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ORIGINAL PAPER

Demographic and clinico-pathological characteristics in patients with triple-negative and non-triple-negative breast cancer

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Abstract We investigate retrospectively the demographic and clinico-pathological characteristics of patients with triple-negative breast cancer (TNBC) compared to those with non-TNBC. Patients with breast cancer diagnosed from 1981 to 2008 in our clinic were retrospectively analyzed. Patient demographics including survival data and tumor characteristics were obtained from charts. A total of 795 patients were assessed in the study, including 140 patients (17.6%) with TNBC and 655 patients (82.4%) with non-TNBC. Patients with non-TNBC were further classified into 3 groups according to hormone receptor (HR) and HER-2 status. Median age was 49 (range 38–60 years) and similar between patients with TNBC and non-TNBC. Patients with TNBC had an increased likelihood of a higher histological grade III compared with HR(+) HER-2(−) subgroup ($P > 0.001$) and lower stage compared with HR(+)/HER2(+) and HR(−)/HER2(+) subgroups ($P < 0.001$ and $P = 0.002$, respectively). In patients with TNBC, the disease-free survival (DFS) rate was 66% at 5 years. In subgroup analysis of non-TNBCs, 5-year-DFS rates of the patients in HR(+)/HER2(−), HR(+)/HER2(+) and HR(−)/HER2(+) subgroups were 59, 66, and 57%, respectively. There was no significant difference between the TNBC and non-TNBC subgroups ($P = 0.238$). In multivariate analysis, nodal involvement (RR = 2.8, 95% CI: 0.99–8.3, $P = 0.052$) and the presence of lymphovascular invasion (RR = 3.2, 95% CI: 1.1–9.2, $P = 0.029$) were significantly associated with increased recurrence risk in patients with TNBC. Although there are differences in patient and tumor features, patients with TNBC had similar clinical course with those with non-TNBC.

Keywords Triple negative · Breast cancer · Non-triple negative · Prognosis

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Introduction

Breast cancer is a heterogeneous disease, encompassing a number of distinct biological entities that are associated with specific morphological and immunohistochemical features and clinical behavior. Triple-negative breast cancer (TNBC) accounts for 10–20% of all breast carcinomas [1–3]. Triple-negative cancers have a tendency to affect pre-menopausal and African-American/Hispanic women more frequently [4]. Triple-negative tumors (estrogen receptor (ER), progesterone receptor (PR) and HER-2 negative) have aggressive clinical behavior and poor prognosis. Most TNBC shows a basal-like phenotype [3]. More advanced stage at diagnosis and larger median tumor size are characteristic for TNBC. Triple-negative tumors have high histological and nuclear grade, high mitotic index, low local relapse rate, and more distant recurrence [4]. Relapses and deaths commonly occur within the first 5 years following diagnosis [1, 5]. Breast cancer survival at 3 and 10 years is correlated closely with histological grade, size, and lymph node involvement. After 3 years, the ER, PR, HER-2 negative status diminish in influence, with CK5/6 and/or EGFR positive status becoming the main driving factor. The difference in the rate of relapse and death between TNBC and non-TNBC groups is less marked after 10 years [1, 6]. TNBC has inferior prognosis compared to other forms of breast cancer. Poor prognosis of TNBC is associated with aggressive course of the tumor,

excess risk of distant recurrence, and the lack of specific treatment [7–9]. Since TNBC is resistant to current therapies such as trastuzumab, and hormonal therapies such as tamoxifen and aromatase inhibitors, chemotherapy is the mainstay of treatment.

In this study, we aimed to investigate retrospectively the demographic and clinico-pathological characteristics of patients with TNBC compared to those with non-TNBC.

