RESEARCH ARTICLE

Clinicopathological Features in Bilateral Breast Cancer

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Abstract

Introduction and Purpose: The frequency of bilateral breast cancer is 1.4-11.0% among all breast cancers. It can present as synchronous (SC) or metachronous (MC). Data regarding clinical course of bilateral breast cancer are scarce. In this study, we therefore evaluated demographic, pathological and clinical characteristics, treatments and responses in bilateral breast cancer cases; making distinctions between metachronous-synchronous and comparing with historic one-sided data for the same parameters. Materials and Methods: One hundred fifty bilateral breast cancer cases from ten different centers between 2000 and 2011 were retrospectively scanned. Age of the cases, family history, menopausal status, pathological features, pathological stages, neoadjuvant, surgery, adjuvant and palliative chemotherapy/radiotherapy were examined in the context of the first and second occurrence and discussed with reference to the literature. Results: Metachronous and synchronous groups showed similar age, menopausal status, tumor type, HER2/neu expression; the family history tumor grade, tumor stage, ER-negativity rate, local and distant metastases rates, surgery, adjuvant chemotherapy application rates were identified as significantly different. Palliative chemotherapy response rate was greater in the metachronous group but median PFS rates did not differ between the groups. Conclusion: Although bilateral breast cancer is not frequent, MC breast cancer is different from SC breast cancer by having more advanced grade, stage, less ER expression, more frequent rates of local relapse and distant metastasis and better response to chemotherapy in case of relapse/metastasis.

Keywords: Bilateral breast cancer - synchronous - metachronous - clinicopathological characteristics - Turkey

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Introduction

Breast cancer is the most common malignant tumor in women. 220,000 new cases of breast cancer and expectation of 40000 cases of breast cancer related death were reported in the United States in 2010 (Jemal et al., 2010). Bilateral breast cancer (BBC) is not common and the incidence has been reported between 1.4% and 11% (Michowitz et al., 1985; Donovan et al., 1990; Gogas et al., 1993). The presence of a second tumor is a concern for the patient, and studies regarding whether bilateral disease is worse, are still continuing. Information about BBC is very limited and therefore the present multi-institute review was undertaken.

Materials and Methods

We retrospectively analyzed demographic data, clinicopathological features, treatments and survival of synchronous (SC) or metachronous (MC) breast cancer cases from 10 different centers; by comparing metachronous and synchronous tumors, in terms of these parameters and in terms of survival with each other, historic and one-sided breast cancer (UBC). Between 2000-2011, 150 (90 MC and 60 SC) patients with a diagnosis of MC or SC breast cancer from the 10 different centers were evaluated retrospectively. The discriminations between bilateral or metastatic disease of patients were made according to criteria of Chaundary et al. (1984). After

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standard modified radical mastectomy/lumpectomy, different centers have implemented adjuvant treatment appropriate for their own experience. The presence of breast cancer in first-degree relatives in the family, and menopausal status of the patients were questioned. Patients were divided into 9 main groups as histological tumor type according to ICD-Q3 category (ductal, lobular, comedo, mucinous, inflammatory, tubular, papillary, medullary, and other). However, in statistical evaluation we have created four main groups depending on the descending frequency order: grouped as ductal, lobular, mixed ductal-lobular, and other. The staging and grading of patients were performed according to American Joint Comitte (AJC) TNM staging system. Tumor estrogen receptor (ER), progesterone receptor (PR) status were evaluated by immunohistochemistry (IHC); Her 2 status was evaluated with IHC, FISH was studied in the presence of score II. ER positivity was evaluated >1%. If relapse-metastasis was developed in patients, local recurrence, presence of metastases were evaluated. Treatments (neoadjuvant, surgery, adjuvant chemotherapy, adjuvant radiotherapy, and adjuvant hormonal therapy) and chemotherapies for metastases and responses, and palliative radiotherapy and responses were evaluated. Survival and progression-free survival of patients were analyzed.

