Prognostic factors affecting disease-free survival in patients at age 35 or younger with invasive breast cancer

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AIM: *Our aim is to determine the disease-free survival (DFS) rate, and to investigate the prognostic factors among patients with invasive breast cancer at age 35 or younger.*
PATIENTS AND METHOD: *The medical records of the 67 patients who underwent surgery for invasive breast cancer were retrospectively reviewed. Potential prognostic factors that affect the DFS were investigated. DFS curves were obtained using the Kaplan-Meier method. The comparisons were made by the long-rank test. The prognostic factors affecting the DFS were determined by stepwise Cox proportional hazard regression test. The P value < 0.05 was accepted as significant.*
RESULTS: *The median age was 32 (range, 23-35). The median follow-up interval was 55 months (range, 10-108). The 5-year DFS rate was 69.3%. In univariate analysis the number of pathologic axillary lymph nodes (p=0.035), triple-negative status (p=0.014) and tumor size (p= 0.004) were found to be the prognostic factors affecting the DFS. The 5-year DFS rate was 81% in non-triple negative patients, whereas this was 35% in triple-negative patients. In the multivariate analysis, triple-negative status was the only independent prognostic factor which affected the DFS adversely (HR: 1.48, CI: 0.66-082, p=0.027).*
CONCLUSION: *Triple-negative status was found to be the only independent and adverse prognostic factor which affects the DFS in patients with invasive breast cancer at age 35 or younger.*

KEY WORDS: Breast cancer, Disease-free survival, Triple negative breast cancer, Young age

Introduction

Breast cancer rarely occurs in young females under 36 years old, and constitutes 2-4% of the operable breast cancers [1]. Many studies support that the survival in young patients is shorter than the older counterparts [2,3]. Young age has been reported as an adverse prognostic factor for breast cancer recurrence [4,5], and the DFS rate has been found to be lower in this patients group [3,6-8]. A few studies have investigated the prognostic factors that affect the DFS in patients at or younger than 35 years old with invasive breast cancer [9-11]. To the best of our knowledge, there is no study on the DFS of the young patients with the breast cancer in Turkey. In the present study, we aimed to investigate the prognostic factors affecting the DFS of the young patients with invasive breast cancer.

Patients and Method

The medical records of the 67 female patients who underwent surgery for invasive breast cancer at Ondokuz Mayis University School of Medicine, Department of General Surgery between January 2005 and May 2012

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were retrospectively reviewed. Sixty-seven patients were selected among 1038 breast cancer patients who underwent surgery during this period in our clinic. Data including the pathological diagnoses, the tumor size (1-10 mm, 11-20 mm, >20 mm), the estrogen receptor (ER), the progesterone receptor (PR) status, the Her-2 receptor status, the triple-negative status (triple-negative, non-triple negative), the tumor grade [1-3], the presence of lymphovascular invasion (LVI), the presence of extensive intraductal component (EIC), the type of surgery and the number of the positive axillary lymph nodes (0, 1-3, ≥4), the follow-up interval, the local or regional recurrence and the distant organ metastases in the records were registered (Table I). Sentinel lymph node (SLN) biopsy was performed with isosulphan blue in patients with clinically negative axilla. Level 1-2 axillary dissection was performed in patients who had positive SLN in the frozen section, who had unsuccessful SLN biopsy, and in patients with clinically positive axilla. The patients who had distant metastases or T4 tumor or ductal carcinoma in situ or who had neoadjuvant chemotherapy were not included in the study. Hormonotherapy was given to the patients who had positive ER or PR. Herceptin therapy was given to the patients who had positive axillary lymph nodes and had positive Her-2 receptor. Adjuvant chemotherapy was given to all patients except one patient with a tumor less than 1 cm, histopathologically negative axillary lymph node and grade-1 tumor. The adjuvant radiotherapy was applied to the breast of patient who had breast-conserving surgery, to the chest wall of the patients who had ≥4 positive axillary lymph node or T3 tumor. Adjuvant radiotherapy was administered also to the peripheral lymphatics of the breast plus chest wall of the patients who had ≥4 positive axillary lymph nodes. The follow-up interval was calculated in months, and defined as the

TABLE I - *Clinicopathological characteristics of the patients*

Characteristics	Patients (n= 67)	5-year disease-free survival	P value
Tumor size			0.004
1-10 mm	18 (27%)	81%	
11-20 mm	42 (63%)	74%	
> 20 mm	7 (10%)	27%	
Grade			0.38
1	7 (10%)	100%	
2	36 (54 %)	70%	
3	24 (36%)	62%	
LVI			0.11
Present	29 (43%)	62%	
Absent	38 (57%)	79%	
EIC			0.36
Present	20 (30%)	56%	
Absent	47 (70%)	80%	
ER			0.80
Positive	39 (58%)	71%	
Negative	28 (42%)	67%	
PR			0.10
Positive	32 (48%)	75%	
Negative	35 (52%)	65%	
Her-2			0.716
Positive	20 (30%)	80%	
Negative	47 (70%)	70%	
Triple-negative status			0.014
Triple negative	16 (24%)	35%	
Non-triple negative	51 (76%)	81%	
The number of positive lymph nodes in the axilla			0.035
0	27 (40%)	72%	
1-3	21 (31%)	82%	
≥4	19 (29%)	51%	
Type of surgery			0.47
Breast conserving surgery	23 (34%)	66%	
Mastectomy	44 (66%)	70%	

