported that axillary node involvement is not an independent factor for overall survival (OS) [3]. It remains important to

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perform nodal staging in breast cancer in order to provide prognostic information and to stratify patients according to their risk for recurrence and mortality.

Currently, at least ten different molecular subtypes have been determined via gene copy number and expression analyses [4]. An immunohistochemical study of the primary tumor classifies invasive breast cancer into subtypes based on the presence of estrogen receptors (ER) and progesterone receptors (PR). Early breast cancer's systemic therapy could be guided by molecular subtypes. According to the St Gallen consensus main subtypes are Luminal A-like, luminal B-like, human epidermal growth factor receptor 2 (HER2), and basal-like [5,6].

Our aim is to compare the lymph node metastasis rates in breast cancer subtypes statistically.

Material and Methods

After taking ethics committee approval numbered 46418926, dated 26/05/2022 from Gulhane Training and Research Hospital, the retrospectively designed clinical study was conducted with 208 women diagnosed and treated with the breast cancer in Gulhane Training and Research Hospital and Diskapi Research and Training Hospital general surgery clinics between 2014 to 2019. The inclusion criteria used for this study were women diagnosed and treated with invasive breast cancer and older than 18 age. The exclusion criteria were unknown hormone receptor (HR) status, missing surgical or pathologic information, the pathology with ductal carcinoma in situ or benign pathologies. Patients were then divided into five groups: Group 1-Luminal A-like subtype [ER or PR positive, or both, HER2 negative, low proliferation (pN0-1)]; Group 2- Luminal B-like subtype [ER or PR positive, or both, HER2 negative, high proliferation (pN2-3)]; Group 3- Luminal (HER2 positive and ER or PR positive, or both); Group 4- HER2 subtype, non-luminal (HER2 positive and ER and PR negative); Group 5-Basal-like subtype (HER2 negative and ER and PR negative; triple-negative breast cancer) [7].

Variables

Information obtained and analysed from the Gulhane Training and Research and Diskapi Research and Training hospitals data bases included patient age at diagnosis, pathological grade of the disease, tumor type, status of lymph node metatstasis rate, type of the used surgery (either breast-conserving, mastectomy, or none); clinicopathologic features included AJCC clinical nodal (N) designation, HER2 receptor status, ER status, and PR status. All data were enrolled and analysed statistically.

Statistical Analysis

While the mean ± standard deviation, median (minimum, maximum) descriptive statistics are given for the numerical variable examined in the study; Number (n) and percentage (%) were given for categorical variables. One-way analysis of variance (ANOVA) was used to compare ages in the groups. Pearson chi-square test was used to compare categorical variables in groups. Statistical analyzes were performed in IBM SPSS Statistics for Windows, Version 21.0 (2012 Armonk, NY: IBM Corp). Statistical significance level was accepted as $p<0.05$.

Results

The mean age of 208 female patients was 57.3±12.8 (median =57.5; min=23; max=92) years. There were a total of 197 patients aged 40 years and over. The age distribution was similar in the groups (x^2=6.321; p=0.176). The percentages of patients for ≥40 years in the groups were 96.9% (n=94) at Group 1, 91.7% (n=33) at Group 2, 88.9% (n=40) at Group 3, 100.0% (n=13) at Group 4 and 100.0 (n=17) at Group 5, respectively (Table 1).

While 150 (72.1 %) of the patients were postmenopausal, 58 female (27.9%) patients were either premenopausal or perimenopausal. A statistically significant difference was determined in groups in terms of menopause status (x^2=19.261; p=0.014). As a result of the binary comparisons; the postmenopausal ratio obtained for group 3 was 53.3% (n=24) significantly lower than those determined for Group 4 and Group 5, while it was similar to Group 1 and Group 2 [Table 1].

Lymph node distribution is significantly different in at least one of the groups (x^2=139.454; $p<0.001$). High proliferative (pN2 and pN3) rate in Group 2, low proliferative (pN0 and PN1) rate in Group 4 is 100.0%.

The distribution varies in pathological stages in groups ($p<0.001$). The observation rates of each phase in the groups and the results of the binary comparison are given in Table 1. Tumor type and surgical type distributions are similar in groups ($p>0.05$).

The lymph node metastasis rates according to the patients' ages, menopause status, and tumor types are given in Table 2 both for groups and in general. There are no patients with age <40 years in Group 4 and 5. The age of all 13 patients in group 4 is ≥40 years and low proliferative. The low proliferative rate of 17 patients aged ≥40 years in Group 5 is 76.5% (n=2).

