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Biological Subtypes and Distant Relapse Pattern in Breast Cancer Patients After Curative Surgery (Study of Anatolian Society of Medical Oncology)

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Keywords

Breast cancer · Relapse pattern · Molecular subtype

Summary

Purpose: The aim of the study was to investigate the association between the molecular subtypes and patterns of relapse in breast cancer patients who had undergone curative surgery. **Methods:** We retrospectively evaluated 1,350 breast cancer patients with relapses after curative surgery between 1998 and 2012 from referral centers in Turkey. Patients were divided into 4 biological subtypes according to immunohistochemistry and grade: triple negative, HER2 overexpressing, luminal A and luminal B. **Results:** The percentages of patients with luminal A, luminal B, HER2-overexpressing, and triple-negative breast cancer were 32.9% (n = 444), 34.9% (n = 471), 12.0% (n = 162), and 20.2% (n = 273), respectively. The distribution of metastases differed among the subgroups: bone (66.2% and 53.9% in luminal A and B vs. 38.9% in HER2-overexpressing and 45.1% in triple negative, $p < 0.001$), liver (40.1% in HER2-overexpressing vs. 24.5% in luminal A, 33.5% in luminal B, and 27.5% in triple negative, $p < 0.001$), lung (41.4% in triple negative and 35.2% in HER2-overexpressing vs. 30.2% and 30.6% in luminal A and B, $p = 0.008$) and brain (25.3% in HER2-overexpressing and 23.1% in triple negative vs. 10.1% and 15.1% in luminal A and B, $p < 0.001$). **Conclusions:** Organ-specific metastasis may depend on the molecular subtype of breast cancer. Tailored strategies against distant metastasis concerning the molecular subtypes in breast cancer should be considered.

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Table 1. Clinicopathological characteristic and treatment outcome of the 1,350 patients

Characteristics	Luminal A		Luminal B		HER2-overexpressing		Triple negative		p value
Age at diagnosis, years (range)	49 (21–88)		46 (22–87)		49 (21–89)		50 (21–90)		0.081
n (%)	444 (32.9)		471 (34.9)		162 (12.0)		273 (20.2)		
	n	%	n	%	n	%	n	%	
Menopause									
Premenopausal	230	51.8	249	52.9	72	44.4	136	49.8	0.295
Postmenopausal	214	48.2	222	47.1	90	55.6	137	50.2	
Tumor stage at diagnosis (n = 1,341)									
< 2 cm	144	32.4	148	31.4	48	28.8	64	23.4	0.001
2–5 cm	242	54.5	231	49.8	79	49.4	150	54.9	
> 5 cm	58	13.1	85	18.3	33	20.6	59	21.6	
n.a.			7		2				
Histology (n = 1,347)									
Ductal	360	81.1	410	87.4	143	88.3	222	81.6	0.016
Other	84	18.9	59	12.6	19	11.7	50	18.4	
n.a.	0		2		0		1		
Grade (n = 1,190)									
1	204	54.7	62	14.5	20	14.3	49	19.7	< 0.001
2	169	45.3	65	15.2	47	33.6	87	58.4	
3	0	0	301	70.3	73	52.1	113	45.4	
n.a.	71		43		22		24		
LVI (n = 847)									
Positive	161	49.1	144	61.0	57	59.4	97	51.9	0.03
Negative	167	50.9	92	39.0	37	40.6	90	48.1	
n.a.	116		235		68		86		
Initial surgery									
MRM	284	64.0	310	65.8	108	66.7	212	77.7	0.001
BCS	160	36.0	161	34.2	54	33.3	61	22.3	
Systemic therapy (n = 1,340)									
Chemoendocrine	416	94.1	448	96.3	138	86.3	239	87.5	< 0.001
Endocrine	393	88.9	418	89.9					
Chemotherapy	276	62.4	399	85.8	138	86.3	239	87.5	
Trastuzumab	0	0	170	36.5	86	53.7	0	0	
n.a.	2		6		2		0		
OS, months									
From diagnosis	108.3		84.7		73.4		69.8		< 0.001
From relapse	42.5		33.9		34.1		25.7		
DFS, months	35.8		29.1		20.0		27.6		< 0.001

n.a. = not available (missing), LVI = lymphovascular invasion, MRM = modified radical mastectomy, BCS = breast-conserving surgery, OS = overall survival, DFS = disease-free survival.