Statistics

Statistical analysis was performed using the SPSS 15.0 package program. For comparisons between groups, the Mann-Whitney U, Chi-square, Student's t-tests were used. Survival rates were estimated by Kaplan-Meier analysis. Overall survival (OS) was calculated from death date since date of diagnosis or time duration until the date of last visit, progression free survival (PFS) was calculated as time duration of local-regional recurrence or development of distant metastasis from date of diagnosis.

Results

A total of 150 patients were evaluated (60 SC and 90 MC). Of 150 patients, one was male and 149 were women. The patients charecterictics showed in (Table 1). The median age was 53.6 years (54.9 in SC tumor patients and 52.4 in MC tumors). Median follow-up period was 113 months in MC group and 37.7 months in SC group. The median duration between first and second breast cancer in MC was 46.9 months. Fifty one percent of SC group was premenopausal, 46.7 % was postmenopausal and 1.7% was unknown; in MC group it was 41.1%, 52.2 % and 6.7 %, respectively. Family history of breast carcinoma in SC group it was present in 16.7%, and unknown in 11.7%; in MC group it was present in 6.7% and unknown in 27.8%. When the patients were evaluated histopathologically in 1st and 2nd breast as separate, in synchronous tumors the invasive ductal carcinoma (IDC) in first breast was 81.7%, and 76.7% in 2nd breast. 2nd and 3rd frequent were bilateral lobular and invasive lobular and mixed breast (invasive ductal and lobular), respectively. In MC tumors, IDC was observed most frequently (70% and 76.7%), second and third frequently seen were invasive lobular and medullary carcinoma. The most common tumor grade for first and second breast was grade 2 (55%, and 55) in synchronous group. In MC breast it was grade 2 (26.7% and 38.9%).

Table 1. Patient Characteristics

	Synchronous N=60 First/Second breast N (%)	Metachronous N=90 First/Second breast	p value
Median Age(Years)	54.9	52.4	0.08
Menopause			0.16
Pre-	31(51.6)	37(41,2)	
Post-	28(46.6)	47(52,2)	
Unknown	1(1.6)	6(6.6)	
Family History			0.032
Yes	10(16.6)	6(6.6)	
No	43(71.6)	59(98.3)	
Unknown	7(11.6)	25(27.7)	
Pathology			0.90
İnvasive ductal*	49(81.6)	63(70)	
Invasive lobuler*	5(8.3)	5(5.6)	
Mixed**	1(1.6)	2(2.2)	
Other	5(8.3)	20(22.2)	
Grade			0.045
1	8(13.3)/10(16.6)	9(10)/7(7.8)	
2	33(55)/33(55)	24(26.6)/35(38.8)	
3	15(25)/12(20)	20(22.2)/26(28.8)	
Unknown	4(6.6)/5(8.3)	37(41.1)/22(24.4)	
Stage(TNM)			0.001
I	11(18.3)/17(28.3)	10(11.1)/13(14.4)	
II	24(40)/23(38.3)	24(26.6)/28(31.1)	
III	14(23.3)/7(11.6)	35(38.8)/34(37.7)	
IV	4(6.6)/5(8.3)	5(5.6)/6(6.6)	
Unknown	7(11.6)/8(13.3)	16(17.7)/9(10)	
Estrogen receptor			0.005
Positive	43(71.6)/42(70)	39(43.3)/45(50)	
Negative	13(21.6)/14(23.3)	28(31.1)/30(33.3)	
Unknown	4(6.6)/4(6.6)	23(25.5)/15(16.6)	
Progesteron receptor			0.07
Positive	39(65)/36(60)	42(46.6)/38(42.2)	
Negative	15(25)/19(31.6)	23(25.5)/36(40)	
Unknown	6(10)/ 5(8.3)	5(5.6)/16(17.7)	
HER 2			0.144
Positive	13(21.6) /16(26.6)	21(23.3)/28(31.1)	
Negative	39(65)/37(61.6)	41(45.5)/44(48.8)	
Unknown	8(13.7)/7(11.6)	28(31.1)/18(20)	
Local relapse			0.028
Yes	5(8.3)/5(8.3)	12(13.3)/19(21.1)	
No	55(91.6)/55(91.6)	78(86.6)/71(78.8)	
Distant metastasis			<0.0001
Yes	12(20)	47(52.2)	
No	48(80)	43(47.7)	
Neoadjuvant chemotherapy			0.62
Yes	6(10)	7(7.7)	
No	54(90)	83(92.2)	
Surgery			0.002
Yes	59(98.3)	85(94.4)/85(94.4)	
No	1(1.6)	5(5.6)/5(5.6)	
Adjuvant chemotherapy			0.001
Yes	51(85)	58(64.4)/65(72.2)	
No	9(15)	32(35.5)/25(27.7)	
Adjuvant hormonotherapy			0.28
Yes	32(53.3)	37(41.1)/40(44.4)	
No	28(46.6)	53(58.8)/50(55.5)	
Adjuvant radiotherapy			0.07
Yes	30(50)/25(41.6)	45(50)/41(45.5)	
No	30(50)/35(58.3)	45(50)/49(54.4)	
First-line palliative chemotherapy			<0.0001
Yes	11(18.3)	37(41.1)	
No	49(81.6)	43(47.7)	
Unknown	0	10(11.1)	
Second-line palliative chemotherapy			<0.0001
Yes	6 (10)	27 (30)	
No	54 (90)	63 (70)	

