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Breast Cancer Subtypes Based on ER PR and HER2 Expression: ER/PR Status may be More Powerful Predictor of the Outcome than the HER2 Status

Parisa Ghaffari[1], Davood Bashash[2], Ardeshir Ghavamzadeh[1] and Seyed H Ghaffari[1]*

[1]*Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Shariati Hospital, Tehran, Iran*

[2]*Department of Hematology and Blood banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

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***Corresponding author:** Seyed H Ghaffari, PhD, Professor, Hematology, Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran, Iran

Abstract

Background: Breast cancer (BC) subtypes, based on the expression of estrogen receptor (ER), progesterone receptor (PR) and Her2, are known to have unique response to treatment and are associated with differing prognostic outcomes. We investigated the clinicopathological characteristics and prognosis of BC subtypes classified by the expression of ER, PR and HER2.

Patients and Methods: A total of 892 patients with primary BC were retrospectively analyzed. Four molecular subtypes were constructed based on the immunohistochemical results of hormonal receptors (HR) and HER2 status, which were classified as luminal-A (ER+/PR+/HER2-), luminal-B (ER+/PR+/HER2+), HER2-positive (ER-/PR-/HER2+), and triple-negative (ER-/PR-/HER2-) subtypes. Association of these subtypes with clinicopathological characteristics and outcome of the disease were evaluated. Log-rank and Cox regression analyses were used to assess the associations with recurrence and survival.

Results: The 100-month disease-free survival (DFS) rates were 89.0%, 87.9%, 69.0%, and 75.0% (P=0.005), and overall survival (OS) rates were 85.1%, 82.9%, 77.3%, and 69.5% (P=0.000) for luminal-A, luminal-B, HER2+, and TN, respectively. Moreover, we found a significant association (P< 0.001) between immunoreactivity of p53 and the absence of hormonal receptors and poor prognosis.

Conclusion: BC subtyping based on ER, PR, and HER2 expression may be predictive of the prognosis. Patients with HR- tumors (TN and HER2+ subgroups) had a worse outcome compared to patients with HR+ status (luminal-A and -B subgroups), it seems that HR status is a more powerful predictor of the outcome than HER2.

Keywords: Breast Cancer; Molecular Subtypes; Triple Negative; Estrogen Receptor; Progesterone Receptor; HER2

Abbreviations: BC: Breast cancer; HR: hormone receptors; ER: estrogen receptor, PR: progesterone receptor; TNBC: triple-negative breast cancer; DFS: disease-free survival; OS: overall survival; UICC: Union against Cancer; IHC: immunohistochemical; DFS: Disease-free survival; OS: Overall survival; HR: hazard ratios; HR: hormone receptors; TN: triple-negative

Introduction

Breast cancer (BC) is the most frequent form of malignant neoplasia affecting women all over the world and is assumed to be the leading cause of cancer-related deaths in females [1]. The annual incidence of BC is on the rise, but the reported occurrence rates vary throughout the world. Even though the highest reported prevalence is in developed nations, in many developing countries, the incidence of breast cancer is also rising sharply due to changes in reproductive factors, lifestyle, and increased life expectancy [2,3]. In Iran, BC is now the first leading cause of tumor-related death among adult women of all ages [4,5] and existing data confirms an increasing trend within the past two decades [6].

Currently our understanding of the biological etiologies of BC has undergone a major change, shifting from a generally homogeneous approach to a more sophisticated one, understanding that it is a collection of clinically, histopathologically and molecularly heterogeneous disease, consisting of distinct biological subtypes, as guided by gene expression [7-9] and high-throughput protein expression analyses [10,11]. Each subtype is known to have a unique response to treatment and is associated with differing prognostic outcomes. To improve patient's outcome, distinguishing subgroups with poor prognosis is required. At the present, steroid hormone receptors (HR) such as estrogen receptor (ER) and progesterone

receptor (PR) in concert with the human epidermal growth factor receptor-2 (HER-2) still remain critical determinants of breast cancer subtypes and are widely accepted as prognostic markers, therapeutic targets and determinants of the treatment decision used in daily clinical practice. Among all the subtypes, triple-negative breast cancer (TNBC) neither expresses hormone receptors (ER and PR) nor overexpresses HER2, and has been defined by poor prognosis, aggressive behavior, high recurrence rates and lack of targeted therapies.

Racial differences in BC patients with regard to incidence, stage, mortality and treatment have been well documented. It has been shown that the distribution of the molecular subtypes of breast cancer vary by race/ethnicity [12-16], highlighting the importance of host factors in breast tumor biology [17]. A number of published studies described the incidence of triple-negative breast cancer subgroup among different races and ethnicities compared to the other subgroups [13,18-20]; however, a small number of studies have focused on the Iranian population. In this study, we used IHC information to classify Iranian breast cancer patients to several subtypes and then to evaluate the correlation of each subtype with demographic, clinicopathological characteristics and long-term outcome, including disease-free survival (DFS) and overall survival (OS).

Patients and Methods

Patients

In this retrospective study, we conducted a study from a database of BC patients who underwent preoperative therapies from 1977 to 2008. The study procedures were approved by the institutional review board of the hospital. From a total of 2500 BC patients in our data base, 892 cases were included into our analysis. The collected records and clinicopathologic parameters evaluated in each tumor included age, occupation, date of incidence, family history, menopausal status at diagnosis, laterality of the mass, tumor size, tumor stage, histologic grade, pathological data, nodal status, number of positive lymph nodes, type of chemotherapy, type of surgery, other treatment modalities (hormone therapy, radiotherapy, and chemotherapy), survival status, and follow up information, as well as the date and type of relapse. Tumor staging was performed according to the TNM classification of the International Union against Cancer (UICC).

Immunohistochemical Staining

ER, PR and HER2 status of biopsy samples were determined by the department of pathology using standard immunohistochemical (IHC) analysis. ER and PR were considered as positive if more than 1% of cells were positive. Molecular subtypes were constructed from the IHC results of hormonal receptors (ER and PR) and HER2 status, which were classified as Luminal A (ER+ and/or PR+, HER2-), Luminal B (ER+, and/or PR+, HER2+), HER2 positive (ER-, PR-, HER2+), and triple negative (ER-, PR-, HER2 -) subtypes.