Patients and methods

This analysis included women with breast cancer diagnosed from 1981 to 2008 in our clinic. Patient demographics were obtained from charts. Tumors were graded according to the modified Bloom–Richardson scoring system and staged according to the TNM criteria. The data on ER, PR, and HER2/neu were obtained through standard clinical testing, using immunohistochemistry (IHC) for ER and PR and the HerceptTest for HER2/neu. For ER and PR, receptor positivity was based on more than 5% of cells testing positive. IHC was scored on a qualitative scale from 0 to 3+, based on interpretation of staining intensity, with 0 and 1+ classified as negative (incomplete membrane staining in 10% of the tumor cells), 2+ as borderline, and 3+ as positive (strong and complete membrane staining in >10% of cells). Tumors scored as 2+ were further analyzed for HER-2 amplification by means of FISH. We further categorized the patients as triple-negative if they were negative for estrogen receptor, progesterone receptor, and Her2/neu.

Statistical analysis

SPSS for Windows, version 12.0 was used for all statistical analyses. Kaplan–Meier survival analysis was carried out for recurrence-free survival. 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. This was used to compute hazard ratios and 95% confidence intervals, adjusting for known prognostic variables. Two-sided P values of <0.05 were considered statistically significant.

Results

A total of 795 patients were included in the study. Six hundred and fifty five patients (82.4%) had non-TN breast cancer. One hundred and forty (17.6%) patients showed a triple-negative phenotype. Median age was 48 and similar between TNBC patients and non-TNBC patients. Patients with non-TNBC were further classified into HR(+)/HER2(−), HR(+)/HER2(+) and HR(−)/HER2(+) subgroups, and clinical and pathological features were re-assessed (Table 1). Patients with TNBC had an increased likelihood of a higher histological grade III compared with HR(+) HER-2(−) subgroup ($P > 0.001$) and lower stage compared with HR(+)/HER2(+) and HR(−)/HER2(+) subgroups ($P < 0.001$ and $P = 0.002$, respectively).

In survival analysis, 19% of the patients relapsed and 0.6% died on follow-up. Median overall survival rates could not be obtained. In patients with TNBC, the disease-free survival (DFS) rate was 94, 80, and 67% in the first, third, and fifth years, respectively. In subgroup analysis of non-TNBCs, 1, 3, and 5 years DFS rates were 98, 80, and 59% in HR(+)HER2(−) patients, 95, 73, and 66% in HR(+)HER2(+) patients, 90, 66, 57% in HR(−)HER2(+) patients, and there was no significant difference between the TNBC and non-TNBC subgroups ($P = 0.238$) (Fig. 1). In both groups, menopausal status had no effect with respect to the risk of recurrence. The presence of lymphovascular invasion was associated with 2.5 times higher risk of recurrence in patients with TNBC (RR: 2.5, 95% CI 1.0–6.2; $P = 0.03$). Higher stage and lymph node involvement were also associated with a higher risk of recurrence in patients with TNBC (Table 2). In multivariate analysis, nodal involvement (RR = 2.8, 95% CI: 0.99–8.3, $P = 0.052$) and the presence of lymphovascular invasion (RR = 3.2, 95% CI: 1.1–9.2, $P = 0.029$) were significantly associated with increased recurrence risk in patients with TNBC.

Discussion

In this study, we appraised the demographic, clinical and pathological features and prognosis of the patients with TNBC in comparison with those with non-TNBC. We have found the TNBC prevalence as 17.6%. Patients with TNBC had higher grade tumors, lower disease stage and lower rate of axillary lymph node positivity compared to those with non-TNBC. Recurrence-free survival rates were similar between the groups. Lymph node metastasis and the presence of LVI were the significant determinants of RFS in multivariate analysis in patients with TNBC.