* Carcinoma, ** invasive lobuler and ductal carcinoma

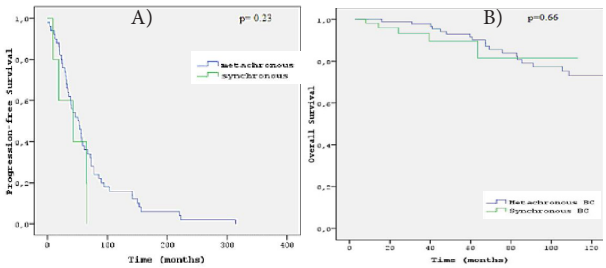

Figure 1. A) Progression-Free Survival in Metachronous and Synchronous Breast Cancer and B) Overall Survival in Metachronous and Synchronous Breast Cancer.

The stages of SC tumors were; the most frequent stage of the 1st and 2nd breast was stage II (38.3 and 36.7%), the second and third most common stages were stage I and stage III. The most common stage in MC tumors was stage III (37.8 and 37.8%). Second and third most common stages were stage II and I in MC tumors (Table 1).

Estrogen receptor status (ER) and progesterone receptor status (PR) in SC tumors of first and second breast were 71.7%, 70% and 65%, 60%, respectively. In MC tumors, ER was 43.3%, 50%; PR is 46.7%, 42.2%. The HER2 status of patients for 1st and 2nd breast in SC tumors was 21.7% and 26.7%, in MC tumors, 23.5% and 31.1%, respectively. Relapse/metastasis ratios were as following: local relapse in SC and MC tumors was 8.3% and 17.2%, respectively. Distant metastasis was present in 20% of SC tumors and in 52.2% of MC tumors. The most frequent metastasis sites in SC tumors as descending order were; bone, brain, liver and lung. In MC tumors it was bone, lung, brain and liver (Table 1).

The treatments were in 10% of patients in SC group and mean 8.3% patients received neoadjuvant therapy in MC group. Total response rate to neoadjuvant treatment consisting of complete response, partial response and stable response were 66.6% in SC group and 85.7% in MC group. Surgery was performed in 97.9% in SC group and 93.5% in MC group. Adjuvant chemotherapy was applied to 85% in SC group and 68.1% patients in MC group. Adjuvant RT was given to 45.8% in SC group and 52.2% patients in MC group. Adjuvant hormonal treatment was applied to 53.3% in SC group and 42.7% in MC group. Palliative chemotherapy/hormonal therapy in first line, was administered to 81.7% of SC patients, 57.8% of MC patients. Response rates to first line palliative treatment (total of complete response, partial response and stable disease) were as following: total response rates were 75% in SC group and 80% in MC group (Table 1). Second line chemotherapy/hormonal therapy was administered to 90% of patients in SC group, 58.9% of patients in MC group and response rates were 66.7% and 47.8%, respectively. Third and fourth line treatment ratios in SC and MC groups were 85%, 88% and 68.9%, 76.7%, respectively; response rates were 75%, 50% and 73%, 80%, respectively. Palliative radiotherapy (brain and bone) was applied to 8.3% of SC patients and 18.9% of MC group. Median follow-up period in SC group was 9.6 months (2.6-113.1); in MC group it was 90 months (8.1-341).