Statistical Analyses

Disease-free survival (DFS) was defined as the time from date of the initial diagnosis to the first recurrence of the disease (local and regional). Overall survival (OS) was defined as the time from initial diagnosis to the time of death. Patients who were alive at the last follow-up were censored at the last follow-up date. Survival curves were derived from Kaplan-Meier estimates, and the log-rank test was used to examine the statistical significance of the differences observed between the groups. A multivariate Cox regression model was also employed to estimate the hazard ratios (HR) for DFS and OS between the breast subtypes in a multivariate analysis. A 95% confidence interval (95% CI) was set as the criterion to establish the statistical significance. Differences between the breast cancer subtypes with regard to the clinicopathologic characteristics were examined using the Chi-square and t-tests. A two-sided P-value ≤0.05 was considered statistically significant. All statistical analyses were performed by using SPSS version 18.0.

Results

Patient Characteristics and Immunohistochemical Subtypes

The clinical and pathological characteristics of 892 patients with BC are summarized in Table 1. The mean age of the patients at the time of diagnosis was ~48 years (range 22-86), and nearly 4% were single. The family history of breast and other cancers was positive in 8.3% and 6.6% of the cases, respectively. Stage II was the most frequent cancer stage among the study samples (n = 473, 70.9%). Most of the patients (81.7%) had a tumor size of <5 cm and lymph nodes were involved in 61.8% of the cases. Chemotherapy was received by 94.8%, radiotherapy was applied for 49.3% of the patients and hormone therapy was received by 90.2%. During follow-up, 150 (17.4%) patients developed either a local recurrence or distant metastases.

Table 1: Comparison of prognostic factors and demographic characteristics between triple-negative and other breast cancers.

	Triple Negative	Non-Triple Negative	P-value	Total No
Number of patients	136 (15.2%)	756 (84.8%)		892
Tumor size > 5 cm < 5 cm	19 (15.0%) 108 (85.0%)	138 (18.9%) 593 (81.1%)	0.322	157 (18.3%) 701 (81.7%)

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Axillary lymph node status Positive Negative	75 (61.5%) 47 (38.5%)	434 (61.9%) 267 (38.1%)	0.92	509 (61.8%) 314 (38.2%)
Number of Lymph Node <4 10-Apr >10 Negative	34 (28.3) 24 (20.0) 15 (12.5) 47 (39.2)	204 (29.1%) 144 (20.6%) 85 (12.1%) 267 (38.1%)	0.796	234 (29.0) 167 (20.5) 100 (12.2) 314 (38.3)
Metastases After treatment Yes No	5 (3.7%) 131 (96.3%)	19 (2.5%) 737 (97.5%)	0.395	24 (2.7%) 868 (97.3%)
Metastases After treatment Yes No	28 (20.7%) 107 (79.3%)	104 (13.8%) 652 (86.2%)	0.048	132 (14.8%) 759 (85.2%)
Location of Metastases Bone Brain Lung other liver Lung +Bone Bone + Liver Brain +Lung	7 (25.0%) 2 (7.1%) 3 (10.7%) 11 (39.3%) 3 (10.7%) 0 (.0%) 2 (7.1%) 0 (.0%)	47 (45.6%) 3 (2.9%) 13 (12.6%) 19 (18.4%) 12 (11.7%) 2 (1.9%) 6 (5.8%) 1 (1.0%)	0.585	54 (41.2%) 5 (3.8%) 16 (12.2%) 30 (22.9%) 15 (11.5%) 2 (1.5%) 8 (6.1%) 1 (0.8%)
Location of Tumor Right Left	59 (44.4%) 73 (54.9%)	350 (47.4%) 73 (52.5%)	0.446	409 (46.9%) 461 (52.9%)
Stage I II III IV	14 (13.5%) 66 (63.5%) 9 (8.7%) 15 (14.4%)	41(7.3%) 407 (72.3%) 58 (10.3%) 57 (10.1%)	0.923	55 (8.2%) 473 (70.9%) 67 (10.0%) 72 (10.8%)
Grade 1 2 3 4	3 (3.3%) 18 (20.0%) 67 (74.4%) 2 (2.2%)	53(9.7%) 236 (43.2%) 250 (45.8%) 7 (1.3%)	0	56 (8.8%) 254 (39.9%) 317 (49.8%) 9 (1.4%)
Estrogen receptor Positive Negative	0 (0.0%) 136 (100%)	573 (75.8%) 132 (24.2%)	0	573 (64.2%) 319 (35.8%)
Progesterone receptor Positive Negative	0 (0.0%) 136 (100%)	525 (69.2%) 233 (30.8%)	0	523 (58.6%) 369 (41.4%)
Her 2/neu Positive Negative	0 (0.0%) 136 (100%)	371 (49.1%) 385 (50.9%)	0	371 (41.6%) 521 (58.4%)
Ki 67 Positive Negative	20 (95.2%) 1 (4.8%)	87 (81.3%) 20 (18.7%)	0.195	107 (83.6%) 21 (16.4%)