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer-related deaths among women [1]. The majority of breast cancer patients have early stage disease [2]. Distant metastasis is the major cause of failure in the treatment of patients with early breast cancer [3, 4]. Despite all adjuvant treatment strategies, approximately 20–30% of patients with early stage breast cancers will experience relapse with distant metastases [5]. Tumor size, nodal status, lymphovascular invasion, grade, estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status are risk factors for relapse [6, 7].

The specific site of distant metastases is associated with the prognosis [4, 8]. The seed and soil theory proposes that specific organs are in some way predisposed targets for secondary growth [9]. Recently, the gene signatures of lung and bone metastasis in breast cancer have been identified [10–13]. However, to the best of our knowledge, few studies have described patterns of metastasis in relation to the biological subtypes of breast cancer according to gene expression profile [14–19] or immunohistochemical (IHC) bio-

markers [20–23]. The aim of the current study was to investigate whether biological subtypes of breast cancer were related to site of distant metastasis.

Material and Method

Of the 14,232 early breast cancer patients from 16 referral centers in Turkey, we retrospectively evaluated clinical data from 1,350 patients with distant relapses occurring after curative surgery between 1998 and 2012. Recurrence was diagnosed through clinical evaluations including imaging studies or biopsy. Distant recurrence was defined as recurrence of breast cancer beyond the ipsilateral or contralateral breast. Sites of first distant recurrence were categorized as follows: brain, liver, lung, bone, and others (distant nodal metastases, pleural/peritoneal, skin, ovaries, and other organs not elsewhere classified). ER, progesterone receptor (PR) and HER2 status were obtained from patients' charts. Patients who had no available information of ER, PR or HER2 were excluded from the study. Patients who had distant metastases at the time of diagnosis were excluded from the study. ER and PR status were detected by IHC. HER2 status was evaluated using IHC and fluorescence in situ hybridization (FISH). IHC scoring was based on a 0 to 3+ intensity point scale. Tumors with HER2 scores of 0 or 1+ were considered negative and those of 3+ were considered positive. For the borderline positive (2+) staining, HER2 amplification was confirmed by FISH. Patients were divided into 4 biological subtypes according to IHC and grade: luminal A (ER and/or PR positive, HER2 negative), luminal B (ER and/or PR positive, HER2 positive, or ER and/or PR positive, HER2 negative, grade 3), HER2 overexpressing (ER negative, PR negative, and HER2 positive), and triple negative (ER negative, PR negative, and HER2 negative). Age, menopausal status, tumor histology, tumor size, nodal status, operation type, lymphovascular invasion, ER, PR, and HER2 status, treatment options, site of first recurrence, date of first recurrence, and date of death were evaluated through patients' charts.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). A 2-tailed $p < 0.05$ was considered statistically significant. Descriptive statistics were determined for the patient demographics and clinical characteristics. To compare tumor features between subgroups, a chi-square test, an independent-samples t-test, and a Kruskal-Wallis test were used. Distant recurrence-free survival (disease-free survival, DFS) was defined as the time from curative surgery to the first distant recurrence. Overall survival (OS) was defined as the time from curative surgery to death or the last follow-up. Survivals were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results

We analyzed the records of 14,232 patients with early stage breast cancer. Median follow-up time was 89 months (range 24–166 months). Among these patients, 1,657 had relapses (11.7%). Patients who had no information of ER, PR and/or HER2 (n = 30) and patients who had local recurrence only (n = 237) were excluded from the study, so that 1,350 patients were included in the analyses. İnformation about Ki-67 was available for only 211 patients (15.6%).

