Association between Molecular Subtypes and Survival in Patients with Breast Cancer

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Abstract: *Background*: Aim of this study is to classify intrinsic subtypes and evaluate the differences in clinical/pathological characteristics and survival outcomes among the molecular types.

Patients and Methods: Breast cancer subtypes were classified according to the 2013 St. Gallen Consensus. Five molecular subtypes were determined, Luminal A, Luminal B-like HER2 negative, Luminal B-like HER2 positive, HER2 positive, and triple negative. Data was obtained from the records of patients with invasive breast cancer retrospectively. The differences in clinical/pathological parameters, overall survival and disease-free survival among the molecular subtypes were analyzed. The Kaplan-Meier method, log-rank test and Cox regression tests were used to compare groups.

Results: The median follow-up period is 48 months. The Luminal B-HER2 negative was the most prevalent type (26.6%). Patient demographics, tumor characteristics and survival data were analyzed. The Luminal A and Luminal B-HER2 negative subtypes had significantly higher overall survival and disease-free survival rates. Multivariate Cox analysis revealed that tumor stage, more than 3 positive axillary lymph node involvement, and breast cancer subtype as significant factors for overall survival and disease-free survival ($p<0.05$). Triple Negative subtype had a higher relative hazard of local recurrence and distant metastasis (HR=2.69, 95% CI=1.47; 4.95).

Conclusions: Breast cancer subtype has significant impact on overall survival and disease-free survival rates. While Luminal A and luminal B HER2 negative subtypes have better outcome, triple negative and HER2- subtypes remain poor.

Keywords: Breast cancer, molecular subtypes, radiotherapy, survival.

INTRODUCTION

Breast cancer is the most common malignancy in women and the leading cause of death from cancer amongst females worldwide [1-3]. To date, clinical and pathological characteristics such as age, menopausal status, histological tumor grade, tumor size, lymph node involvement, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status have been considered the most significant prognostic factors for breast cancer [4]. However, breast cancer is a clinically and biologically heterogeneous, complex group of diseases. It has been shown that inherited genetic factors affect the prognosis of breast cancer as well as other factors [5]. With recent, rapid improvements in genomics and cancer biology, gene expression profiling has become more precise; thus, these findings are becoming more important as prognostic factors than the traditional factors mentioned above [6, 7].

Studies of gene expression profiling using DNA microarrays and molecular biology have identified a range of intrinsic molecular subtypes, as well as different prognoses and clinical outcomes [8-10]. The molecular subtypes of breast cancer depend on the expression of ER, PR, and HER2 [11]. As cost considerations limit the number of gene-expression-based studies, immunohistochemistry (IHC) is used across the globe for defining these subtypes [12]. In 2011, the St. Gallen International Expert Consensus also stated that subtypes can be defined via the IHC method [13]. Recent studies have identified four main subtypes for breast cancer: Luminal A (ER-positive, PR-positive, HER2-negative), Luminal B (ER-positive, PR-positive/negative, HER2-positive), HER2 Positive (ER-negative, PR-negative, HER2-positive) and Triple Negative (ER-negative, PR-negative, HER2-negative) [6, 8, 13-14]. Furthermore, in 2011 and 2013, the St. Gallen expert panel divided the Luminal B subtype into two groups: Luminal B-HER2-negative (ER-positive,

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HER2-negative, and a type with high ki-67 expression/PR-negative) and Luminal B-HER2-positive (ER-positive, HER2-positive) [13, 14]. It has also been confirmed that these breast cancer subtypes are associated with different epidemiological risk factors, responses to systemic/local therapies, and clinical outcomes [15-18]. The objectives of this study are: (a) to analyze the relationship between molecular subtypes and clinical/pathological characteristics, and (b) to assess the breast cancer outcomes related to distinct subtypes.

MATERIALS AND METHODS

A retrospective cohort study was conducted. Data from between the years 2007 and 2013 was obtained from Cumhuriyet University Radiation Oncology Department. 604 female patients with invasive breast cancer were evaluated. They did not have in-situ disease. They had not received preoperative systemic therapy previously. Twenty-five patients without IHC data were excluded. Thus, 579 breast cancer patients were deemed eligible for the current study. Written, informed consent was obtained from all the patients before any treatment was administered as the part of routine practice. All the patients underwent local and/or systemic treatment, including surgery, chemotherapy, radiotherapy, and endocrine therapy. The surgical procedures used consisted of mastectomies and breast-conservation therapies. All patients with breast conserving surgery and lymph node positive patients after mastectomy received postoperative radiotherapy to whole breast/chest-wall and or regional lymphatics. The following clinical and pathological data was collected from the patients' medical records: age at diagnosis, pathological tumor size, tumor grade, axillary node status, treatment history, histological type, co-morbidity, and IHC biomarkers for specifying the molecular subtype of the breast cancer. Categorizations of tumor size, nodal status, and staging were made using the American Joint Committee on Cancer (AJCC) TNM Staging System for Breast Cancer.