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P53 Positive	61 (51.7%)	207 (31.6%)	0	268 (34.7%)
Negative	57 (48.3%)	448 (68.4%)		505 (65.3%)
P21 Positive Negative	17 (23.0%) 57 (77.0%)	113 (26.2%) 319 (73.8%)	0.666	130 (25.7%) 376 (74.3%)
Cathepsine Positive Negative	74 (76.3%) 23 (23.7%)	443 (74.8%) 149 (25.2%)	0.802	517 (75.0%) 172 (25.0%)
Chemotherapy Positive Negative	129 (94.9%) 7 (5.1%)	715 (94.8%) 39 (5.2%)	1	844 (94.8%) 46 (5.2%)
Chemotherapy regimen CE-CMF CE-TE CMF CE others	64 (50.0%) 23 (18.0%) 32 (25.0%) 8 (6.3%) 1 (.8%)	321 (45.0%) 79 (11.1%) 252 (35.3%) 39 (5.3%) 23 (3.2%)	0.07	385 (45.8%) 102 (12.1%) 284 (33.8%) 46 (5.5%) 24 (2.8%)
Epirubicin Positive Negative	32 (25.0%) 96 (75.0%)	264 (37.1%) 447 (62.9%)	0.009	296 (35.3%) 543 (64.7%)
CMF Positive Negative	31 (24.2%) 97 (75.8%)	124 (17.4%) 588 (82.6%)	0.082	155 (18.5%) 685 (81.5%)
CE (or EC ?) Positive Negative	41 (32.0%) 87 (68.0%)	311 (43.6%) 402 (56.4%)	0.015	352 (41.9%) 489 (58.1%)
TE Positive Negative	128 (100.0%) 0 (.0%)	711 (99.7%) 2 (0.3%)	0.958	839 (99.8%) 2 (.2%)
Type of Surgery Lumpectomy MRM Biopsy partial mastectomy Unknown	26 (20.2%) 92 (71.3%) 5 (3.9%) 1 (.8%) 5 (3.9%)	88 (11.8%) 591 (79.5%) 40 (5.4%) 14 (1.9%) 10 (1.3%)	0.318	114 (13.1%) 683 (78.3%) 45 (5.2%) 15 (1.7%) 15 (1.7%)
Radiotherapy Yes No	67 (57.3%) 50(42.7%)	292 (47.8%) 319 (52.2%)	0.069	359 (49.3%) 369 (50.7%)
Hormone therapy Tamoxifen Orimiten Decapeptil Femara Aromasin Unknown	26 (25.2%) 0 (.0%) 0 (.0%) 59 (57.3%) 0 (.0%) 18 (17.5%)	561 (79.3%) 2 (0.3%) 2 (0.3%) 80 (11.3%) 18 (2.5%) 44 (6.2%)	0	587 (72.5%) 2 (.2%) 2 (.2%) 139 (17.2%) 18 (2.2%) 62 (7.7%)
Hormone therapy Yes No	86 (72.3%) 33 (27.7%)	667 (93.2%) 49 (6.8%)	0	753 (90.2%) 82 (9.8%)

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Relapse Yes No	31 (23.3%) 102 (76.7%)	32 (25.0%) 96 (75.0%)	0	150 (17.4%) 714(82.6%)
Survival Dead Alive	44 (37.6%) 73 (62.4%)	132 (20.8%) 504 (79.2%)	0	176 (23.4%) 576 (76.6%)
	Mean; Std Deviation		Mean; Std Deviation (Range)	
Mean age (years)	47.7; 10.4	48.4; 10.4	0.461	48.28 (10.4) (22-86)
Total evaluated nodes	18.0; 7.6	17.6; 8.0	671	17.68 (8.0) (2-66)
Number of positive nodes	4.0; 6.2	4.0; 6.4	0.849	4.02 (6.4) (0-42)
DFS (months)	30.4; 19.9	37.2; 24.1	0.002	36.13 (23.7) (2-170)
OS (months)	31.3; 19.9	38.3; 23.8	0.001	37.41 (23.8) (3-171)
Follow-up: (mean 36.1) (range 2-170) months 10-year DFS 10-year OS	76.70% 62.10%	83.70% 79.20%	0.005 0.001	

Significant two-tailed p value at an alpha of 0.05.

Among the 892 patients in the study, ER was observed in 573 (64.2%), PR in 523 (58.6%) and HER2 in 371 (41.6%) cases. A total of 136 (15.2%) patients which were negative for both hormone receptors (HR) and Her2 were categorized as triple-negative (TN) breast cancer. The remaining of the cases, 756 (84.8%), also known as non-TN patients, were further classified into 3 groups and the proportions of HER2+, luminal A and Luminal B groups were 132 (14.6%), 385 (43.2%) and 239 (26.8%), respectively. The differences in the baseline characteristics of these two subtypes (TN and non-TN) are presented in Table 1. Furthermore, the differences in baseline characteristics between the four subtypes (TN, HER2+, luminal A and Luminal B) are also presented in Table 2.

Table 2: Comparison of prognostic factors and demographic characteristics in breast cancer subgroups (Triple negative, HER2+, Luminal A and Luminal B).

	ER-, PR-, HER2- (Triple Neg)	ER-, PR-, HER2+ (HER2)	ER+ &/or PR+, HER2- (Luminal A)	ER+ &/or PR+, HER2+ (Luminal B)	P-value	Total No
Number of patients	136 (15.2%)	132 (14.6%)	385 (43.2%)	239 (26.8%)		892
Tumor size > 5 cm < 5 cm	19 (15.0%) 108 (85.0%)	28 (22.0%) 99 (78.0%)	68 (18.1%) 308 (81.9)	42 (18.4%) 186 (81.6%)	0.977	157 (18.3%) 701 (81.7%)
Axillary lymph node status Positive Negative	75 (61.5%) 47 (38.5%)	70 (56.5%) 54 (43.5%)	222 (62.7%) 132 (37.3%)	142 (63.7%) 81 (36.3%)	0. 284	509 (61.8%) 314 (38.2%)
Number of Lymph Node <4 10-Apr >10 Negative	34 (28.3) 24 (20.0) 15 (12.5) 47 (39.2)	26 (21.1) 23 (18.7) 20 (16.3) 54 (43.9)	112 (31.6) 75 (21.2) 35 (9.9) 132 (37.3)	66 (28.6) 46 (20.6) 30 (13.5) 81 (36.3)	0.148	234 (29.0) 167 (20.5) 100 (12.2) 314 (38.3)
Metastases before treatment Yes No	5 (3.7%) 131 (96.3%)	3 (2.3%) 129 (97.7%)	10 (2.6%) 375 (97.4%)	6 (2.5%) 233 (97.5%)	0.736	24 (2.7%) 868 (97.3%)