Discussion

It is known that breast cancer has the direct transition from the primary tumor to the systemic circulation in the systemic metastasis pathway, and in addition, lymph node metastasis may also occur coincidentally [8]. The presence of lymphovascular invasion can be demonstrated with the use of immunohistochemistry via presenting lymphatic endothelial cell marker and in case of invasion, the risk of SLNB positivity and systemic metastasis is significantly higher due to the inclusion of the tumor into the systemic circulation [9].

Demonstrating metastasis organotropisms in the effect of molecular subtypes of breast cancer is necessary to understand tumor mechanism. While ER and PR-positive tumors usually metastasize to bones, HER2-positive or

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Table 1. Distribution of multiple variables in groups (n (%))

	Total(n=208)	Group1(n=97)	Group2(n=36)	Group3(n=45)	Group4(n=13)	Group5(n=17)	F, x^2;p
Age (year)							
Mean±SD	57.3±12.8	59.0±13.4	54.8±12.2	53.6±13.1	61.3±10.3	60.1±8.7	2.231;
Median (min; max)	57.5(23-92)	59(23-92)	55.5(26-76)	51(33-88)	58(49-78)	61(46-74)	0.067
Age group							
< 40 year	11(5.3)	3(3.1)	3(8.3)	5(11.1)	0(0.0)	0(0.0)	6.321;
≥ 40 year	197(94.7)	94(96.9)	33(91.7)	40(88.9)	13(100.0)	17(100.0)	0.176
Status of Menopaus							
Premenopausal	50(24.0)	21(21.6)	11(30.6)	17(37.8)	0(0.0)	1(5.9)	19.261;
Perimenopausal	8(3.8)	3(3.1)	1(2.7)	4(8.9)	0(0.0)	0(0.0)	0.014
Postmenopausal	150(72.1)	73(75.3)[a,b]	24(66.7)[a,b]	24(53.3)[b]	13(100.0)[a]	16(94.1)[a]	
Lymph Node							
Low proliferative	151(72.6)	97(100.0)[a]	0(0.0)[b]	28(62.2)[c]	13(100.0)[a,c]	13(76.5)[c]	139.454;
High proliferative	57(27.4)	0(0.0)	36(100.0)	17(37.8)	0(0.0)	4(23.5)	<0.001
Pathological Grade							
1a	26(12.5)	18(18.6)[a,b]	0(0.0)b	4(8.9)[a,b]	3(23.1)[a]	1(5.9)[a,b]	
1b	2(1.0)	2(2.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
2a	80(38.5)	44(45.4)[a]	2(5.6)b	16(35.6)[a]	9(69.2)[a]	9(52.9)[a]	120.625;
2b	39(18.8)	28(28.9)[a]	2(5.6)b	5(11.1)[a,b]	1(7.7)[a,b]	3(17.6)[a,b]	<0.001*
3a	29(13.9)	5(5.2)[a]	16(44.4)b	6(13.3)[a]	0(0.0)[a]	2(11.8)[a,b]	
3c	27(13.0)	0(0.0)[a]	15(41.7)b	10(22.2)[b]	0(0.0)[a,b]	2(11.8)[b]	
4	5(13.0)	0(0.0)[a]	1(2.8)a,b	4(8.9)[b]	0(0.0)[a,b]	0(0.0)[a,b]	
Type of Tumor							
Invasive ductal	183(88.0)	83(85.6)	34(94.4)	42(93.3)	12(92.3)	12(70.6)	
Invasive lobular	5(2.4)	4(4.1)	0(0.0)	1(2.2)	0(0.0)	0(0.0)	15.887;
Mikst	2(1.0)	2(2.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.190*
Diğer	18(8.7)	8(8.2)	2(5.6)	2(4.4)	1(7.7)	5(29.4)	
Type of Surgery							
MRM+RM	197(94.7)	90(92.8)	34(94.4)	43(95.6)	13(100.0)	17(100.0)	2.464;
BCS	11(5.3)	7(7.2)	2(5.6)	2(4.4)	0(0.0)	0(0.0)	0.651

Meant±SD : Mean±Standart Deviation, F: ANOVA test,x^2: Pearson Ki kare test / *Monte Carlo Ki kare test. a, b, c: There is a diffirence between the two groups shown with the same letter(adjusted p value<0.05)

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Table 2. Distribution of lymph nodes in groups in terms of age, status of menapaus, type of tumor (n(%))

