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Clinicopathologic Features and Survival of Breast Cancer Subtypes in Northeast Iran

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Abstract

Background: Breast cancer can be categorized into different histopathological subtypes based on gene expression profiles. This study aims to evaluate the clinicopathological features and overall survival of various subtypes of breast cancer to assist diagnosis and guide treatment.

Methods: The clinicopathologic features of 1095 patients with breast cancer diagnosed over a 10–year period between 2001 and 2011 were analyzed. The Kaplan–Meier method was used to analyze disease-free survival and overall survival. Calculation of the hazard ratio was conducted by multivariate Cox regression.

Results: According to the clinicopathologic characteristics of 1095 cases, there were 42% luminal A subtype, 19.2% luminal B, 23% triple negative, and 15% HER2+. The lowest (46.88±12.59 years) and highest (50.54±12.32 years) mean ages were in the triple negative and HER2+ groups, respectively. There was a significant correlation between histology subtype and age, BMI, lymph node, type of surgery, and stage of disease. There was significantly shorter overall survival and disease free survival in HER2+ breast cancer patients (P<0.001). Multivariate analysis showed that age had the highest hazard ratio of 2.481 (95% Confidence Interval: 1.375-4.477).

Conclusion: The results of this study showed the importance of clinicopathological studies of molecular types which help early diagnosis and identification of the best strategy to treat breast cancer.

Keywords: Breast neoplasm, Survival, Receptor, Triple negative breast neoplasms, Iran

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Introduction

Breast cancer is the most frequent malignancy in females, with approximately greater than one million new cases diagnosed worldwide each year.[1,2] Despite current treatments, more than 450,000 deaths due to breast cancer

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occur annually.[3] The disease can be classified based on various clinical and pathological features.[4] Three immunohistochemistry (IHC) tumor markers that include estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor-2 (HER2/neu, erb-B2) determine subtypes of the disease.[5] Gene expression profiling has an important impact on our understanding of breast cancer biology.[6] Breast cancer is categorized into four main molecular subtypes according to their gene expression profiles, which include luminal-A, luminal-B, HER2 positive, and basal cell-like (BCL) or 'triple-negative' phenotype.[7] Luminal A is the most common breast cancer subtype in 40% of all cases and is characterized by ER+ and/or PR+, HER2-, and low Ki-67. This subtype is generally a low-grade tumor with good prognosis and high survival rate.[6,8] Luminal B subtype accounts for approximately 20% of all breast cancer cases and is distinguished by ER+ and/or PR+, HER2+ or HER2- with high Ki-67 (>14%) status. Women with luminal B tumors are generally younger than those with luminal A tumors and, compared to luminal A tumors, they tend to have a higher tumor grade, larger tumor size, and positive lymph nodes.[6, 8, 9]

Breast cancer subtypes that have ER-, PR-, HER2 status are called "triple negative (TN) or basal-like breast cancers. The basal-like subtype is more common in premenopausal, younger, and African American women. Most BRCA1 breast cancers are in this subtype. The HER2-enriched subtype (ER-, PR-, HER2+) is less common and characterized by high grade tumors and a poor prognosis. Clinicopathological features in these subtypes are very important to understand the occurrence, development, prognosis, and treatment of breast cancer.[6,8,9] Breast cancer can be managed better by the clinical data provided to help diagnosis and guide treatments.[10] Pathological features such as tumor size, tumor grade, nodal involvement, and hormone receptor status are essential for management and prognosis of this disease.[7] In this study, we evaluate the clinico-pathological aspects in various molecular subtypes of breast cancer.

Patients and Methods

This was a retrospective cohort study. We reviewed medical reports of 2825 breast cancer cases that referred to radiation oncology centers in Mashhad, Iran between 2001 and 2011. In this study, we evaluated female patients older than 18 years of age whose hormone receptor status, HER2, and Ki-67 were recorded in their medical forms. All clinicopathological information of patients (patient demographic information, stage of disease, lymph node status, surgical type, and adjuvant treatment) were collected in this database. Exclusion criteria consisted of: cases with HER2 (2+) in IHC who did not have a fish test; cases of luminal A and B subtypes with unknown Ki-67; and patients with follow up periods of less than 3 months. In total, 1095 patients entered this study.