EIC: Extensive Intraductal Component, LVI: Lymphovascular invasion, ER: Estrogen receptor, PR: Progesterone receptor

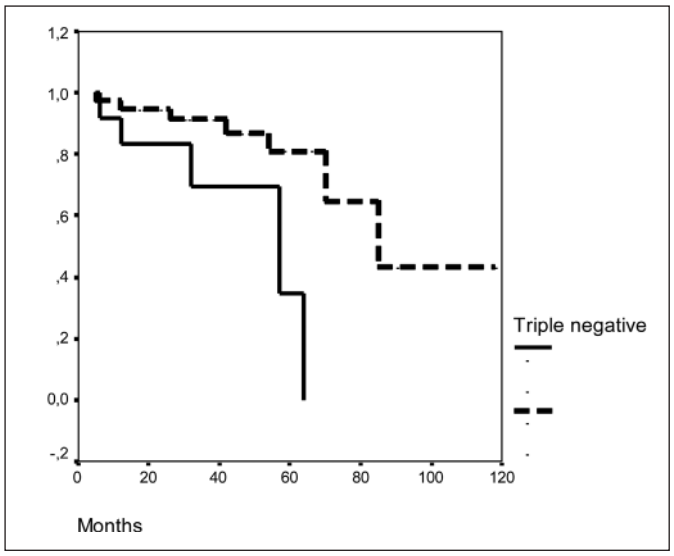

Fig. 1: The disease-free survivals of the triple-negative and non-triple negative patients (p=0.014).

time between the date of surgery and date of the disease (local or regional recurrence or distant metastases) or the date of the last follow-up. The date of disease was accepted as the date of the first documented local or regional recurrence or distant metastases whichever occurred earlier.

Statistical analysis was performed using Statistical Program for Social Science (SPSS) 15.0 for windows computer program. The 5-year disease-free survivals were calculated by the Kaplan-Meier method. Categorical data were described in numbers and percentages whereas continuous data were described by mean ± standard deviation. Comparisons of the DFS were made using log rank test, and the independent prognostic factors affecting the DFS were defined through stepwise Cox proportional hazard regression test. P value < 0.05 was accepted as the significant.

Results

Median age was 32 (range, 23-35). The median follow-up interval was 55 (range, 10-108) months. The characteristics of the patients were given in the Table I. Invasive ductal carcinoma, invasive lobular carcinoma, medullar carcinoma and apocrine carcinoma were detected in 60 (90%), 3, 3, and 1 of the patients, respectively. Twenty-three patients (34%) underwent breast conserving surgery whereas 44 patients (66%) underwent mastectomy. Local or regional recurrence or distant organ metastasis were found in 4 (6%) and 12 patients (18%), respectively. Single organ metastases and multiple distant organs metastases were detected in 7 and 5 of those 12 patients, respectively. Out of 17 organ metastases bone, brain and lung metastases were found in 8, 5, and 4 patients, respectively. Five patients (10%) died and all deaths resulted from the breast cancer metastases. No contralateral breast cancer metastasis was detected. Adjuvant hormonal therapy was given to 42 patients with ER or PR positive, and adjuvant chemotherapy was given to 66 patients. Herceptin was given to 10 patients. The adjuvant radiotherapy was administered to 23 patients who underwent breast conserving surgery and to 20 patients who had ≥4 positive axillary lymph nodes or T3 tumor. The 5-year DFS rate was 69.3%.

In univariate analysis the number of the pathological axillary lymph nodes (p=0.035), triple-negative status (p=0.014) and tumor size (p=0.004) were determined as the factors affecting the DFS. The 5-year DFS rate was 35% in the triple-negative patients, whereas the DFS was 81% in patients with non-triple negative status (Figure 1). Multivariate analysis showed that the triple-negative status (HR: 1.48, CI: 0.66-0.82, p=0.027) was the only independent prognostic factor which affects the DFS adversely.

Discussion

Breast cancer in young females constitutes 2-4% of all the operable breast cancers [1]. Unlike elderly patients, young patients usually consult the physicians complaining of a palpable mass on their breasts since the screening methods aren't used in young patients. In this age group, especially during the periods of pregnancy and lactation, breast is very dense. Thus, it is difficult to realize the breast cancer in the early stage [12,13]. Most of the patients aged under 36 years and the patients aged above 35 years were found to be in the stage II or III, and stage 0 or 1, respectively in the study of Gajdos and colleagues [14]. As for our study, 7 patients were found to be in stage 1 whereas all other patients (90%) were found to be in stage II or III.

