

Prognostic factors and survival of women with breast cancer under 40 years old: A single-centre experience

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Abstract

Objective: This retrospective research aimed to evaluate the results of treatment outcome and clinicopathological features of breast cancer patients under 40 years old.

Material and methods: A total of 80 patients who were receiving radiotherapy and/or chemotherapy treatment for breast cancer (<40 years old) were included in the study.

Results: First-degree relatives with breast cancer history ($p=0.028$), oestrogen receptor positivity ($p=0.012$) and progesterone receptor positivity ($p=0.017$) were associated with overall survival. No prognostic factors were found in the multivariate Cox regression analysis for overall survival. In multivariate Cox regression analysis, we found breast-conserving surgery type (hazard ratio = 6.104, 95% confidence interval = 1.037–53.928, $p=0.045$), lymphovascular invasion presence (hazard ratio = 0.127, 95% confidence interval = 0.016–1.025, $p=0.005$) and curative radiotherapy doses (hazard ratio = 185.976, 95% confidence interval = 5.342–6474.1, $p=0.004$) as independent prognostic factors for disease-free survival. Overall, survival of 1, 3 and 5 years was 88%, 74% and 65%, respectively. Median was 48 ± 2.6 (42.8–53.19) months. Also, 1-, 3- and 5-year disease-free survival was 85%, 67% and 27%, respectively. Median was 30 ± 1.8 (27.4–32.5) months.

Conclusion: Breast cancer patients under the age of 40 years are highly heterogeneous and are a complex patient group. The prognosis is worse in these patients, and prognostic factors and pathological subtypes should be taken into consideration when making treatment decisions.

Key words: breast cancer, prognostic factors, younger patients

40 ЖАСҚА ДЕЙІНГІ СҮТ БЕЗІНІҢ ҚАТЕРЛІ ІСІГІ БАР ӘЙЕЛДЕРДІҢ БОЛЖАМДЫ ФАКТОРЛАРЫ ЖӘНЕ ТІРІ ҚАЛУЫ: БІР ОРТАЛЫҚТАН ТҰРАТЫН ЗЕРТТЕУ

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ТҰЖЫРЫМДАМА

Мақсаты: Бұл ретроспективті зерттеу емдеудің нәтижелерін және 40 жасқа дейінгі сүт безі қатерлі ісігі бар науқастардың клиникалық және патологиялық сипаттамаларын бағалауға бағытталған.

Материалы және әдістері: Зерттеуге сүт бездерінің қатерлі ісігі кезінде сәулелік терапия және/немесе үшін химиотерапия алған (<40 жас) 80 пациент кірді.

Нәтижелері: Сыртартқысында сүт безі қатерлі ісігі бар бірінші кезеңнің туыстары ($p = 0.028$), эстроген рецепторларының позитивтілігі ($p = 0.012$) және прогестерон рецепторларының позитивтілігі ($p = 0.017$) жалпы өмір сүрумен байланысты болды. Кокстың көпжақты регрессиялық талдауы кезінде жалпы өмір сүрудің болжамды факторлары табылған жоқ. Кокстың көп мөлшерлі регрессиялық талдауында біз аурудан арылудың тәуелсіз болжамды факторлары ретінде ағзаны сақтайтын хирургия түрін алдық (қауіп коэффициенті = 6.104, 95% сенімділік интервалы = 1.037–53.928, $p = 0.045$), лимфо-тамырлы инвазияның болуы (қауіп коэффициенті = 0.127, 95% сенімділік интервалы = 0.016–1.025, $p = 0.005$) және сәулелік терапияның дозалары (қауіп-қатер коэффициенті = 185.976, 95% сенімділік интервалы = 5.342–6474.1, $p = 0.004$). Жалпы, 1, 3 және 5 жасқа дейінгі өмір сүру деңгейі сәйкесінше 88%, 74% және 65% құрады. Медианасы 48 ± 2.6 (42.8–53.19) айды құрады. Сонымен қатар, 1, 3 және 5 жыл аурусыз өмір сүру сәйкесінше 85%, 67% және 27% болды. Медианасы 30 ± 1.8 (27.4–32.5) айды құрады.

Қорытынды: 40 жасқа дейінгі сүт бездерінің қатерлі ісігі бар науқастар жоғары гетерогенді және пациенттердің күрделі тобын құрайды. Бұл пациенттерде болжам нашар, сондықтан емдеу туралы шешім қабылдаған кезде болжамды факторлар мен патологиялық кіші типтерді ескеру қажет.