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Metastases After treatment Yes No	28 (20.7%) 107 (79.3%)	27 (20.5%) 105 (79.5%)	41 (10.6%) 344 (89.4%)	36 (15.1%) 203 (84.9%)	0.05	132 (14.8%) 759 (85.2%)
Location of Metastases Bone Brain Lung other liver Lung + Bone Bone + Liver Brain + Lung	7 (25.0%) 2(7.1%) 3(10.7%) 11(39.3%) 3(10.7%) 0(.0%) 2(7.1%) 0(.0%)	11(42.3%0 0(.0%) 5(19.2%) 6(23.1%) 2(7.7%) 0(.0%) 1(3.8%) 1(3.8%)	21(51.2%) 2(4.9%) 3(7.3%) 6(14.6%) 6(14.6%) 2 (4.9%) 1 (2.4%) 0 (.0%)	15 (41.7%) 1 (2.8%) 5 (13.9%) 7 (19.4%) 4 (11.1%) 0 (.0%) 4 (11.1%) 0 (.0%)	0	54 (41.2%) 5 (3.8%) 16 (12.2%) 30 (22.9%) 15 (11.5%) 2 (1.5%) 8 (6.1%) 1 (.8%)
Location of tumor Right Left	59 (44.4%) 73 (54.9%)	59 (44.4%) 73 (54.9%)	172 (46.1%) 200 (53.6%)	172 (46.1%) 200 (53.6%)	0.066	409 (46.9%) 461 (52.9%)
Stage I II III IV	14 (13.5%) 66 (63.5%) 9 (8.7%) 15 (14.4%)	13 (12.6) 69 (67.0) 11 (10.7) 10 (9.7)	19 (6.7) 209 (74.1) 25 (8.9) 29 (10.3)	9 (5.1) 129 (72.6) 22 (12.4) 18 (10.1)	0.385	55 (8.2%) 473 (70.9%) 67 (10.0%) 72 (10.8%)
Grade 1 2 3 4	3 (3.3%) 18 (20.0%) 67 (74.4%) 2 (2.2%)	3 (3.0%) 29(29.0%) 66(66.0%) 2(2.0%)	32(12.5%) 119(46.5%) 104(40.6%) 1(0.4%)	32(12.5%) 119(46.5%) 104(40.6%) 1(0.4%)	0	56 (8.8%) 254 (39.9%) 317 (49.8%) 9 (1.4%)
Estrogen receptor Positive Negative	0 (0.0%) 136 (100%)	0 (0.0%) 132 (100%)	363 (94.3%) 22 (5.7%)	210 (87.9%) 29 (12.1%)	0	573 (64.2%) 319 (35.8%)
Progesterone receptor Positive Negative	0 (0.0%) 136 (100%)	0 (0.0%) 132 (100%)	326 (84.7%) 59 (15.3%)	197 (82.4%) 42 (17.6 %)	0	523 (58.6%) 369 (41.4%)
Her 2/neu Positive Negative	0 (0.0%) 136 (100%)	132 (100%) 0 (0.0%)	0 (0.0%) 385 (100%)	197 (82.4%) 0 (0.0%)	0	371 (41.6%) 521 (58.4%)
Ki 67 Positive Negative	20 (95.2%) 1 (4.8%)	21 (95.5%) 1 (4.5%)	45 (75.0%) 15 (25.0%)	21 (84.0%) 4 (16.0%)	0.075	107 (83.6%) 21 (16.4%)
P53 Positive Negative	61 (51.7%) 57 (48.3%)	59 (50.4%) 58 (49.6%)	59 (50.4%) 58 (49.6%)	60 (31.7%) 129 (68.3%)	0	268 (34.7%) 505 (65.3%)
P21 Positive Negative	17 (23.0%) 57 (77.0%)	17 (23.0%) 57 (77.0%)	17 (23.0%) 57 (77.0%)	32 (29.4%) 77 (70.6%)	0.646	130 (25.7%) 376 (74.3%)
Catepsine Positive Negative	89 (81.7%) 20 (18.3%)	89 (81.7%) 20 (18.3%)	225 (72.8%) 84 (27.2%)	225 (72.8%) 84 (27.2%)	0.232	517 (75.0%) 172 (25.0%)

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Chemotherapy Positive Negative	129 (94.9%) 7 (5.1%)	131 (100.0%) 0 (.0%)	352 (91.7%) 32 (8.3%)	232 (97.1%) 7 (2.9%)	0.744	844 (94.8%) 46 (5.2%)
Chemotherapy regimen CE-CMF CE-TE CMF CE others	64 (50.0%) 23 (18.0%) 32 (25.0%) 8 (6.3%) 1 (.8%)	60 (45.5%) 28 (21.2%) 31 (23.5%) 9 (6.8%) 2 (1.5%)	165 (47.1%) 31 (8.9%) 127 (36.3%) 15 (4.3%) 12 (3.4%)	96 (41.6%) 20 (8.7%) 94 (40.7%) 14 (6.1%) 6 (2.6%)	0.022	385 (45.8%) 102 (12.1%) 284 (33.8%) 46 (5.5%) 21 (2.5%)
Epirubicin Positive Negative	32 (25.0%) 96 (75.0%)	31 (23.5%) 101 (76.5%)	135 (38.8%) 213 (61.2%)	98 (42.4%) 133 (57.6%)	0	296 (35.3%) 543 (64.7%)
CMF Positive Negative	31 (24.2%) 97 (75.8%)	41 (31.1%) 91 (68.9%)	48 (13.8%) 301 (86.2%)	35 (15.2%) 196 (84.8%)	0	155 (18.5%) 685 (81.5%)
CE (or EC ?) Positive Negative	41 (32.0%) 87 (68.0%)	43 (32.6%) 89 (67.4%)	154 (44.0%) 196 (56.0%)	114 (49.4%) 117 (50.6%)	0	352 (41.9%) 489 (58.1%)
TE Positive Negative	128 (100.0%) 0 (.0%)	131 (99.2%) 1 (.8%)	350 (100.0%) 0 (.0%)	230 (99.6%) 1 (.4%)	0.958	839(99.8%) 2(.2%)
Type of Surgery Lumpectomy MRM Biopsy partial mastectomy Unknown	26 (20.2%) 92 (71.3%) 5 (3.9%) 1 (.8%) 5 (3.9%)	8 (6.1%) 110 (84.0%) 10 (7.6%) 2 (1.5%) 1 (.8%)	64 (17.0%) 271 (72.1%) 23 (6.1%) 11 (2.9%) 7 (1.9%)	16 (6.8%) 210 (89.0%) 7 (3.0%) 1 (.4%) 2 (.8%)	0.762	114 (13.1%) 683 (78.3%) 45 (5.2%) 15 (1.7%) 15 (1.7%)
Radiotherapy Yes No	67 (57.3%) 50(42.7%)	56 (53.3%) 49 (46.7%)	152 (47.8%) 166 (52.2%)	84 (44.7%) 104 (55.3%)	0.027	359 (49.3%) 369 (50.7%)
Hormone therapy Tamoxifen Orimiten Decapeptil Femara Aromasin Unknown	26 (25.2%) 0 (.0%) 0 (.0%) 59 (57.3%) 0 (.0%) 18 (17.5%)	12 (11.5%) 0 (.0%) 0 (.0%) 71 (68.3%) 0 (.0%) 21 (20.2%)	344 (92.5%) 1 (.3%) 1 (.3%) 6 (1.6%) 9 (2.4%) 11 (3.0%)	205 (88.7%) 1 (.4%) 1 (.4%) 3 (1.3%) 9 (3.9%) 12 (5.2%)	0	587 (72.5%) 2 (.2%) 2 (.2%) 139 (17.2%) 18 (2.2%) 62 (7.7%)
Hormone therapy Yes No	86 (72.3%) 33 (27.7%)	84 (75.0%) 28 (25.0%)	363 (96.5%) 13(3.5%)	220(96.5%) 8(3.5%)	0	753(90.2%) 82(9.8%)
Relapse Yes No	31 (23.3%) 102 (76.7%)	32(25.0%) 96 (75.0%)	48(12.9%) 325(87.1%)	39(17.0%) 191 (83.0%)	0	150 (17.4%) 714(82.6%)
Survival Dead Alive	44(37.9%) 72 (62.1%)	27(25.2%) 80(74.8%)	60(18.5%) 264(81.5%)	45(22.2%) 158 (77.8%)	0	176(23.5%) 574 (76.5%)