The tumors are larger and the lymph node involvement rates are higher in young patients [15,16]. Some studies refuting this view report that there is no such a difference in tumor size and the rate of axillary lymph nodes metastases between younger breast cancer patients and their older counterparts [1]. The tumor size of 60 patients (90%) were 2 cm or smaller in our study.

Poorly differentiated breast cancer, EIC and LVI had been more frequently seen in the young patients [5,9,13,17]. The rates of positive estrogen and progesterone receptors were found to be lower in these patients [1,5,9]. In our study, the LVI was detected in 43% of the patients whereas the EIC was found to be lower (30%). Jmor and colleagues reported that LVI was one of the independent prognostic factors that negatively affect the DFS of the patients under 35 years old with invasive breast cancer [10]. In the present study, we found that LVI had no impact on the DFS. While estrogen receptor was pos-

itive in 58%, progesterone receptor was positive 48% of the patients. Her-2 receptor was detected as positive in 20 (%30) patients. Sixteen (%24) patients were found to have triple-negative status. Elkum and colleagues, and de la Rochefordiere et al. reported hormone receptor status as a prognostic factor affecting the DFS of the patients aged under 40 and 30, respectively [15,18]. In our study, we found that either ER or PR alone didn't have any impact on the DFS. Some studies report that Her-2 positive status is an indicator for poor prognosis, and is associated with shorter DFS and higher local recurrence [19,20-22]. We found that Her-2 positive status did not have any impact on the DFS. Our findings showed that the triple-negative status was an independent and adverse prognostic factor affecting the disease-free survival. A study that was carried out among patients who had invasive breast cancers smaller than 1 cm and who had negative axillary lymph nodes reported that the young age (<35) and the triple-negative status was associated with increased the breast cancer recurrence [20]. Yoshida and colleagues also reported that triple-negative status was the independent prognostic factor affecting the DFS of the patients aged under 35 [11].

Tumor size, grade, the number of pathological axillary ymph nodes were found to be significant factors in the studies in which prognostic factors affecting the DFS of the patients aged 35 and under with invasive breast cancer were investigated [9,15,18]. Livi et al. found that having 4 or more positive axillary lymph nodes was a significant prognostic factor for DFS in patients aged under 35 [23]. In our study, although having 4 or more pathological axillary lymph nodes, and the tumor size greater than 2 cm were found to be significant in the univariate analysis, these factors were not found to be independent prognostic factors for DFS in multivariate analysis. Grade was also not an independent factor for the DFS in our study. Gajdos and colleagues reported that 5-year DFS rate was 87% in patients aged under 36 and 91% in patients aged above 35 [14]. Yoshida et al., and Kim et al., and Guerra et al. reported that the 5-year DFS rate in the young patients aged 35 and under were %72.9, %69.9, and %44.2, respectively (9,11,24). Our study revealed that the 5-year DFS rate as 69.3 %.

Limitations of the study

Being a retrospective study, covering relatively few patients and a relatively short follow-up interval were the primary limitations of this study.

Our findings suggest that triple-negative status is an independent and adverse prognostic factor which affects the DFS among patients at or younger than 35 years old with invasive breast cancer. Young patients with triple-negative status should be informed that they might have more breast cancer recurrence and therefore, should be followed closely.

Riassunto

Lo scopo di questo studio era quello di valutare l'incidenza della sopravvivenza libera da malattia (DFS) ed i relativi fattori di rischio di una gruppo di pazienti di 35 anni o più giovani affette da cancro mammario infiltrante.

Per questo sono state analizzate retrospettivamente le cartelle cliniche di 67 pazienti operate per cancro invasivo della mammella, indagando sui fattori potenzialmente negativi dal punto di vista prognostico in vista di una sopravvivenza libera da malattia. Le curve di DFS sono state determinate con il metodo Kaplan-Meyer e facendo la comparazione con i test di livello prolungato. I fattori prognostici riguardo la DFS sono stati determinati con il test di regressione di rischio graduale proporzionale di Cox. È stato accettato come significativo il valore di $P < 0.05$.

I risultati ottenuti sono stati: età media delle pazienti 32 anni (da 23 a 35); il follow-up mediano è stato di 55 mesi (da 10 a 108); la DFS a 5 anni globale è stata del 69,3%.

Nell'analisi plurivariata i fattori prognostici nei confronti della DFS sono risultati il numero dei linfonodi ascellari patologici (p=0.035), il triplice stato negativo (p=0.014) e la grandezza del tumore (p=0.004).

L'incidenza della DFS a 5 anni è risultata del 81% nelle pazienti non negative al triplice stato, laddove è risultata del 35% nelle pazienti negative al triplice stato. Nell'analisi multivariata il triplice stato negativo è risultato l'unico fattore prognostico indipendente in grado di incidere negativamente sulla DFS (HR:1.48, CI:0.66-0.82, p=0.027).

In conclusione è risultato che il triplice stato negativo è l'unico fattore prognostico negativo preso singolarmente in grado di incidere sulla DFS in pazienti con cancro mammario infiltrante all'età di 35 anni o inferiore.

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