Негізгі сөздер: сүт безінің обыры, болжамды факторлар, жас пациенттер

ПРОГНОСТИЧЕСКИЕ ФАКТОРЫ И ВЫЖИВАЕМОСТЬ ЖЕНЩИН С РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ В ВОЗРАСТЕ ДО 40 ЛЕТ: ОДНОЦЕНТРОВОЕ ИССЛЕДОВАНИЕ

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РЕЗЮМЕ

Цель: Настоящее ретроспективное исследование было направлено на оценку результатов лечения и клинико-патологических особенностей больных раком молочной железы в возрасте до 40 лет.

Материал и методы: В исследование было включено 80 пациентов, которые получали лучевую терапию и/или химиотерапию при раке молочной железы (<40 лет).

Результаты: Родственники первой степени с раком молочной железы в анамнезе ($p=0,028$), положительностью эстрогенного рецептора ($p=0,012$) и положительностью прогестеронового рецептора ($p=0,017$) были связаны с общей выживаемостью. При многофакторном регрессионном анализе Кокса прогностические факторы для общей выживаемости не обнаружены. При многофакторном регрессионном анализе Кокса мы получили тип органосохраняющей операции (отношение рисков = 6,104, 95% доверительный интервал = 1,037–53,928, $p=0,045$), наличие лимфососудистой инвазии (отношение рисков = 0,127, 95% доверительный интервал = 0,016–1,025, $p=0,005$) и дозы лучевой терапии (отношение рисков = 185,976, 95% доверительный интервал = 5,342–6474,1, $p=0,004$) в качестве независимых прогностических факторов безрецидивной выживаемости. В целом выживаемость 1, 3 и 5 лет составила 88%, 74% и 65% соответственно. Медиана составила $48\pm 2,6$ (42,8–53,19) месяцев. Кроме того, 1, 3 и 5 лет безрецидивной выживаемости составили 85%, 67% и 27% соответственно. Медиана составила $30\pm 1,8$ (27,4–32,5) месяцев.

Заключение: Пациенты с раком молочной железы в возрасте до 40 лет являются высоко гетерогенными и представляют собой сложную группу пациентов. У этих пациентов прогноз хуже, и при принятии решения о лечении следует учитывать прогностические факторы и патологические подтипы.

Ключевые слова: рак молочной железы, прогностические факторы, молодые пациенты

Introduction

Breast cancer is the most common malignancy in women and the most common cause of death after lung cancer [1]. The treatments for invasive and non-invasive breast cancer are different and complex. Invasive breast cancer is the most common type in the world and in Turkey. Although its frequency increases with age, it is more common in Asia at the age of 50 years [2]. Breast cancer, especially under the age of 40 years, is more heterogeneous and has many subtypes, and treatment is complicated.

Although there are standards related to the treatment of breast cancer, molecular subtypes are defined every year, and treatments change accordingly. Treatment response and disease-free survival (DFS) are different compared with elderly patients, especially in women with breast cancer under the age of 40 years [3,4]. In young breast cancer patients, the disease is more aggressive, and the treatment response is less likely. The personalisation of treatment decisions according to clinical and biological subtypes has become prominent in recent years. Therefore, family history and clinicopathological factors such as tumour size, lymph node, histologic type, grade, lymphovascular invasion (LVI) vs. molecular subtypes and hormone receptor expression play key roles in the treatment decision.

In this study, we aimed to evaluate the clinicopathological features and treatment response of patients with breast cancer under 40 years old and discuss which subgroups may further benefit from treatment.

Material and methods

In this retrospective study, we evaluated 80 patients under 40 years old who were diagnosed with invasive breast cancer. Patients' records were evaluated between 2012 and 2018. Although all related pathology results were obtained from hospital data, information about treatment follow-up was obtained from clinical files. Patients with ductal carcinoma in situ, insufficient record information, male sex and age >40 years were excluded.

This study examined the mean age, family history, pathology, tumour size, surgery type, adjuvant or neoadjuvant chemotherapy, tumour stage, nodal stage, histologic and nuclear grades, LVI, perineural invasion (PNI), adjuvant radiotherapy doses and hormone receptor status.

Overall survival (OS) was defined as the time between the date of diagnosis and the last contact or death. DFS was

the period between the date of diagnosis and the time of local tumour recurrence and metastasis.

Statistical analysis

Nominal and ordinal data were described with frequency analysis and scale parameters with mean and standard deviations. Kaplan–Meier analysis was used for DFS analysis and OS for different patient groups. Prognostic factors were analysed using univariate and multivariate Cox regression. All analyses were performed at 95% confidence level with a 0.05 significance level using SPSS 17.0 (Chicago, IL, USA) for windows programme.