We have found the mean age of the patients with TNBC and non-TNBC similar (49.4 vs. 49.7, $P = 0.76$). A large cohort study of 1601 patients with breast cancer (including 180 triple-negative cases) showed that the mean age at diagnosis was younger for those women with triple-negative tumors (53 vs. 58 years, $P < 0.0001$) [8]. However, mean age of our patients (~49) with breast cancer in both TNBC and non-TNBC subtypes is significantly lower than that reported in this study. In various studies, the average age of patients with basal-like cancers appears to range

Table 1 Clinico-pathological features of the patient subgroups according to hormone receptor and HER-2 expression

	HR(+)HER2(−)		HR(+)HER2(+)		HR(−)HER2(+)		Triple negative		*P*-value
	N	%	N	%	N	%	N	%	
Age (years)									0.569
<50	193	54.2	56	50	35	61.4	74	53.2	
≥50	163	45.8	56	50	22	38.6	65	46.8	
Menopausal status									0.197
Pre	170	47.5	52	48.6	37	65	60	43.1	
Peri	28	7.8	8	7.5	2	3.5	14	10	
Post	160	44.7	47	43.9	18	31.5	65	46.9	
Family history of breast cancer (%)	3.5		8		5.9		4.6		0.349
Cancer history other than breast cancer in family (%)	33.1		30.2		35.8		20.7		0.073
Age at menarche									0.379
≤12 years	63	24.4	25	33.3	15	32	28	26.2	
≥13 years	196	75.6	50	66.6	32	68	79	73.8	
Age at first full-term pregnancy									0.212
<26 years	154	71.9	45	83.3	31	77.5	71	81.6	
≥26 years	60	28.1	9	16.7	9	22.5	16	18.4	
Parity									0.462
Nulliparous	38	11.5	13	14	4	7.2	11	8.6	
Parous	295	88.5	80	86	52	92.8	118	91.4	
Lifetime duration lactation									0.428
1–3 months	33	14.7	5	8.8	4	8.9	7	8.4	
≥4 months	192	85.3	52	91.2	41	91.1	77	91.6	
Tumor size (cm)									0.100
<2	123	38.4	28	27.7	17	36.1	39	31.4	
2–5	151	47.1	57	56.4	20	42.5	71	57.2	
≥5	46	14.4	16	15.9	10	21.4	14	11.4	
Histological grade									**<0.001**
I + II	235	72.3	55	55	23	41	46	38.9	
III	90	27.7	45	45	33	59	72	61.1	
Lymphovascular invasion									0.698
Yes	97	27.3	28	25	19	33.3	37	26.4	
No	267	72.7	84	75	38	66.7	103	73.6	
Lymph node status									0.115
N0	142	43.9	40	40.8	18	36.7	68	53.5	
N+	181	56.1	58	59.2	31	63.3	59	46.5	
Stage									**<0.001**
I + II	220	66.4	51	49.5	26	49	94	73.4	
III + IV	111	33.6	52	50.5	27	51	34	26.6	
Relapse									0.317
No	298	81.8	87	77.6	42	73.6	117	83.5	
Yes	66	18.2	25	22.4	15	26.4	23	16.5	

Bold values indicate $P < 0.05$

from 46 to 54 years. Similar with our study, the Polish Breast Cancer Study found no significant difference in patient age between the different breast cancer groups [10]. Therefore, epidemiologic characteristics of TNBC may vary in different ethnicities.

Our patients with TNBC tended to have higher grade, consistent with the literature [11] but interestingly had lower disease stage and lymph node involvement rate. Some studies have found higher rate of axillary LN metastases [8] while the others have found lower rates [12].