The breast cancer subtypes were classified via the definitions of the subtypes recommended by the 2013 St. Gallen International Expert Consensus [14]. Five molecular subtypes were determined, as follows: (1) Luminal A (ER+/PR+, HER2-, Ki67 < 14% or PR ≥ 20%), (2) Luminal B-like HER2- (ER+, PR- or PR < 20%, HER2-, Ki67 ≥ 14%), (3) Luminal B-like HER2+ (ER+, HER2+, any PR, any Ki67), (4) HER2+ (ER-, PR-, HER2+), and (5) Triple Negative "basal-like" (ER-, PR-, HER2-). Samples with a score of 2 were evaluated further by fluorescence in-situ hybridization (FISH) and IHC testing to confirm HER2-positive or negative status. Here, IHC 3+ or FISH+ results were considered to be positive for HER2 expression.

Statistical Analysis

Counts and frequencies were used to describe the patients' characteristics (age, menopausal status, presence of co-morbidity conditions), tumors (grade, overall stage, tumor stage, node involvement, subtype), and treatment courses (chemotherapy, radiation therapy, hormone therapy). The end points of this study were overall survival (OS) and disease-free survival (DFS). OS was defined as the length of time, in months, from the pathological diagnosis date to death from any cause. DFS was defined as the length of time, in months, from the pathological diagnosis date to local-regional recurrence, metastasis, or death. Univariate survival curves were plotted using the Kaplan-Meier method, and differences in survival were evaluated using the log-rank test. Cox regression was used to estimate the multivariable-adjusted association between the tumor subtype and the relative-hazard rate of death, recurrence, and/or metastasis. All the analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC). $P<0.05$ was considered statistically significant.

RESULTS

We analyzed 579 eligible patients with stage I–IV breast cancer. The median follow-up period was 48 months, and the most dominant subtype was Luminal B-HER2 (-) (n= 154, 26.6 %), followed by Luminal B-HER2 (+) (n= 142, 24.5 %), Luminal A (n= 134, 23.1 %), Triple Negative (n= 89, 15.4 %), and HER2+ (n= 60, 10.4 %). Table **1** lists the demographics and clinical pathological characteristics of the patients (age, menopausal status, co-morbidity, histological grade, T stage, N stage, TNM stage, subtype, chemotherapy status, radiotherapy status, and hormonal therapy status). OS and DFS curves for the molecular subtypes classified via IHC are shown in Figure **1A** and **1B**. OS and DFS were significantly different among subtypes. The 5-year OS rate for the Luminal A subtype (89.8%) was higher than (87.6%) for Luminal B-HER2 (-), (79.9%) for Luminal B-HER2 (+), (72.4%) for HER2+, and (75.5 %) for Triple Negative (Figure **1A**). Additionally the Luminal B-HER2 (-) subtype had a higher 5-year DFS (83.1 %) than Luminal A (81.9 %), Luminal B-HER2 (+) (75.9 %), HER2+ (80.5 %), and

Triple Negative (81.9 %) (Figure **1B**). The Luminal A and Luminal B-HER2 (-) subtypes had significantly higher OS and DFS rates than the other subtypes, but there were no differences in OS (log-rank P=0.1479) or DFS (log-rank P=0.1393) between these two subtypes.