Results

Table 1 presents some baseline characteristics of patients and treatment features. The mean age of the patients was 35.5 (range 24–40) years. Although 61 (76.3%) patients did not have a family history of cancer, 14 (17.5%) patients had a first-degree family history, and five (6.3%) patients of the other family members had a cancer history. In our hospital, 75.3% (61) of the patients had invasive ductal carcinoma, 3.7% (3) invasive lobular carcinoma, 4.9% (4) apocrine carcinoma and 16% (14) mixed subtypes. The mean tumour diameter of patients was 3.2 ± 1.8 (range 0.8–11) cm. In terms of surgery type, 45.9% (39) of patients underwent breast-conserving surgery and 50.6% (42) modified radical mastectomy. Since 3.5% (4) of patients were stage 4, only biopsy was performed. In the context of chemotherapy, 64.6% (52) of patients received adjuvant chemotherapy and 35.4% (28) neoadjuvant chemotherapy. For tumour stage, 17.5% (14) of patients had T1, 62.5% (50) T2, 18.8% (15) T3 and 1.3% (1) T4. For nodal stage, 27.5% (22) of patients had N0, 55.0% (44) N1, 8.8% (7) N2 and 8.8% (7) N3. Histologically grade patients had 3.8% (3) grade I, 52.5% (42) grade II and 43.8% (35) grade 3. Similarly, 5% (4) of the patients were nuclear grade 1, 50% (30) grade 2 and 45% (36) grade 3. Although LVI was present in 56.4% (45) of patients, it was absent in 43.6% (35). The majority of the patients (90%; 70) did not have PNI.

Radiotherapy doses were different. Curative radiotherapy doses (50Gy and 60Gy) were taken by 88.6% (70) of patients. Palliative radiotherapy was given in only to 5.3% (5) of patients. Of patients, 5.1% (4) were oligometastatic who first received palliative (30Gy) and then curative radiotherapy. There were 86.3% (69) oestrogen hormone receptor (ER)-positive and 75% (60) progesterone hormone receptor (PR)-positive patients. There

Table 1 Characteristics of patients and treatment features

	No of patients	%
Age Mean±SD	35.55 ± 3.9 (24-40)	
Family history		
First-degree relative	14	17.5
Absent	61	76.3
Other positive family history	5	6.3
Pathology		
Invasive ductal carcinoma	61	75.3
Invasive lobular carcinoma	3	3.7
Apocrine carcinoma	4	4.9
Mixed	14	16
Tumour diameter(cm) Mean±SD	3.27b± 1.83 (0.8-11)	
Surgery type		
Breast-conserving	39	45.9
Mastectomy	42	50.6
Biopsy	4	3.5
Neoadjuvant chemotherapy	28	35.4
Adjuvant chemotherapy	52	64.6
Tumour stage		
T1	14	17.5
T2	50	62.5
T3	15	18.8
T4	1	1.3
Nodal stage		
N0	22	27.5
N1	44	55.0
N2	7	8.8
N3	7	8.8
Histologic grade		
I	3	3.8
II	42	52.5
III	35	43.8
Nuclear grade		
I	4	5
II	30	50
III	36	45
Lymphovascular invasion		
Absent/Present	35/45	43.6/56.4
Perineural invasion		
Absent/Present	70 /10	88.5/11.5
Adjuvant radiotherapy doses		
Curative radiotherapy	70	88.6
Palliative 30 Gy	5	6.3
Oligometastatic and received curative radiotherapy	4	5.1
ER		
Positive/Negative	69/11	86.3/13.8
PR		
Positive/Negative	60/20	75/25
HER-2		
Positive/Negative	55/25	68.8/31.3
Triple-negative		
Yes/No	9/71	11.3/88.8

ER, oestrogen hormone receptor, PR, progesterone hormone receptor; HER-2, human epidermal growth factor receptor-2, SD, Standart derivaion

were 68.8% (55) human epidermal growth factor receptor-2 (HER-2)-positive and 11.3% (9) triple-negative patients.

DFS rates at 1, 3 and 5 years were 85%, 67% and 27%, respectively, and the median was 30 ± 1.8 (27.4–32.5) months. OS rates at 1, 3 and 5 years were 88%, 74% and 65%, respectively, and the median was 48 ± 2.6 (42.8–53.19) months.