We classified breast cancer into four subtypes based on expressions of the ER, PR, HER2, and Ki-67 proliferation index: i) Luminal A: ER+ and/or PR+, HER2-, low Ki-67; ii) luminal B: ER+ and/or PR+, HER2+ (or HER2- with Ki-67 >14%); iii) TN/basal-like: ER-, PR-, HER2-; and iv) HER2 type: ER-, PR-, HER2+.[6]

Statistical analysis

Statistical analysis was performed using SPSS software version 11. The relationship between different breast cancer subtypes and main clinico-pathologic characteristics of prognostic significance was evaluated by one-way ANOVA and the chi-square test.

Overall survival (OS) and disease-free survival (DFS) were analyzed by the Kaplan–Meier method from which the median OS and 95% confidence intervals (CI) were calculated. The log rank test was used to compare survival rates between IHC subtypes. A multivariate Cox regression was carried out to calculate hazard ratio (HR) and 95% CI.

Results

Of the 2825 individuals with breast cancer,

Table 1. Clinicopathologic characteristics of molecular breast cancer subtypes.

Variables	All cases	Luminal A	Luminal B	TN	HER2+	*P*-value
N (%)	1095	460 (42)	210 (19.2)	261(23.8)	164 (15)	
Age (years)						
Mean±SD	48.93±11.72	50.21±11.37	47.41±10.29	46.88±12.59	50.54±12.32	<0.001
Age-specific group – n (%)						
≤35	130 (11.9)	35 (7.7)	23 (11)	51 (19.6)	21 (12.8)	<0.001
35-70	904 (82.9)	393 (86.2)	182 (86.7)	198 (76.2)	131 (79.9)	
>70	56 (5.1)	28 (6.1)	5 (2.4)	11 (4.2)	12 (7.3)	
BMI						
Mean±SD	27.39±5.19	28.03±5.64	26.92±4.65	27.08±4.86	26.71±4.87	0.017
BMI (specific group) - n (%)						
≤18.5	27 (3)	12 (3.2)	3 (1.8)	6 (2.8)	6 (4.3)	0.45
18.5-25	278 (31.3)	102 (27.5)	56 (34.4)	72 (33.6)	48 (34)	
>25	584 (65.7)	257 (69.3)	104 (63.8)	136 (63.6)	87 (61.7)	
Metastases - n (%)						
0	1035 (94.5)	434 (94.3)	199 (94.8)	252 (96.6)	150 (91.5)	0.165
1	60 (5.5)	26 (5.7)	11 (5.2)	9 (3.4)	14 (8.5)	
Lymph node - n (%)						
0	313 (34.2)	121 (31.3)	58 (33.5)	97 (44.1)	37 (27)	0.013
1	308 (33.6)	139 (36)	54 (31.2)	71 (32.3)	44 (32.1)	
2	207 (22.6)	92 (23.8)	43 (24.9)	36 (16.4)	36 (26.3)	
3	88 (9.6)	34 (8.8)	18 (10.4)	16 (7.3)	20 (14.6)	
Tumor size - n (%)						
1	326 (32.8)	154 (36.8)	63 (32.3)	65 (27.1)	44 (31.2)	0.22
2	501 (50.4)	203 (48.4)	103 (52.8)	130 (54.2)	65 (46.1)	
3	111 (11.2)	40 (9.5)	21 (10.8)	30 (12.5)	20 (14.2)	
4	57 (5.7)	22 (5.3)	8 (4.1)	15 (6.2)	12 (8.5)	
Surgery - n (%)						
MRM	904 (90.4)	371 (89.4)	174 (90.6)	214 (88.1)	145 (96.7)	0.032
BCS	96 (9.6)	44 (10.6)	18 (9.4)	29 (11.9)	5 (3.3)	
Stage – n (%)						
I	112 (12.2)	58 (14.9)	19 (10.9)	23 (10.8)	12 (8.6)	0.031
II	425 (46.3)	175 (44.9)	83 (47.4)	115 (54)	52 (37.4)	
III	320 (34.9)	131 (33.6)	62 (35.4)	66 (31)	61 (43.9)	
IV	60 (6.5)	26 (6.7)	11 (6.3)	9 (4.2)	14 (10.1)	
Adjuvant chemotherapy - n (%)						
Yes	986 (90.8)	403 (88.6)	189 (90.9)	245 (94.2)	149 (91.4)	0.092
No	100 (9.2)	52 (11.4)	19 (9.1)	15 (5.8)	14 (8.6)	
Adjuvant radiotherapy - n (%)						
Yes	739 (68.2)	310 (68.1)	150 (72.1)	176 (68)	103 (64)	0.423
No	344 (31.8)	145 (31.9)	58 (27.9)	83 (32)	58 (36)	
Hormone therapy - n (%)						
Yes	487 (44.5)	324 (70.4)	132 (62.9)	18 (6.9)	13 (7.9)	<0.001
No	608 (55.5)	136 (29.6)	78 (37.1)	243 (93.1)	151 (92.1)	
HER2 status - n (%)						
Negative	807 (73.7)	460 (100)	86 (41)	261 (100)	0 (0)	<0.001
Positive	288 (26.3)	0 (0)	124 (59)	0 (0)	164 (100)	
Hormone receptor status - n (%)						
ER+/PR-	77 (7)	51 (11.1)	26 (12.4)	0 (0)	0 (0)	<0.001
ER-/PR+	46 (4.2)	34 (7.4)	12 (5.7)	0 (0)	0 (0)	
ER+/PR+	547 (50)	375 (81.5)	172 (91.9)	0 (0)	0 (0)	
ER-/PR-	425 (38.8)	0 (0)	0 (0)	261 (100)	164 (100)	