Age	Lymph node	Total(n=208)	Group1(n=97)	Group2(n=36)	Group3(n=45)	Group4(n=13)	Group5(n=17)
< 40 year	Low proliferative (pN0-pN1)	6(54.5)	3(100.0)	0(0.0)	3(60.0)	-	-
	High proliferative (pN2-pN3)	5(45.5)	0(0.0)	3(100.0)	2(40.0)	-	-
≥ 40 year	Low proliferative (pN0-pN1)	145(73.6)	94(100.0)	0(0.0)	25(62.5)	13(100.0)	13(76.5)
	High proliferative (pN2-pN3)	52(26.4)	0(0.0)	33(100.0)	15(37.5)	0(0.0)	4(23.5)
Status of Menopaus							
Premenopausa	Low proliferative (pN0-pN1)	33(66.0)	21(100.0)	0(0.0)	11(64.7)	-	1(100.0)
	High proliferative (pN2-pN3)	17(34.0)	0(0.0)	11(100.0)	6(35.3)	-	0(0.0)
Perimenopausal	Low proliferative (pN0-pN1)	5(62.5)	3(100.0)	0(0.0)	2(50.0)	-	-
	High proliferative (pN2-pN3)	3(37.5)	0(0.0)	1(100.0)	2(50.0)	-	-
Postmenopausal	Low proliferative (pN0-pN1)	113(75.3)	73(100.0)	0(0.0)	15(62.5)	13(100.0)	12(75.0)
	High proliferative (pN2-pN3)	37(24.7)	0(0.0)	24(100.0)	9(37.5)	0(0.0)	4(25.0)
Type of Tumor							
Invasive ductal	Low proliferative (pN0-pN1)	130(71.0)	83(100.0)	0(0.0)	25(59.5)	12(100.0)	10(83.3)
	High proliferative (pN2-pN3)	53(29.0)	0(0.0)	34(100.0)	17(40.5)	0(0.0)	2(16.7)
Invasive lobuler	Low proliferative (pN0-pN1)	5(100.0)	4(100.0)	-	1(100.0)	-	-
	High proliferative (pN2-pN3)	-	-	-	-	-	-
Mixt	Low proliferative (pN0-pN1)	2(100.0)	2(100.0)	-	-	-	-
	High proliferative (pN2-pN3)	-	-	-	-	-	-
The others*	Low proliferative (pN0-pN1)	14(77.8)	8(100.0)	0(0.0)	2(100.0)	1(100.0)	3(60.0)
	High proliferative (pN2-pN3)	4(22.2)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(40.0)

* Medullar Carsinom, Invasive Carsinom which is differantiated as Neuroendocrinal Tumor, Recurrent Invasive Carsinom, Metastatic, Musinous Carsinom, Metaplastic Carsinom

triple-negative breast cancers usually tend to have visceral metastasis, including the central nervous system [10].

The difference in metastasis tendency may affect the frequency of visceral metastasis or bone metastasis even in ER-positive and PR-positive breast cancers due to the change in receptor expression [11]. Once Luminal A and B subtypes were compared with HER2 subtypes and Triple Negative Breast Cancer (TNBC), it was shown that they were significantly associated primarily with bone metastasis and especially with isolated bone metastasis in Luminal A subtypes [10]. Hepatic metastasis was observed more frequently in HER2 subtypes, while lung metastases were found less frequently in Luminal A and B subtypes [10]. No statistically significant difference was found in terms of distant organ metastasis in luminal A and B subtypes [12].

Similar to distant metastasis habits, the lymph node metastasis rates of molecular subtypes of breast cancer may also change. Awaring the metastasis possibilities in question is also useful in understanding the clinical behavior of the disease. It is important to know molecular subtypes and lymphatic metastasis susceptibility, as well as trying to avoid complications of unnecessary axillary dissection using the SLNB sampling technique. Thanks to the regular and predictable structure of the lymphatic system, finding the first regional lymph node to be reached by lymphatic drainage and the fact that this sentinel lymph node acts as an effective filter for tumor cells provides the clinical success of the technique. In addition, this technique provides protection of a significant group of patients from seroma, lymphedema, and nerve damage secondary to trauma that may develop due to axillary dissection [13,14]. While the axillary region involvement and staging of

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the patient are provided with SLNB, it is important to remember that the pathological diagnosis of the patient is metaplastic and its molecular subtype is important in axillary lymph node involvement and disease behavior [15]. The behavioral patterns of the molecular subtypes of the disease are valuable in the effective use of the SLNB technique and in determining the approach to the axilla.