Table 1: Demographic and Clinical Characteristics of Patients

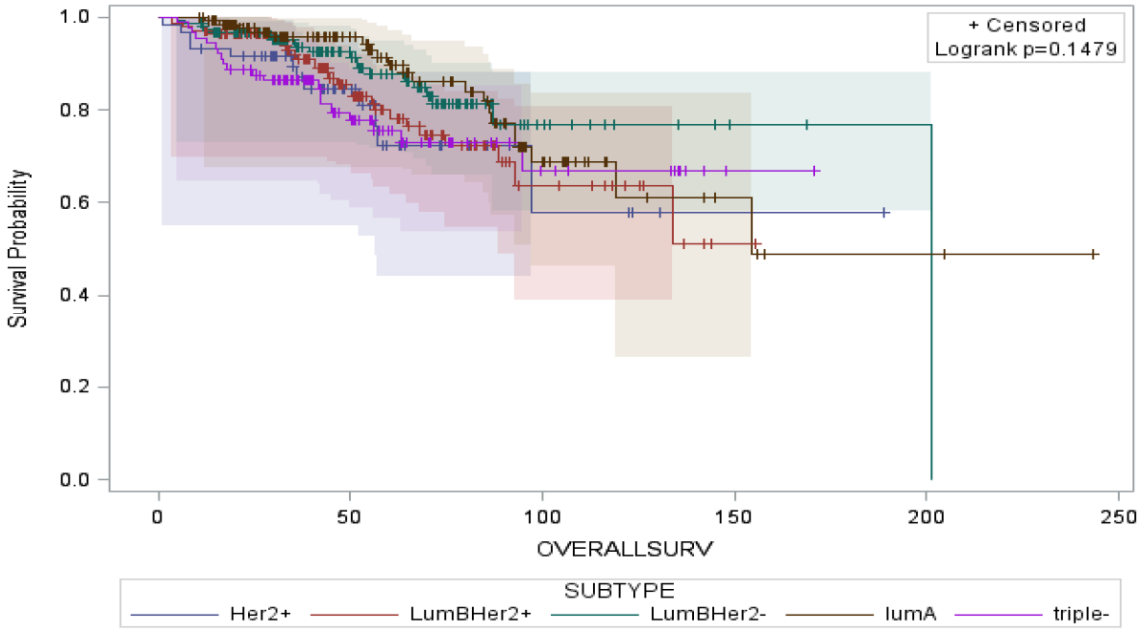
	n	%
Age of diagnosis		
<40 years	83	14,3 %
to<55 years	273	47,2 %
≥55 years	223	38,5 %
Menopausal status		
premenopausal	248	42,8 %
postmenopausal	331	57,2 %
Comorbidity		
No	323	55,8 %
Yes	256	44,2 %
Histologicgrade		
Grade 1	130	22,5 %
Grade 2	254	43,9 %
Grade 3	149	25,7 %
Unknown	46	7,9 %
T stage		
T1	181	31,3 %
T2	302	52,2 %
T3	58	10,0 %
T4	38	6,6 %
N stage		
N0	229	39,6 %
N1	148	25,6 %
N2	125	21,6 %
N3	77	13,3 %
TNM Stage		
Stage 1	103	17,8 %
Stage 2	252	43,5 %
Stage 3	213	36,8 %
Stage 4	11	1,9 %
Subtype		
Luminal A	134	23,1 %
Luminal B, HER2+	142	24,5 %
Luminal B, HER2-	154	26,6 %
HER2+	60	10,4 %
Triple negative	89	15,4 %

(Table 1). Continued.

Chemotherapy		
No	67	11,6 %
Yes	512	88,4 %
Radiotherapy		
No	145	25,0 %
Yes	434	75,0 %
Hormonal therapy		
No	157	27,1 %
Yes	422	72,9 %

The multivariate Cox hazard model for survival indicated that there were differences in the relative hazard of death for each subtype, after adjusting for age, menopausal status, co-morbidity, tumor grade, TNM stage, N stage, chemotherapy status, radiotherapy status, and disease-free status (Table **2**). Multivariate Cox analysis revealed that the following were significant independent predictors for OS (P<0.05): (1) age 40 to <55 years, (2) tumor stage II, (3) more than three positive lymph nodes, (4) HER2+ and Triple Negative subtypes, and (5) no chemotherapy. On the other hand, the significant independent predictors for DFS (P<0.05) were: (1) tumor stage IV, (2) more than three positive lymph nodes, (3) Triple Negative subtype, and (4) no radiotherapy. Furthermore, when compared with the Luminal A subtype, the HER2+ subtype was found to have a nearly three-fold relative hazard of death (HR=2.86, 95% CI=1.30-6.30), while the Triple Negative subtype had a two-and-a-half-fold relative hazard of death (HR=2.44, 95% CI=1.24-4.78). When using the same model (excluding disease-free status as a covariate), only the Triple Negative subtype had a higher relative hazard of recurrence or metastasis (HR=2.69, 95% CI=1.47, 4.95).

Recurrence patterns varied for the different molecular subtypes (Table **3**). A total of 117 patients (20.2%) had breast cancer recurrence. There were 23 local-regional recurrences and 94 distant metastases. Local-regional recurrence was most common in patients with HER2+ (6.7%) and Triple Negative (7.9%) subtypes, whereas distant metastasis was most common in patients with Luminal B/HER2+ (19.7%) and Triple Negative subtypes (20.2%) of the disease. Eventually, it was determined that the Triple Negative subtype had the worst survival outcomes, when compared with the other molecular subtypes.