Table 2 Univariate and multivariate for OS

	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age (years)						
20-30	1	1				
31-40	0.764	0.085-6.868	0.810	—	—	0.888
Family history						
First degree relative vs absent	0.134	0.022-0.802	0.028			0.871
First degree relative vs other positive family history	0.000	0.000-	0.984			0.860
Histopathology						
Invasive ductal	1	1				
Other	0.219	0.037-1.313	0.097			0.854
Neoadjuvant chemotherapy						
Yes	1	1				
No	1.339	0.223-8.034	0.750			0.842
Surgery type						
Breast-conserving vs mastectomy	0.000	0.000-3.402	0.958			
Breast-conserving vs Biopsy	0.310	0.035-2.908	0.311			0.828
Tumour stage						
T1-T2	1	1				
T3-T4	0.351	0.059-2.106	0.252			0.826
Nodal stage						
0-1	1	1				
2-3	0.032	0.000-229.841	0.448			0.929
Histologic grade						
I vs II	0.000	0.000-	0.991			0.943
I vs III	1.359	0.227-8.147	0.991			0.917
Nuclear grade						
I vs II	0.000	0.000-	0.990			0.941
I vs III	0.226	0.025-2.021	0.183			0.963
Lymphovascular invasion						
Present	1	1				
Absent	0.467	0.049-4.490	0.509			0.963
Perineural invasion						
Present	1	1				
Absent	0.412	0.043-3.963	0.443			0.944
Radiotherapy doses						
Curative vs palliative	3.074	0.340-27.802	0.318			0.994
Curative vs Oligometastatic and received curative radiotherapy	0.000	0.000-	0.990			0.902
ER						
Positive	1	1				
Negative	0.101	0.017-0.609	0.012			0.990
PR						
Positive	1	1				
Negative	0.069	0.008-0.623	0.017			0.945
HER-2						
Positive	1	1				
Negative	0.453	0.051-4.066	0.480			0.949
Triple- negative						
Yes	1	1				
No	0.169	0.028-1.018	0.052			0.931

OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; ER, oestrogen hormone receptor; PR, progesterone hormone receptor; HER-2, human epidermal growth factor receptor-2

Table 3

Univariate and multivariate for DFS

	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age (years)						
20-30	1	1				
31-40	0.189	0.025-1.43	0.105	0.293	0.018-4.874	0.392
Family history						
First degree relative vs absent	1.085	0.355-3.313	0.866	1.808	0.236-13.858	0.569
First degree relative vs other positive family history	2.245	0.647-7.799	0.203	0.906	0.122-6.757	0.923
Histopathology						
Invasive ductal	1	1				
Other	1.167	0.459-2.969	0.745	1.208	0.256-5.701	0.811
Neoadjuvant chemotherapy						
Yes	1	1				
No	0.690	0.294-1.618	0.394	0.181	0.026-1.262	0.084
Surgery Type						
Breast-conserving vs mastectomy	2.094	0.800-5.117	0.136	6.104	1.037-35.928	0.045
Breast-conserving vs biopsy	5.217	1.253-22.179	0.023	0.001	0.00-5.366	0.119
Tumour stage						
T1-T2	1	1				
T3-T4	0.540	0.210-1.384	0.199	3.445	0.309-33.097	0.284
Nodal stage						
0-1	1	1				
2-3	1.565	0.609-4.024	0.353	0.282	0.027-2.908	0.288
Histologic grade						
I vs II	0.000	0.000-	0.979	0.000	0.000-	0.993
I vs III	0.803	0.354-1.822	0.600	1.831	0.155-21.672	0.631
Nuclear grade						
I vs II	0.587	0.072-4.763	0.618	0.117	0.002-5.995	0.288
I vs III	1.227	0.159-9.436	0.844	0.124	0.008-1.834	0.124
Lymphovascular invasion						
Present	1	1				
Absent	0.468	0.181-1.209	0.117	0.127	0.016-1.025	0.005
Perineural invasion						
Present	1	1				
Absent	0.888	0.261-3.015	0.849	2.852	0.283-28.700	0.374
Radiotherapy doses						
Curative vs palliative	4.505	1.608-12.618	0.004	185.976	5.342-6474.1	0.004
Curative vs Oligometastatic and received curative radiotherapy	5.380	1.764-16.407	0.003	37.537	3.593-392.113	0.002
ER						
Positive	1	1				
Negative	4.345	1.832-10.305	0.001	47.799	0.887-2570.3	0.057
PR						
Positive	1	1				
Negative	4.360	1.879-10.118	0.001	4.212	0.406-38.082	0.200
HER-2						
Positive	1	1				
Negative	1.345	0.547-3.319	0.516	4.426	0.696-28.155	0.115
Triple-negative						
Yes	1	1				
No	0.485	0.163-1.442	0.193	22.831	0.721-722.76	0.076

DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; ER, oestrogen hormone receptor; PR, progesterone hormone receptor; HER-2, human epidermal growth factor receptor-2

For OS, the univariate analysis revealed that family history (first-degree relative cancer history vs absent) and oestrogen receptor (ER) and PR positivity were statistically significant ($p < 0.05$). In the multivariate analysis, no statistical significance was found (Table 2).