TN: Triple negative; Her2: Human epidermal receptor 2; ER: Estrogen receptor; PR: Progesterone receptor; SD: Standard deviation; BMI: Body Mass Index; n: Number; T: Tumor size; N: Lymph node

there were 2787 (98.7%) female patients from which 1095 cases had accessible information for inclusion in the present study. Table 1 lists clinicopathological features of the 1095 cases with IHC data. We classified the patients according to ER, PR, HER2 status, and Ki-67 as luminal A (42%),

Table 2. Log-rank for disease-free survival (DFS).

	Mean survival % (SD)	95% CI	*P*-value	Death frequency	5-year survival
Luminal A	118.04	(111.33, 124.74)	<0.001	73	70 ±4
Luminal B	103.68	(92.27, 115.08)		42	63 ±6
TN	86.13	(79.02, 93.23)		66	59 ±5
HER2+	79.89	(70.63, 89.14)		55	51 ±6

TN: Triple negative; Her2: Human epidermal receptor 2; SD: Standard deviation; CI: Confidence interval; DFS: Disease-free survival

luminal B (19.2%), TN (23.8%) and HER2+ (15%). The median age of the patients was 48.93±11.72 years (22 to 85 years). There was a significant difference among breast cancer subtypes according to the mean age at diagnosis (P>0.001). The lowest mean age was detected in the TN group (46.88±12.59 years) while the highest mean age was in the HER2 positive group (50.54±12.32 years). We observed no statistically significant difference in tumor size (P=0.22) between the subgroups. The distribution of IHC subtypes showed a significant difference regarding node involvement (P<0.013). The highest percentages of lymph node involvement were observed in luminal A and TN. In addition, almost a third (34/2%) of the cases were node negative.

More HER2+ (8.5%) patients had metastases compared to the other subtypes. There was no significant correlation between the subtypes and metastasis (P=0.165). However, a significant relationship existed among subgroups and disease stage (P=0.031). Most stage IV patients were HER2+, whereas luminal A patients comprised the largest prevalence of patients with stage II disease.

The median time for follow-up was 119.83 months. Comparatively, the luminal A group had the highest mean DFS rate (118.04 months) while the lowest mean DFS was observed in HER2+ (79.89 months) patients. There was a significant association among molecular subtypes (P<0.001; Table 2; Figure 1). The five-year OS was 64±5% in luminal A, 63±7% in luminal B, 60±5% in TN, and 52±6% in the HER2+ groups. There was a significant correlation between the subtype and five-year OS (P<0.001; Table 3; Figure 2).

According to multivariate analysis, we observed a significant relationship between OS and age, hormone, and disease stage (P<0.01). Age had the highest HR of 2.481 (95% CI: 1.375-4.477; Table 4). The same results were obtained for DFS. Age had the highest HR ratio (3.945) in the luminal A subtype (P<0.001; Table 5). However, there was no statistical relationship between age and the other subtypes.