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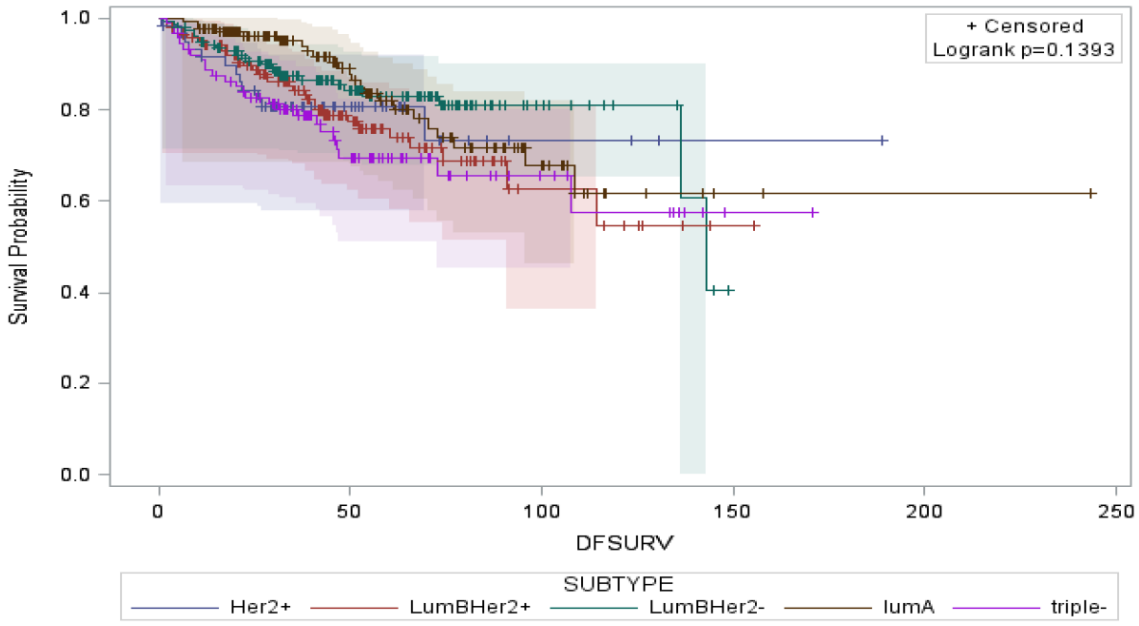

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Figure 1: A: Overall survival (OS) rates according to molecular subtypes. **B:** Disease free survival (DFS) rates according to molecular subtypes.

Table 2: Multivariate Cox-Analysis of Overall Survival and Disease Free Survival

	Overall Survival			Disease-free Survival		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age at diagnosis						
< 40 years	0,60	0.23, 1.59	0,3046	0,91	0.40, 2.10	0,8278
40 to < 55 years	0,45	0.21, 0.94	0,0345	0,56	0.30, 1.02	0,0578
55+ years	1	–	–	1	–	–

(Table 2). Continued.

Menopausal status						
Premenopausal	1	–	–	1	–	–
Postmenopausal	0,55	0.26, 1.18	0,1242	0,67	0.36, 1.24	0,1969
Comorbidity						
No	1	–	–	1	–	–
Yes	1,03	0.64, 1.64	0,9089	1,12	0.75, 1.67	0,5718
Histologic grade						
Grade 1	1	–	–	1	–	–
Grade 2	0,95	0.52, 1.75	0,8786	1,08	0.62, 1.89	0,7814
Grade 3	1,02	0.52, 1.98	0,9596	0,95	0.51, 1.77	0,8775
Unknown	0,50	0.20, 1.27	0,1442	1,61	0.76, 3.41	0,2167
TNM stage						
Stage 1	1	–	–	1	–	–
Stage 2	2,74	1.04, 7.20	0,0415	0,83	0.37, 1.86	0,6493
Stage 3	1,15	0.31, 4.23	0,8351	2,12	0.64, 7.01	0,2161
Stage 4	1,14	0.28, 4.59	0,8595	13,71	3.35, 56.13	0,0003
N stage						
N0	1	–	–	1	–	–
N1	0,97	0.42, 2.25	0,9422	0,91	0.42, 1.95	0,8052
N2	4,4	1.33, 14.60	0,0155	2,03	0.68, 6.04	0,2027
N3	8,13	2.39, 27.63	0,0008	3,54	1.16, 10.80	0,0261
Subtype						
Luminal A	1	–	–	1	–	–
Luminal, HER2+	1,52	0.80, 2.87	0,1993	1,29	0.73, 2.27	0,3806
Luminal, HER2-	1,30	0.67, 2.50	0,4403	0,96	0.54, 1.72	0,8875
HER2+	2,86	1.30, 6.30	0,0093	1,23	0.60, 2.54	0,5748
Triple negative	2,44	1.24, 4.78	0,0094	2,69	1.47, 4.95	0,0014
Chemotherapy						
No	1	–	–	1	–	–
Yes	0,34	0.14, 0.83	0,0161	0,77	0.36, 1.63	0,4929
Radiation therapy						
No	1	–	–	1	–	–
Yes	0,64	0.37, 1.13	0,1263	0,54	0.31, 0.93	0,0252
Disease-free status						
No metastasis/recurrence	1	–	–	–	–	–
Recurrence	7,04	3.34, 14.86	<0.0001	–	–	–
Metastasis	8,13	4.82, 13.71	<0.0001	–	–	–