Median age was 49 (range 21–90) years at the time of first breast cancer diagnosis. Among the 1,350 eligible patients, 32.9% of tumors (n = 444) were luminal A, 34.9% (n = 471) luminal B, 12.0% (n = 162) HER2 enriched, and 20.2% (n = 273) triple negative. Clinical, pathological, and treatment characteristics are listed in table 1. Patients with luminal B tumors were younger than patients in other groups (p = 0.081) at the time of first breast cancer diagnosis. At the time of diagnosis, 56.6% patients had stage 3 tumor, with the highest rate being observed among luminal B group (62.3%). Invasive ductal carcinoma was the most common histological subtype (84.3%), with the highest rate being observed among HER2-overexpressing patients (88.3%). The majority of patients (92.6%) had adjuvant systemic treatment (60.0% had endocrine therapy, 88.2% had chemotherapy and 19.0% had trastuzumab), with the highest frequency being in the luminal B group (96.3%). The most commonly used chemotherapy regimen was anthracycline-based (63.8%), with an anthracycline plus taxane regimen being the second most common (36.2%).

Table 2. Median DFS according to metastatic site

	DFS, months	p value
Bone metastases		
Present	33.6	<0.001
Absent	24.8	
Lung metastases		
Present	34.3	<0.001
Absent	27.0	
Liver metastases		
Present	27.8	0.117
Absent	30.4	
Brain		
Present	24.4	0.018
Absent	30.9	

DFS = disease-free survival.

Median OS differed significantly among subgroups ($p < 0.001$); 108.3 months for luminal A, 84.7 months for luminal B, 73.4 months for HER2-enriched, and 69.8 months for triple-negative patients. Median OS from time of first distant metastasis also differed significantly ($p < 0.001$), with luminal A patients having the longest OS (42.5 months), followed by HER2-enriched (34.1 months), luminal B (33.9 months), and triple-negative patients (25.7 months). Median DFS among patients with relapse also differed significantly ($p < 0.001$), with patients with luminal A tumors having the longest DFS (35.8 months), followed by luminal B (29.1 months), triple-negative (27.6 months), and HER2-enriched tumors (20 months). Median DFS showed differences according to metastatic site (table 2). In patients with bone or lung metastases, median DFS was longer than those without (33.6 vs. 24.8 months, in bone metastasis positive and negative patients, $p < 0.001$; 34.3 vs. 27.0 months, in lung metastasis positive and negative patients, $p < 0.001$), while median DFS was shorter in patients with brain metastases than those without (24.4 vs. 30.9 months, in brain metastasis positive and negative patients, $p = 0.018$). Median DFS was not statistically significant different between patients with or without liver metastasis (27.8 vs. 30.4 months, in liver metastasis positive and negative patients, $p = 0.117$). For patients with multiple or single metastases, median DFS (27.6 and 31.0 months for patients with multiple and single metastases, $p = 0.127$) and OS (77.2 and 86.3 months for patients with multiple and single metastases, $p = 0.186$) were not statistically different.

Table 3. Pattern of the first distant recurrence site according to the biological subtypes

Subtype	Bone		Liver		Lung		Brain		Other	
	n	%	n	%	n	%	n	%	n	%
Luminal A (n = 444)	294	66.2	109	24.5	134	30.2	45	10.1	51	11.5
Luminal B (n = 471)	254	53.9	158	33.5	144	30.6	71	15.1	53	11.3
HER2-overexpressing (n = 162)	63	38.9	65	40.1	57	35.2	41	25.3	15	9.3
Triple negative (n = 273)	123	45.1	75	27.5	113	41.4	63	23.1	34	12.5
p value	< 0.001		< 0.001		0.008		< 0.001		0.790	

Among the 1,350 relapsed patients, 484 patients (35.9%) had multiple distant metastases as the first distant recurrence. Multiple metastases were less common in the luminal groups (luminal A and B) than in the other groups (HER2-overexpressing and triple negative) (n = 310, 33.9% and n = 174, 40.0%, p = 0.028). The most common site of first recurrence was bone (n = 734, 54.4%), followed by lung (n = 448, 33.2%), liver (n = 407, 30.1%), brain (n = 220, 16.3%), and other sites (n = 153, 11.4%). The relationship between the site of relapse and biological subtypes was evaluated (table 3). Bone was the predominant site of metastases for the luminal A (66.2%) and luminal B (53.9%) groups compared with HER2-overexpressing (38.9%) and triple-negative (45.1%) groups (p < 0.001). The most frequent rate of liver metastases was observed in the HER2-overexpressing (40.1%) group compared to other groups (24.5% in luminal A, 33.5% in luminal B, and 27.5% in triple negative, p < 0.001). The triple-negative (41.4%) and HER2-ovexpressing (35.2%) groups had higher rates of lung metastases than luminal A (30.2%) and B (30.6%) groups (p = 0.008). High rates of brain metastases were observed among HER2-overexpressing (25.3%) and triple-negative (23.1%) groups, whereas brain metastases were seen less frequently in luminal A (10.1%) and B (15.1%) groups (p < 0.001). There were no differences between subtypes according to other metastatic sites (p = 0.790).