For DFS, the univariate analysis showed that surgery type, adjuvant radiotherapy doses and positive ER and PR were statistically significant ($p < 0.05$). The multivariate analysis revealed that surgery type (breast-conserving vs mastectomy), LVI and radiotherapy doses (curative vs palliative and curative vs oligometastatic and received curative radiotherapy) were independent prognostic factors (Table 3). ER positivity is statistically close to the meaning and can be considered statistically significant ($p = 0.057$).

Discussion

Breast cancer is still the leading cause of death in women in the world. It is a histologically and clinically heterogeneous and complex disease, especially in young patients. Identifying prognostic factors in young patients can make treatments more successful. In our hospital, we tried to determine subtypes that benefited from the treatment by examining our breast cancer patients under 40 years of age. Moreover, we tried to identify prognostic factors.

Young age in breast cancer is an independent risk factor for survival in many studies [5–7]. We did not find this difference in patients between 20–30 and 31–40 years old. The most important prognostic factor in young patients is having a history of breast cancer in their first-degree relatives. Brewer et al. showed that first-degree relatives with a history of breast cancer and the risk of breast cancer increased in young patients [8]. Similarly, in our study, although it was significant in univariate analysis for OS, it was not significant for DFS.

Many studies have shown that OS is the same in patients undergoing mastectomy and breast-conserving surgery [9,10]. In terms of OS, this study did not find any difference between the two surgery types, but breast-conserving surgery was found to be a prognostic factor in terms of DFS in multivariate analysis. The reason for this is that most of the patients undergoing mastectomy were from locally advanced patients who had previously received neoadjuvant chemotherapy.

The presence of LVI has been associated with distant metastasis and axillary lymph node involvement in patients with breast cancer [11]. In many studies, the presence of LVI affects OS and DFS in young breast cancer patients [11,12]. The presence of LVI was found to be an independent risk factor. In our study, the presence of LVI was found to be an independent prognostic factor for DFS ($p = 0.05$).

Adjuvant chemotherapy and radiotherapy are known to increase OS and DFS in young breast cancer patients. Adjuvant radiotherapy is especially important in preventing local

recurrence for patients under 60 years old [13,14]. Similarly, curative radiotherapy application was found to be statistically significant in our study according to both palliative radiotherapy and radiotherapy dose applied in oligometastatic disease ($p = 0.004$ and 0.002 , respectively). The adjuvant curative dose of radiotherapy (50Gy and/or 60Gy) is an independent prognostic factor in multivariate analysis.

Approximately 80% of patients with breast cancer are ER-positive patients. In these patients, endocrine therapy is added to adjuvant therapy after surgery. Endocrine therapy causes prolonged DFS and OS and decreases the risk of recurrence in patients with breast cancer, both early and advance [15,16]. In our study, although ER and PR positivity were found to be statistically significant in univariate analysis for OS, this could not be demonstrated in multivariate analysis. However, ER positivity can be evaluated as a prognostic factor in multivariate analysis for DFS ($p = 0.057$). This may be because our patients' follow-up is short. In our hospital, endocrine therapy (Tamoxifen $10\text{mg} \times 2$) was initiated in all patients with hormone receptor positivity, and endocrine therapy was not given in hormone-negative patients.

Another important problem is the triple-negative patient group (negative ER, PR and HER-2), which accounts for about 15–20% of all breast cancers. The prognosis of patients in this group is poor because of early recurrence and distant metastases [17,18]. In addition, triple-negative patients are generally those with young patients with breast cancer [19]. Although our study was a group of young breast cancer patients, it was not found to be statistically significant for OS and DFS as our number of triple-negative patients was low, and our follow-up time was short.

This study has three important limitations. Firstly, the most important prognostic factor in the young patient group is the absence of breast cancer BRCA-1 and BRCA-2 results. Secondly, patient follow-up is short. Thirdly, this group of patients should be evaluated separately in patients who were originally oligometastatic.

Conclusion

In young breast cancer patients, OS and DFS are shorter than the elderly group, and their treatment varies according to complex and subgroups. When making a treatment decision, prognostic factors and molecular subtypes should be taken into consideration. According to the results of the study, there are numerous prognostic predictors of a worse DFS, and the most important were operation type, LVI presence and radiation doses. The most important prognosis factor for OS was a family history of first-degree breast cancer.

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