When we investigate the stereoid hormone and HER2 status of breast cancer, nearly 80% of breast cancers are ER-positive and also in 55-65% of them are detected in PR expression. When the distribution of molecular subtypes of 3,198 breast cancer patients is examined by Zhu et al; 2,089 were found as luminal A (65.3%), 608 were luminal B (19.0%), 208 were HER2 overexpression (6.5%) and 293 were basal-like subtype (9.2%) [16]. Additionally, in one of the large series with 2260 patients, Luminal A was 61.1%, Luminal B 16.1%, HER2 enriched 8.6%, and Basal-like 14.2% [17]. In another series of 1134 patients, 116 (10.2%) were ER / PR (+), HER2 (+), 781 (68.9%) were ER / PR (+) and HER2 (-), 85 (7.5%) were ER / PR (-), HER2 (+), and the remaining 152 (13.4 %) were classified as triple negative [18]. Demircioglu et al; in their analysis of 469 patients, they reported Luminal A 231 (49.3%), Luminal B 104 (22.2%), HER2 (+) 62 (13.2%) and Basal-like 72 (15.3%) [19]. In the current study, when evaluated together with the last classification, these rates are Luminal A-like subtype: 97 (46.6%), Luminal B-like subtype: 36 (17.3%), Luminal HER2: 45 (21.6%), Non-luminal HER2: 13 (6.25%), and Basal-like subtype was found to be 17 (8.17%).

When these molecular subtypes are evaluated in terms of prognosis, Luminal A group, which is the largest group, is known as the group that responds well to treatment and has a good prognosis with its effect on hormonotherapy. Luminal B group is known for its high Ki67 level and/or HER2+, with its aggressive features and higher grade compared to Luminal A group. The HER2 +group is a molecular subtype that tends to grow and spread rapidly and has a poor prognosis compared to the hormone + groups. In the HER2 + positive subgroup, with anti-HER2 therapies combined with adjuvant chemotherapies, up to 40 % pathological complete response can be achieved, but the natural course of the disease is aggressive compared to hormone positive groups. The Triple Negative group is the most aggressive subtype compared to the other groups and has a worse prognosis.

When the groups were evaluated in terms of lymph node metastases and frequency; Si et al. in 814 disease series, Luminal HER2 (+) group was defined as the group with the highest rate of lymph node positivity (49.0%), while the other subgroup rates were: Luminal HER2(-) (46.8%); HER2 (+) (44.4%); Luminal A (36.5%); TNBC (34.7%), and statistical significance could not be presented between molecular subtypes and lymph node positivity. Similar to the relationship between stage and proliferation and lymph node metastasis in our series, Si et al were able to detect a relationship between tumor size increase and lymph node metastasis rate [20]. Falck et al. evaluated molecular subtypes on lymph node metastases, they described lymph node metastases showing molecular subtypes different from the main tumor and emphasized that it was aggressive type synchronous lymph node metastasis that could be useful in treatment planning [21]. In our series, when the frequency of lymph node metastasis was evaluated according to molecular subtypes, this rate was low proliferative (pN1) in the Luminal A-like subtype as 61 % while lymph node metastasis rate was high in the Luminal B-like subtype group (pN2, pN3) as 100%. In the luminal HER2 subtype group, the lymph node metastasis rate was 53.3% and in the non luminal HER2 subtype group, the lymph node metastasis rate was only around 23.1%. Finally, the rate of lymph node metastasis in the Basal-like subtype group was 52.9%. In determining the subtype, if we put aside the creation of this group because the Luminal A group has a small amount of metastasis due to its nature, in the Non luminal HER2 Subtype group, very few lymph node metastases were detected. The benefit of neoadjuvant therapy in patients with HER-2-overexpressing tumor is also based on the behavioral patterns of these subtypes [22]. It is thought that the low lymph node metastasis frequency of ER negative and HER2 negative tumors, but the high rate of distant metastasis, and the relationship between the frequency of axillary metastasis in HER2 positive tumors and the tumor size and the frequency of distant metastasis will become clear as biological behaviors are understood [23].

Conclusion

The whole presentation varies among molecular subtypes, and this information is particularly useful in clarifying the subgroups from which neoadjuvant therapy will be selected. The current study evaluates the fact that nodal staging in breast cancer projects the prognosis and evaluates the probability of recurrence and mortality and moreover separates the cases into higher and lower risk groups in the light of the literature. The results obtained in our study showed that breast cancer subtyping applied according to metastasis to lymph nodes, HER2 and hormone status correlated with the literature.

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

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
ethics committee approval numbered 46418926, dated 26/05/2022 from Gülhane Training and Research Hospital

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