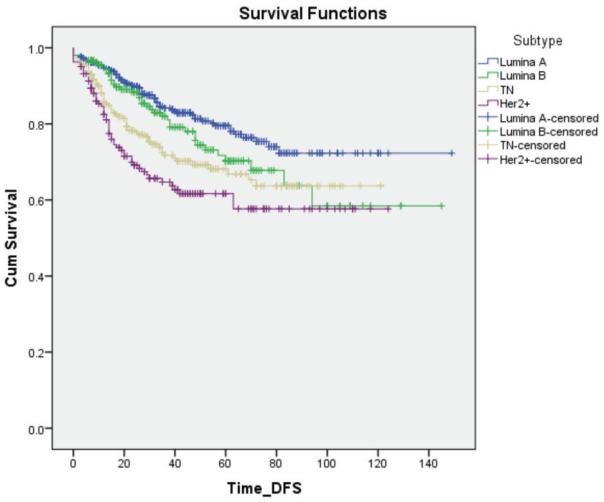

Figure 1. Disease-free survival (DFS) and breast cancer subtype.

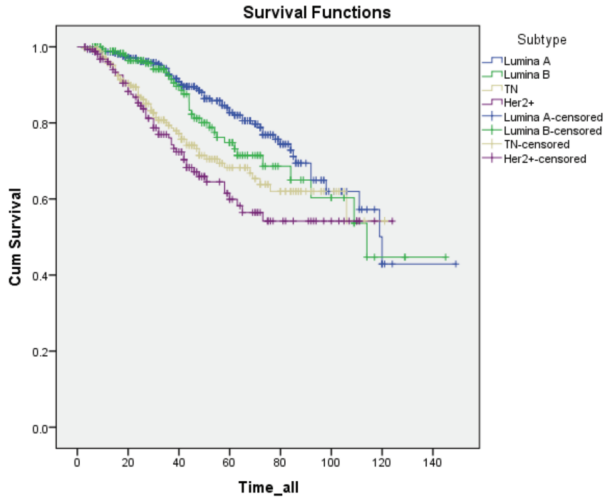

Figure 2. Overall survival (OS) and breast cancer subtype.

Table 3. Log-rank for overall survival (OS).

	Mean survival % (months) (SD)	95% CI	*P*-value	Death frequency	5-year survival
Luminal A	110.24	(101.31, 119.18)	<0.001	62	64 ±5
Luminal B	103.84	(92.15, 115.53)		34	63 ±7
TN	87.85	(80.74, 94.97)		58	60 ±5
HER2+	83.75	(74.93, 95.58)		49	52 ±6

TN: Triple negative; Her2: Human epidermal receptor 2; SD: Standard deviation; CI: Confidence interval; OS: Overall survival

Discussion

Data analysis showed that 42% of patients were classified as luminal A, 19.2% luminal B, 23.8% TN, and 15% HER2+ which supported the findings reported by Spitale et al.[11] The study showed that the highest prevalent subtype was luminal A (73.5%) and the lowest was HER2/neu (5.2%).[11] In a study by Elidrissi et al., the most common subtype was luminal A (65%) and the least prevalent subtype was the HER2 type (6%).[6] Additionally, the obtained results revealed that four major subgroups with different clinical and pathological characteristics mainly differentiated in age, BMI, node involvement, type of surgery, and stage of disease (Table 1). Cheng et al.[12] reported that the differences were mainly observed in age at diagnosis, tumor grade, lymphovascular invasion, and multiple foci of tumors.[12] With regard to age, Osman et al.[13] confirmed higher TN breast cancer (TNBC) in younger patients compared with the other subtypes (mean: 43.1 years; *P*=0.006) which was compatible with the results of the present study (mean: 46.88 years; *P*=0.001) and previous studies.[14-16] In another study, TNBC tumors were observed in older patients (58 years) in Ticino[17] compared to those reported by Bauer et al.[18] in a California study (54 years), and in Poland by Yang et al.[19] (53.7 years). However, TNBC tumors were reported in 35.5% of women <50 years of age in Ticino[17] and 36.2% in California.[18] In the current study, we observed TNBC tumors in 19.4% of women younger than 35 years of age. In contrast, patients above 70 years of age were more frequent in Ticino (26/7%)[17] compared to California (19.5%)[18] as opposed to 4.2% of a similar group of patients with TNBC tumors in the present study. In the Onitilo study,[20] patients had an average age of 62.7±13.8 years which was higher than the average age of patients in the current study (46.93±11.72 years). The presence of positive lymph nodes was detected more frequently in the luminal A and TN groups. Similarly, the rate of node positivity was slightly higher in the TN group (54.6%) compared to the other groups (45.6%; *P*=0.02).[21] In the current study, HER2+ patients had the

Table 4. Multivariate analysis of disease-free survival (DFS) and overall survival (OS) in the entire population.