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	Mean (SD)					Mean (SD)
Mean age (years)	47.67 (10.4)	47.20 (9.3)	48.85 (10.6)	48.28 (10.7)	0.389	48.28 (10.4) (22-86)
Total evaluated nodes	17.98 (7.6)	18.50 (9.5)	16.73 (7.4)	18.59 (8.0)	0. 320	17.68 (8.0) (2-66)
Number of positive nodes	3.92 (6.2)	4.51 (7.1)	3.71 (6.1)	4.30 (6.4)	0.674	4.02 (6.4) (0-42)
DFS (months)	30.38 (19.9)	32.50 (25.2)	35.02 (20.2)	43.25 (28.2)	0.002	36.13 (23.7) (2-170)
OS (months)	31.71 (21.4)	34.35 (26.0)	36.16 (19.8)	44.47 (27.9)	0.001	37.41 (23.8) (3-171)
Follow-up; mean (range), months	36.13 (2-170)					
10-year DFS	76.70%	75.00%	87.10%	83.00%	0	82.60%
10-year OS	62.10%	74.80%	81.50%	77.80%	0	76.50%

Correlation of TN and non-TN subgroups with clinicopathologic features

When the cases were divided into two groups, TN and non-TN, a number of associations were found between these two subtypes in several of the patient's histopathological variables, such as metastases, chemotherapy regimen, recurrence and survival (Table 1). When we investigated the presence of a positive family history of breast and other cancers in the patients with TN and non-TN breast cancer, no significant difference was found between these two groups. Epirubicin positive cases were lower among the TN subgroup compared to the non-TN (25.0% vs. 37.1%; P=0.009) and patients with TN had higher tumor grade than non-TN group (p=0.000). Tumor grade 3 was the most frequent tumor grade in the TN samples (74.4%). During the follow-up, the TN group had a higher metastatic rate (20.7% vs. 13.8%; P=0.048), and p53 positive cases were significantly higher among this group (51.7% vs. 31.6%; P=0.000).

Correlation of Four Subgroups (TN, HER2+, Luminal A and Luminal B) With Clinicopathologic Features

When the analysis was repeated for the four subtypes, associations were found between the different subtypes and several of the patients' histopathological variables such as metastases, chemotherapy, hormone therapy, recurrence and survival. The clinicopathological features and the characteristics of these subgroups are summarized in Table 2. In this study, we found no significant difference in patients' age among the different BC subtypes, with similar median age of approximately 48 years in all subtypes (P = 0.461). Patients in the HR- groups had higher grade III tumors compared to the HR+ group (TN 77.4% and HER2+ 66.0% vs. luminal A 40.6% and luminal B 42.1%). In addition, the HR- groups had a higher metastatic potency compared to the HR+ cases (TN 20.7% and HER2+ 20.5% vs. luminal A 10.6% and luminal B 15.1%). Other than p53, no association was found between the subgroups and the other biomarkers which were included in this study such as Ki67, p21, and Cathepsin.

Correlation of the Subgroups with Clinical Outcomes and Patients' Survival

The clinical outcomes of the cases were regularly followed-up. After a mean follow-up of 37 months (2-171 months) from the initial diagnosis, 17.4% and 23.5% cases were recorded to have disease recurrence and death, respectively. Using Kaplan-Meier survival analysis (Figure 1), the TN group had the poorest DFS and OS. The 3-year estimated DFS was 75% for TN compared to 84% for non-TN group (p=0.005); and OS was 68% for TN compared to 82% for non-TN group (p= 0.000). When we analyzed the correlation of the four subgroups with the clinical outcome, a higher proportion of patients with triple negative and HER2+ BC experienced more recurrence compared to the patients within the other subgroups (TN 23.3% and HER+ 25.0% vs. luminal A 12.9% and luminal B 17.0%; P= 0.000). The mean time of recurrence in patients with triple negative and HER2+ BC was less than that of the luminal A and B groups (30.4 and 32.5 vs. 35.0 and 43.3 years, respectively; P = 0.001). Moreover, the death rate was significantly higher (P< 0.001) in the TN subtype (37.9%) and progressively less in each subsequent phenotypic subtype from HER2+ (25.2%) to luminal B (22.2%) and luminal A (18.5%).