Median PFS duration in SC group was 43 months (0-94.4); in MC group it was 50.6 months (31.4-69.8), there was no significant difference (p=0.23) (Figure 1A). Median survival period was not achieved in SC group, 5 and 10 years survival rates were found to be 90% and 81%. Median survival was not reached in MC group; 5 and 10 years survival rates were 90% and 73%, respectively (Figure 1B).

Discussion

Breast cancer is a common cancer in women. However, probability of bilateral breast cancer is still low. Different criteria for identifying SC breast cancer have been developed in the literature. There are publications suggesting measures taken to identify at the same time (Mersheimer et al., 1965), within one month (Gollamudi et al., 1997), and one year (Heron et al., 2000). The contralateral tumor that was detected within the first 6 months was evaluated as SC, tumors that developed after 6 months as MC. Forty percent of bilateral breast cancer patients was SC and 60% was MC. In a study by Hector de Vuoto et al. assessing 194 patients with the BBC, SC was found in 41% ratio and MC was 59% (Vuoto et al., 2010). In another study, SC and MC ratios were reported as 30% and 70% (Hartman et al., 2007). Ratios are similar with our patients' ratios. The median age in SC tumors was 55 and 52 years old in MC tumors. The median age difference between MC and SC groups was not statistically significant (p= 0.08). In Australia, a BBC cohort study, the median age was found to be 57 and 56 years old (Beckmann et al., 2001). In another study, age was stated as 58 years old in SC tumors, in MC tumors the first and second tumor ages were 51 and 58, respectively, UBC age was stated as 55 years old (Vuoto et al., 2010). Another study evaluated 46 Japanese BBC patients and mean SC age was reported as 50 years, mean MC age as 56 and for unilateral it was reported to be 51 years old (Takahashi et al., 2005). As our study does not include unilateral patient data, the median age comparison cannot be made with the BBC, it is compatible with the literature data. In above studies where BBC and UBC case ages are compared, statistically significant difference in ages of both groups have not seen (Takahashi et al., 2005; Vuoto et al., 2010; Kheirelseid et al., 2011).

Family history in UBC is applicable for 20% of patients (Turnbull et al., 2008). In our study, they were 16.7% in the SC and 6.7% in MC groups and it was statistically higher in the synchronous group (p=0.032). Although there was difference between groups, the possible cause of this lower ratio than proportional UBC historical data is the presence of unknown group emergence with a relatively high rate of 11.7% and 27.8%. In one of two different studies evaluating the familial history in the context of the BBC (Vuoto et al., 2010), there were no significant differences between UBC and the BBC. In another study (Kheirelseid et al., 2011) it is suggested that it is increased in synchronous group with odds ratio of 1.5, also data in our study is in favor of SC.

The tumor histopathology, in both synchronous and metachronous groups, in descending order were; IDC, lobular carcinoma and mixed type. When compared with UBC historical data (70-80% IDC), the histopathology

is similar in BBC patients (SC 81% and 76%; MC 70% and 76%; p=0.9) (Beckmann et al., 2001; Takahashi et al., 2005; Verkooijen et al., 2007; Vuoto et al., 2010). In a study comparing BBC and UBC the IDC ratio was reported as 66% (SC) and 63% (MC), respectively (Verkooijen et al., 2007). BBC tumor pathology is not presented as different ratios and types from UBC. The grade distribution in our study in descending order is grade 2,3, and 1, significant difference between groups was observed (p=0.045), there is no contradiction with literature data (Beckmann et al., 2001; Verkooijen et al., 2007).