	OS			DFS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (years)						
(≤35 vs. >35)	2.481	1.375, 4.477	0.003	2.129	1.187, 3.818	0.011
T						
(T1, 2 vs. T3, 4)	1.11	0.694, 1.775	0.663	0.979	0.633, 1.515	0.924
N						
(N0, 1, 2 vs. N3)	0.653	0.396, 1.076	0.094	0.746	0.467, 1.19	0.218
Hormone						
(ER\PR– vs. ER\PR+)	1.774	1.208, 2.605	0.003	1.68	1.171, 2.411	0.005
HER2						
(Neg. vs. pos.)	0.921	0.622, 1.365	0.682	0.834	0.577, 1.206	0.334
Stage						
(I, II vs. III, IV)	0.514	0.326, 0.809	0.004	0.485	0.316, 0.747	0.001

Her2: Human epidermal receptor 2; ER: Estrogen receptor; PR: Progesterone receptor; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; DFS: Disease-free survival; n: Number; T: Tumor size; N: Lymph node

Table 5. Multivariate analysis of overall survival (OS) in different breast cancer subtypes.

	Luminal A			Luminal B			TN			HER2+		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (years)												
(≤35 vs. >35)	3.945	1.76, 8.842	0.001	2.562	0.927, 7.079	0.07	1.296	0.614, 2.74	0.496	1.154	0.462, 2.883	0.758
T												
(T1, 2 vs. T3, 4)	1.015	0.473,2.175	0.97	0.692	0.262, 1.828	0.458	1.645	0.736, 3.676	0.225	0.68	0.288, 1.61	0.381
(N0, 1, 2 vs. N3)	0.743	0.3, 1.845	0.523	0.663	0.186, 2.364	0.526	0.638	0.306, 1.33	0.23	0.304	0.1, 0.926	0.036
Stage												
(I, II vs. III, IV)	0.371	0.175, 0.785	0.01	0.507	0.186, 1.385	0.185	0.566	0.259, 1.237	0.154	1.164	0.502, 2.7	0.723

TN: Triple negative; Her2: Human epidermal receptor 2; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; n: Number; T: Tumor size; N: Lymph node

highest prevalence of stage IV disease. Spitale et al.[11] reported similar findings. The research showed that a reduced survival probability was detected in TNBC and HER2/neu subtypes in comparison with luminal A and B cases which was consistent with the outcomes of the present study. Haque et al. observed that luminal B and HER2 type subtypes had a worse survival rate compared to the other subtypes, which was not consistent with our results.[22] The reason might be due to the less recent version of their subtype classification system.

The subgroup of cases selected over a ten-year period was followed for 5 years after diagnosis to determine the 5-year survival rate. In the current literature, the OS was calculated to be 92% in target patients (203 deaths out of 1095 cases; Table 3), in which the OS rate was higher in this study compared to the results reported by Cary et al.[16] Hence, the OS was 73% (232 deaths among 861 cases). We observed the shortest OS (52%) and DFS (51%) in the HER2+ subtype which agreed with the findings by Cary et al.[23] The highest OS (64%) and DFS (70%) were in the luminal A group. Xue et al.[24] determined the 5-year OS to be 93.3% (luminal A), 92.2% (luminal B, high Ki-67), 86.6% (luminal B, HER2/neu+), 77.5% (HER2/neu), and 85.5% (TN). Multivariate Cox regression analysis showed worse OS among luminal A patients (Table 5). Particularly, the hazards ratio of cases with luminal A (age >35 years) was 2.481 times greater than patients less than 35 years of age. There was a significant relationship between luminal A subtype and stage of disease (HR=0.514; 95% CI: 0.326–0.809) whereas Spitale et al.[11] reported that TNBC patients showed higher HR compared to luminal A patients.

Conclusion

The results of this study indicated that classification of different breast cancer subtypes based on IHC showed significant differences according to clinicopathological aspects. Evaluation of subgroups according to the molecular pathology classification appeared to assist with identification of effective treatment, early diagnosis, and follow up.

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Conflict of interest

No conflict of interest is declared.

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