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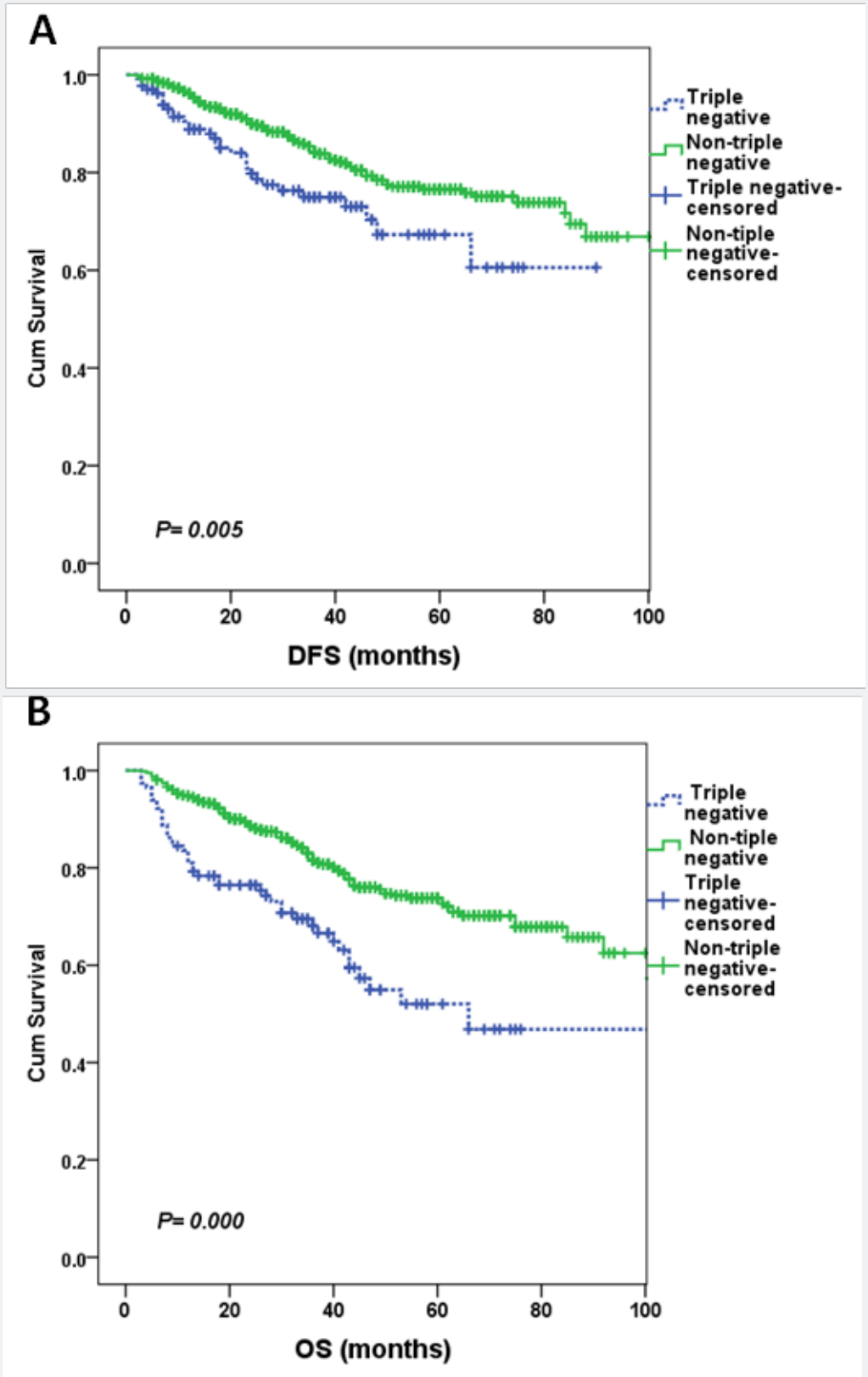

Figure 1: Kaplan-Meier estimate of disease-free survival (DFS) (A) and overall survival (OS) (B) in Triple Negative vs non-Triple Negative.

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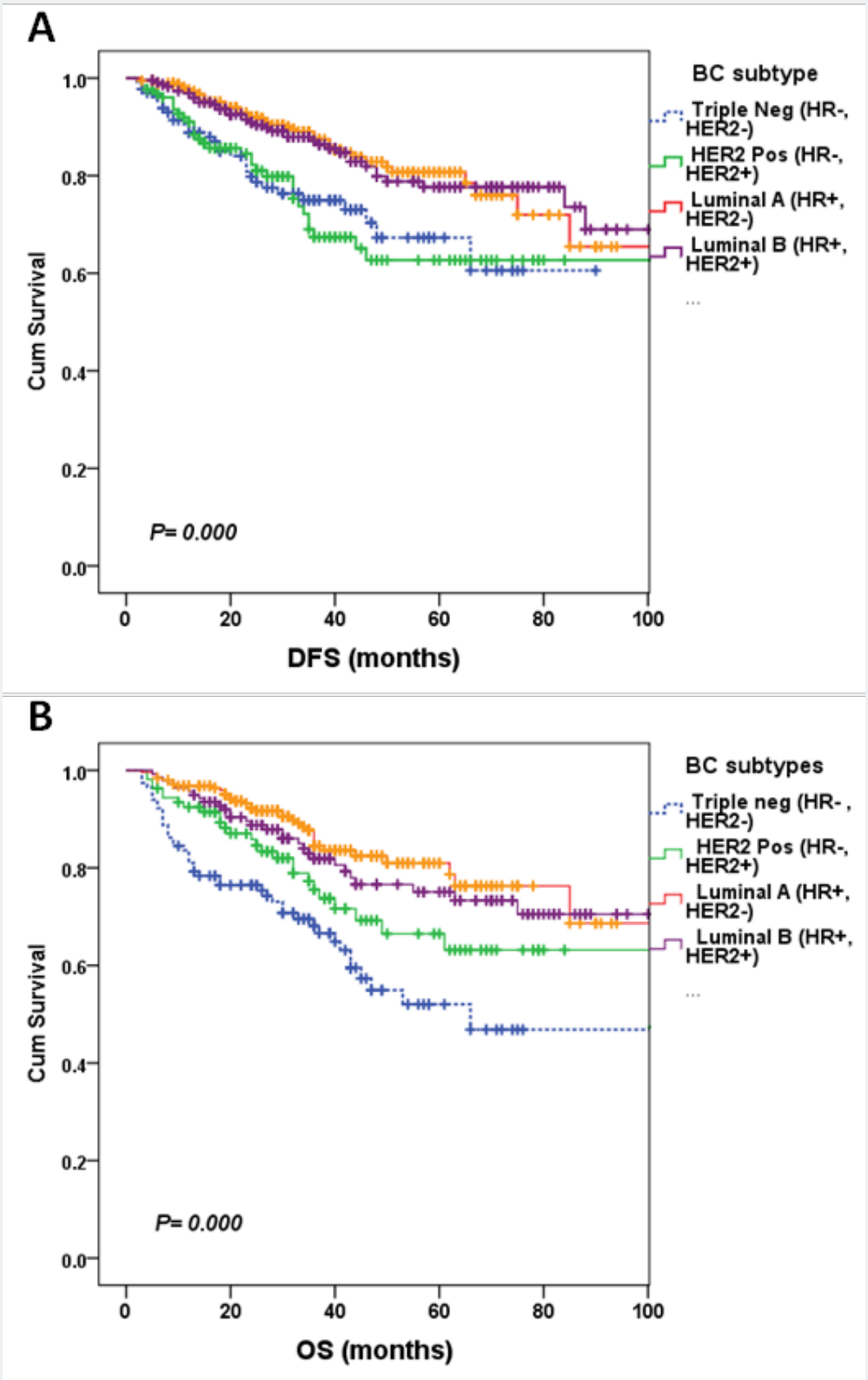