Discussion

This study demonstrates that breast cancer patients with different biological subtypes of tumors have specific patterns of first distant recurrence. One major strength of the current study is that it represents 1 of the largest series published on this subject, and patients were followed over a long period of time. Another key strength is that the treatments are more reflective of current treatment regimens. Previous related studies have had limitations as the treatments utilized were not up-to-date. In those studies patients undergoing treatment between 1992 and 2002 were included, whereas our study included patients treated up to 2012. As a result, our study differs covers more recent treatment results and current practice. On the other hand, the present study also has several limitations. First, it is retrospective. Because of the retrospective nature, the biological subtypes had several differences that affect survival outcomes, such as age, grade, lymphovascular invasion, and systemic therapy usage rate. Secondly, Ki-67 was not detected for each patient and so could not be used to determine biological subtypes. Finally, the determination of biomarkers (ER, PR and HER2) was performed in different pathology laboratories.

Previous studies reported that the different biological subtypes in breast cancer were related to different aggressiveness and treatment response [14, 24–26]. However, most studies evaluated clinicopathological features and responses to systemic therapies [25, 27, 28]. Only a few studies focused on the relationship between distant metastatic patterns and biological subtypes [16–19, 23]. In 2 of these studies, breast cancer biological subtypes were classified according to gene expression profile [16, 17], but in the other studies according to IHC findings [18, 19, 23]. All these studies were retrospective and included 73–1,357 patients with distant recurrence, and the median follow-up time was 93–177 months. In these studies, 84–96% patients had tumor stage 0–2 (< 5 cm) and 53–100% were node negative. Systemic treatment options were used in 54–97% of breast cancer patients in these studies. In our study, the median follow-up time was 89 months and thus similar to the other studies. The tumors in 75.9% of patients were T0–2 and 17.9% were node negative in the current study. The percentage of node-negative patients was lower than the most of the previous studies. Finally, systemic treatment options were used in 92.6% of the patients and this rate was higher than for most of the previous studies. According to subtypes, our data were more likely to reflect current treatment suggestions. In the literature, chemotherapy usage rate was 23.9–98.3% in luminal A, 36.8–97.1% in luminal B, 53.4–100% in HER2-overexpressing and 48–96.7% in triple-negative groups. In our study, this value was 68.7%, 80.0%, 86.3% and 87.5%, respectively.

Previous studies have demonstrated significant differences in terms of DFS and OS [17, 23, 29, 30]. The luminal A group had better results in these studies and their results are consistent with our data. Patients with bone metastases have better OS than those with visceral metastases [23, 31]. Examining metastatic sites in detail on an individual basis, it was observed that results vary across

biological subgroups. Similar to the current study (66.2% and 53.9% in luminal A and B vs. 45.1% and 38.9% in triple-negative and HER2-overexpressing groups), bone metastases in previous studies were more frequent among patients with luminal subgroup than in others [17–19, 23]. Liver was the most common site of first metastases among HER2-overexpressing patients in both previous and our current studies. Again, previous studies and our study suggest that compared with the other biological subtypes, luminal A patients rarely experienced lung metastases as first site [17–19, 23]. Triple-negative and HER2-enriched subgroups were predominant for brain metastases compared with luminal groups [17–19, 23]. Sihto et al. [19] reported that breast cancer patients with basal type had the first distant metastases at multiple sites more frequently than patients with other subtypes (50% vs. 26.9%, p = 0.015). In our study, the rate of first distant metastases at multiple sites was more common among HER2-enriched and triple-negative groups than in luminal groups (40% vs 33.9%, p = 0.028).

In conclusion, this study demonstrates that the biological subtypes in breast cancer are not only distinct in terms of primary tumor characteristics and aggressiveness, but also differ in terms of their ability to metastatize to distant organs. These data can provide useful information for surveillance.

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