The HER2 over expression ratio in UBC is 25-30% (Slamon et al., 1989). In SC disease, the presence of HER2 was found in specified limits in the first and second breast, we identified 31% in the second breast and at a higher rate in MC tumors, but this difference was not statistically significant (p=0.144). In a similar study, in bilateral 2nd breast group, HER2 status was reported as 33% (UBC 20%) and found to be statistically significant (Kheirelseid et al., 2011). In a study, the presence of hormone receptor was detected lower than UBC in metachronous 2nd breast, and the difference was significant (Kheirelseid et al., 2011), in another study, metachronous and synchronous status of HR, significant difference between UBC and BBC have not determined (Beckmann et al., 2001). In another study, in the synchronous BBC and UBC, OR for ER positivity was 1, while for adjusted OR identified as 1.4 (Verkooijen et al., 2007). However, the ratio of sub-group of ER receptor status unspecified in this study is considerably higher (for both of the group 70%) and reduces the value of this data.

Another large patient population study, hormone receptor (HR) status of the first tumor was found to be an important determinant of HR status that will develop second tumor (Huo et al., 2011). In our study, ER positivity in MC tumors was identified in a higher ratio than SC tumors (p=0.005) however there was no difference between PR expressions (p=0.07). Although the patient number in unknown, relatively higher ER status than SC group can be a reason for this deviation in favor of ER receptor in metachronous group, we had difficulty in interpretation of what may be the main reason.

TNM staging of tumors in this study, in descending order with the SC tumor were stage II, I and III; in MC tumors found as stage III, II and I (p=0.001). The difference between groups is due to both tumor size and the mean number of lymph node metastasis, as against the MC. In studies comparing UBC and BBC, stage was determined as, significantly higher in BBC than UBC and in MC than SC (Beckmann et al., 2001; Hartman et al., 2007; Verkooijen et al., 2007; Kheirelseid et al., 2011).

In our study, local recurrence and distant metastasis rates were significantly higher in MC group (p=028 and <0.0001). In study of Vuoto et al., there was no significant difference between UBC and BBC, local relapse rates in descending order was observed as MC, SC and UBC. When biological behavior and survival aspects of MC tumors are considered as worse, our data seem to be more plausible in distant metastasis (Vuoto et al., 2010).

In our study, neoadjuvant chemotherapy rates were similar between groups (p=0.83), surgical and adjuvant chemotherapy application rates were higher in the synchronous group (p=0.002 and p=001, respectively). Adjuvant/hormonal therapy and palliative chemotherapy/ hormonal therapy and palliative radiotherapy rates were not different between SC and MC groups. Although response rates to neoadjuvant chemotherapy were similar between MC and SC groups, the number of patients receiving this treatment was very little in both groups to make a comment.

The response rate to first-line palliative chemotherapy in the MC group was higher (p<0.0001). Inverse relation between hormone receptor expression rate and chemotherapy response is known (Berry et al., 2006). The weaker HR expression than those of synchronous tumors in MC, can explain the higher response rate to chemotherapy. In this study, 5-and 10-year survival rate in MC group were found to be 90% and 73%. Mean follow-up period in SC group was 37.7 months and 5-year survival time was early to evaluate. The 5-year survival of patients of SC group is 90%.

A cohort study (Beckmann et al., 2001) evaluated 2425 patients with breast cancer, 87 BBC cases of synchronous and metachronous and UBC 5-year survival rates were reported as 87.3, 79.3 and 93.7%; and HR was 1.60, 3.56, and 1.0. Survival rate in many studies including case series of 13495 UBC and 300 BBC (Polednak et al., 2003) also referred in the same study are UBC, SC BBC and MC BBC in descending order.

We could not demonstrate the difference of median OS and PFS because the median follow-up period between the groups in our study was probably against the MC group.

However, the presence of poor prognostic factors such as grade, stage, ER expression, shorter PFS and OS durations in MC group than SC group will be expected when adequate follow-up duration is reached. Indeed, for 10 years, the extrapolated OS percentages were 90% in SC group and 73% in MC group.

In conclusion, although bilateral breast cancer is not frequent, MC breast cancer is different from SC breast cancer by having more advanced grade, stage, less ER expression, more frequent rates of local relapse and distant metastasis and better response to chemotherapy in case of relapse/metastasis. Although OS and PFS data are not mature enough, it seems to go against MC at the end of adequate follow-up period.

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