Figure 2: Kaplan-Meier estimate of disease-free survival (DFS) (A) and overall survival (OS) (B) in breast cancer subgroups (Triple negative, HER2+, Luminal A and Luminal B).

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Kaplan-Meier survival analysis was carried out to compare the DFS and OS rates (Figure 2). Luminal A and luminal B had a more favorable DFS and OS compared to the other subtypes. The 3-year estimated DFS was 89% for Luminal A and 87.9% for Luminal B subgroups, compared to 69.0% for HER2+ and 75% for TN subtypes (P=0.000). No significant difference was observed in the 3-year DFS of the two luminal subtypes and, also, between the HER2+ and TN subtypes. Conversely, the luminal A (85.1%) and then the luminal B subtypes (82.1%) were associated with a better OS when compared to the HER2+ (77.3%) and then the TN (69.5%) subtypes (P= 0.000, Figure 2).

Breast Cancer Subtypes and Survival in the Multivariate Analysis

In the multivariate Cox regression analysis with the non-TN subtype taken as a reference, the TN subtype was associated with an increased recurrence and death rate having a hazard ratio (HR) of 1.75 (95% CI 1.18-2.60; P = 0.006) for DFS and 2.21 (95% CI 1.57-3.11, P = 0.000) for OS. In the Cox regression analysis of the four subgroups, Luminal A and luminal B had a similar and favorable DFS compared to the other subtypes. Using the luminal A as a reference, HER2+ and triple-negative subtypes also had a similar and the worst DFS (HR=2.1, 95% CI 1.3 to 3.3, P=0.001). In OS analyses, the TN (HR=2.36, 95% CI 1.60 to 3.48, P<0.001) had the worst OS followed by the HER2+ (HR=1.42, 95% CI 0.90 to 2.24, P=0.128) and luminal B (HR=1.01, 95% CI 0.68 to 1.48, P=0.974) when compared to the reference group (Luminal A) in the multivariate analysis. However, the difference between the luminal A and luminal B or between the HER2+ and TN subtypes was not statistically significant.

Time of Recurrence

To evaluate the time of recurrence for the subgroups, we estimated the incidence of recurrence during a ten-year follow-up period at 2-month intervals (Figure 3). The pattern of recurrence somewhat differed between the subgroups. In patients with triple negative and HER2+ breast cancer, the incidence of any recurrence was higher during the first 2 years as compared to the other groups. However, after 6 years, patients having luminal cancer had higher incidence of recurrence. After 8 years, there was no recurrence in the TN patients.

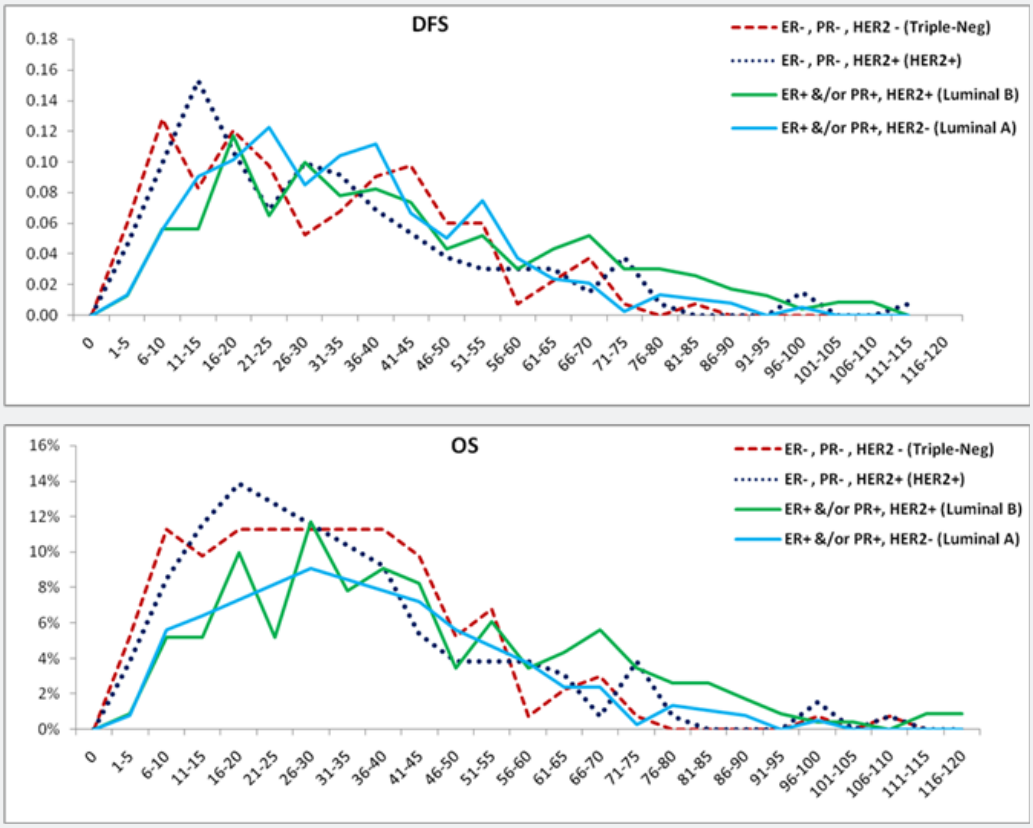

Figure 3: Rate of recurrences in different breast cancer subgroups over 10-year follow-up period. Our study demonstrates that the pattern of recurrence and survival curve over a 10-year follow-up period differs among the different subtypes. Women with triple negative and HER2+ breast cancer were much more likely to develop a recurrence during the first two years following therapy.