DISCUSSION

Many studies have reported different survival and recurrence rates between breast cancer subtypes [19-24]. In this retrospective study, we analyzed the post-radiotherapy pattern of failure and clinical outcome in 579 patients. In general, while luminal A is the most common subtype of breast cancer, in our study the most prevalent molecular subtype was Luminal B-HER2(-). The discrepancy in results between our study and the other studies may be explain due to potential

Table 3: Local Recurrence and Metastasis Rates of each Subtype

	None		Local recurrence		Distant Metastasis	
	n	%	n	%	n	%
Luminal A	111	82,8%	4	3,0%	19	14,2%
Luminal B, HER2+	110	77,5%	4	2,8%	28	19,7%
Luminal B, HER2-	129	83,8%	4	2,6%	21	13,6%
HER2+	48	80,0%	4	6,7%	8	13,3%
Triple negative	64	71,9%	7	7,9%	18	20,2%

racial differences. Moreover, in our study, of the five molecular subtypes, the Luminal A and Luminal B-HER2 subtypes tend to have the best prognosis, high OS, and low DFS, recurrent or metastases rates. On the other hand, the triple negative and HER2 subtypes of breast cancer were associated with a significantly poorer OS and DFS, also earlier recurrence and metastases rates. A previous study on the Korean population, Park *et al*. [19] analyzed OS and DFS in 1006 patients with invasive breast cancer and showed that luminal A and luminal B subtypes had higher and better 5-year OS and DFS rates compared the other subtypes. As mentioned above, survival outcomes; OS and DFS, by subtypes obtained from our study correspond with the previous Korean study. Accordingly the studies, it can be said that the breast cancer subtype is a significant prognostic factor of OS and DFS.

The HER2+ and triple negative subtypes were associated with the worst survival rates. There are existing studies on the relationship between breast cancer's molecular subtypes and recurrence. Nguyen *et al*. [20] investigated a cohort of 793 patients with breast cancer. In mutlivariate analysis, they found that there was an increased risk of local recurrence for the HER2+ and triple negative subtypes, the rates were 8.4% and 7.1%, respectively. When these results were compared with our results, the correlation can be seen. In our study, the rates of local recurrence for the HER2+ and triple negative subtypes were 6.7% and 7.9%, respectively and also triple negative breast cancers had the lowest 5-year DFS, at 69.6%. Moreover, in 2007, Dent *et al*. [21] evaluated 180 out of 1,601 breast cancer patients with triple negative subtype. They compared triple negative subtype with the other molecular subtypes and they showed that patients with triple negative subtype had an increased probability of distant recurrence (33.9% vs. 20.4%; P<0.0001) and death (42.2% vs. 28%; P<0.0001). Similarly, in a further large cohort study of 2,985 patients, Voduc *et al*. [22] demonstrated that the triple negative subtype was associated with an increased risk of local and regional relapse (P< 0.001). Finally, a recent retrospective study also reported that patients with triple negative subtype had an increased recurrence rate comparing to other subtypes (19.2% vs. 4.1%) [23].

The limitations of our study are that this is a retrospective study. In addition, this study was performed in patients from a single institution. Therefore, our patients might not be representative of the general population. A second limitation is the short postoperative follow-up period with 48 months.

Consequently, it can be said that breast cancer is a heterogeneous cancer. Of the five subtypes, the Luminal A and Luminal B (HER2-) subtypes tend to have the best prognosis, higher OS and DFS rates. The HER2- and Triple Negative subtypes of breast cancer were associated with significantly poorer OS and DFS rates. The risk of death increases two or three fold in HER2- and triple negative compared with Luminal A and Luminal B (HER2-). Furthermore, our results demonstrate a significant association between molecular subtype and survival. This study contends, however, that ER, PR, and HER2 over-expression should be evaluated for every new breast-cancer patient.

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