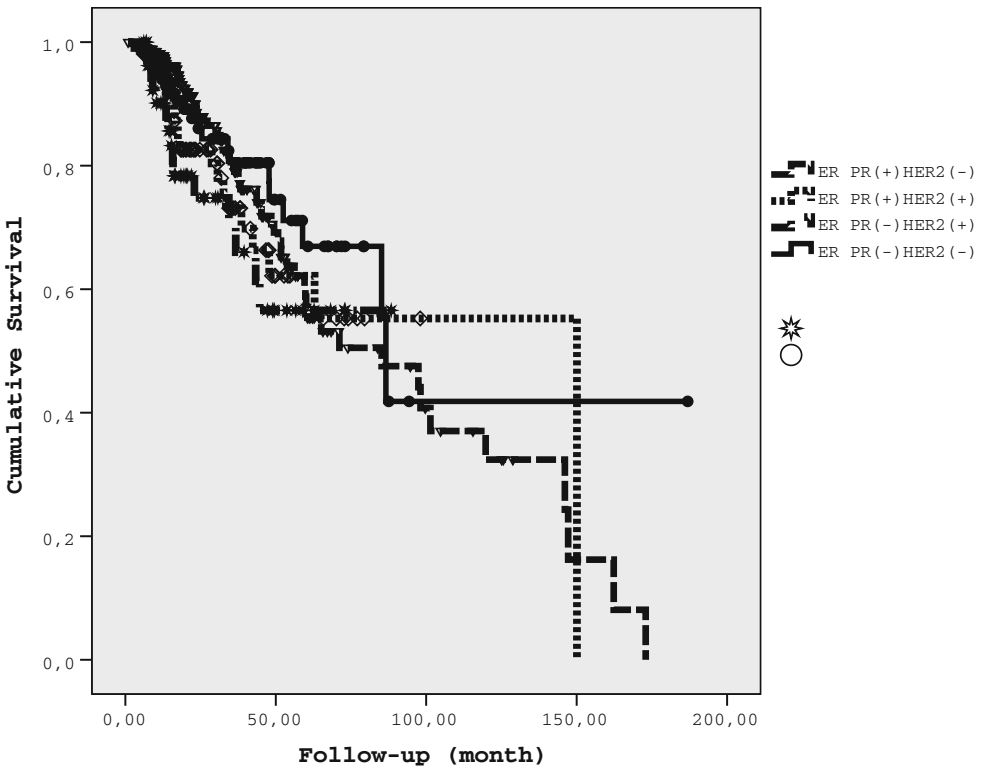

Fig. 1 Analysis of disease-free survival of four breast cancer subtypes by log-rank test

Table 2 Univariate Cox regression analysis of factors associated with recurrence in patients with TNBC

	RR	95% CI	*P*-value
LVI (yes/no)	2.5	1.0–6.2	**0.03**
Grade (III/I or II)	1.67	0.6–4.5	0.31
(T2, T3, T4)/T1	1.8	0.6–5.5	0.27
N(+)/N0	2.8	1.1–7.5	**0.028**
Stage			
2/1	3.5	0.4–27.7	0.22
3/1	8.3	1.0–69.4	**0.048**

Bold values indicate $P < 0.05$

In one study among 1,993 patients with breast cancer, 21.83% of triple-negative patients had four or more axillary lymph nodes involved when compared to 27.40% of ERBB2 + women and 22.75% of HR +/ERBB2-subgroup ($P = 0.0056$) [13]. TNBC tends to metastasize hematogenously rather than lymphatic way, thus showing less axillary lymph node metastasis than non-TNBC [8]. This may account for the lower rate of axillary lymph node involvement in our study.

TNBCs have an aggressive clinical course and a higher risk of recurrence and death compared to those with non-triple-negative tumors, particularly in the first 5 years. On the other hand, the rate of late recurrences and death is lower. They also brain metastasis and lower incidence of bone metastasis [5, 8, 14, 15]. Lymph node positivity and lymphovascular invasion were found to be associated with lower RFS rate in our group with TNBC in multivariate analysis. In the study of Dent et al., after adjustment for age, grade, tumor size, nodal status, chemotherapy, and tamoxifen therapy, the risk of death from breast cancer remained higher for the triple-negative group up to 5 years from diagnosis. However, the increased mortality rate was not sustained for the period from 5 years after diagnosis to the end of follow-up. Thus, the excess deaths among the triple-negative group occurred in the first 5 years after diagnosis. In our patients, the disease-free survival rates at first, third, and fifth years were similar in patients with TNBC and non-TNBC. We have observed that our patients with TNBC had better prognosis than TNBC patients in studies of Europe and America. There are also other studies that showed good response rates and low recurrence rates [13, 16].

In conclusion, although the classification of human breast tumors on the basis of clinical and pathological characteristics has proven useful, considerable variation in response to therapy and clinical outcome exists. Gene expression profiling using microarray-based technology can result in a more precise classification of human breast tumors.

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