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Correlation of Subgroups with P53 Status

In the whole series, about 34.7% of the tumors were p53-positive. The patients with p53 expression showed an association with shorter DFS (P=0.024) (data not shown). Also, it appears that there is an inverse association between p53 and HR expressions, but not with HER2 expression. Patients in the TN (51.7%) and HER+ (50.4%) subgroups had a higher rate of p53 positivity compared to the luminal A (25.2%) and luminal B (31.7%) groups (P<0.001).

Discussion

In this cohort of 892 Iranian women with operable primary BC, we were able to identify four intrinsic subtypes based on the immunohistochemical results of ER, PR and HER2 status, which include two hormone receptor (HR)-positive subtypes (Luminal A and Luminal B) and two HR–negative subtypes (HER2+ and triple-negative). As compared with luminal A and B, we found that patients with HR–negative subtypes were associated with increased recurrence (P=0.000) and death rates (P=0.000). Of all, triple-negative BC (TNBC) has intensified the interest not only because of the lack of targeted therapies, but also because these tumors have been reported to be more aggressive than the other subtypes. Previous population-based studies have observed that the distribution of BC molecular subtypes varies by race/ethnicity and age [12-16]. There are diverse reports regarding the prevalence of TNBC, ranging from 10% in a Japanese study [13] to 26% in a Korean study [21].

Also, the incidence of TNBC in African [22] and African American [23,24] women is reported to be high, and this may be partially responsible for the poor outcomes observed among these patients. The incidence of TNBC in our study was 15.2%, which was somewhat similar to the incidence of 11.2%–26% reported in the literature [18,23,25-27]. Moreover, we found that the average age of patients with TN cancers was 47.7 years which was almost similar to other non-TN subtypes (48.4 years, P = 0.461). Several studies illustrate that TNBC more commonly arise in younger women, although the exact cause for this association is not yet fully understood [13,20,28].

TN subtype has been characterized by several aggressive clinicopathologic features, including onset at a younger age, relatively large tumors size, higher-grade tumors, and, in some cases, a higher rate of nodes involvement [18,23,29]. Given this, it was tempting to analyze whether there are associations between BC subtypes and prognosis of the patients classified by TN and non-TN groups. In our series, there was no difference in clinical tumor stage and regional lymph node involvement among these subtypes; however, patients with TN (also HER2+) had higher tumor grade than the other groups (P=0.000). The results of this study showed that TN (HR- phenotypes in general) had higher metastatic potency compared to HR+ cases.

Multiple studies have indicated that the triple-negative breast cancer exhibits a distinct pattern of recurrence. In our study, we found that the pattern of the survival curve for patients with TNBC also differed from that for patients with other types of BC.

The pattern of TN recurrence was characterized by a rapidly rising rate during the first 2 years after the diagnosis, followed by a decline in recurrence risk over the next 5 years, and a very low risk of recurrence thereafter. Studies have consistently shown that, in addition to a distinct pattern of timing of recurrence, there are unique patterns of relapse site among TNBC patients. It has been demonstrated that luminal A subtype typically causes late bone metastases, whereas TNBC is more likely to cause early visceral metastases [30]. In our study, bone metastasis was more common in non-TNBC subtypes, especially in luminal A (51.2%), and less in TN subtype (25.0%; P<0.001), indicating a less tendency for bone metastasis among patients diagnosed with triple-negative disease.

A number of biological markers have been reported to evaluate the prognosis of BC patients. Table 2 shows the relative prevalence of various molecular markers in different subclasses of tumors. Even though, the prevalence of positivity for Ki-67 proliferation index was not statistically significant (P=0.075), however, higher prevalence was noted in the HR-negative (TN 95%; HER2+ 95%) subtypes, followed by Luminal A (84.0%), and Luminal B (75.0%).

The crucial role of p53 as a mediator of stress in various cell types has been demonstrated; however, its contribution to breast cancer has been difficult to evaluate. Despite numerous studies, the link between p53 and prognosis and prediction remain largely unclear. More than 25 studies to date involving over 6000 patients have revealed the strong prognostic significance of p53 mutations [31]; however, in several recent studies the presence of p53 mutation was the single most adverse prognostic indicator for both recurrence and death [32,33]. Also it has long been thought that normal p53 results in a better chemotherapy response; however, in a very recent finding [34], contrary to dogma, presence of normal p53 in mouse models, hinder breast cancer chemotherapy.

In this study, Jackson et al. reported that doxorubicin-treated mutant p53-expressing tumor cells failed to arrest proliferation, leading to abnormal mitoses and cell death, whereas wild-type p53 tumors arrested, initiating a senescence process, and avoiding mitotic catastrophe. Senescent tumor cells persisted, secreting senescence-associated cytokines exhibiting autocrine/paracrine activity and mitogenic potential that stimulate adjacent cells to grow, fueling the relapse Supporting its poor prognostic role, in our multivariate analysis, p53 expression showed an association with shorter DFS (P=0.024, data not shown). Interestingly, we found a significant (P<0.001) inverse association between HR+ subgroups and immunoreactivity of p53. It appears that p53 expression was much more frequent in the TN (51.7%) and HER2+ (50.4%) subgroups and was

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associated with poor prognosis, compared to luminal A (25.2%) and luminal B (31.7%).

In conclusion, molecular subtypes approximated by ER, PR and HER2 can predict the prognosis of BC in our patients treated with pre-operative therapy. Patients with HR- status (TN and HER2+ subgroups) had progressively worse disease outcomes compared to patients with HR+ status (Luminal A and B subgroups). Moreover, this study suggests that the patients categorized by HER2 status (HER2+ and HER2-) were not significantly different from each other in either HR+ or in HR- groups, which may indicate that HR status is a more powerful predictor of outcome than HER2 status.

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