JBUON 2018; 23(6): 1591-1600
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Synchronous and metachronous bilateral breast cancer: A long-term experience

Alper Ozturk[1], Gul Alco[2], Dauren Sarsenov[3], Serkan Ilgun[4], Cetin Ordu[5], Ulkuhan Koksal[6], Kezban Nur Pilanci[7], Zeynep Erdogan[8], Filiz Izci[9], Filiz Elbuken[10], Filiz Agacayak[11], Fatma Aktepe[12], Vahit Ozmen[13]

[1]Biruni University, Faculty of Medicine, Department of General Surgery, Istanbul, Turkey; [2]Florence Nightingale Gayrettepe Hospital, Department of Radiation Oncology, Istanbul, Turkey; [3]Istanbul Florence Nightingale Hospital, Department of General Surgery, Istanbul, Turkey; [4]Gaziosmanpasa Taksim Training and Research Hospital, Department of General Surgery, Istanbul, Turkey; [5]Gayrettepe Florence Nightingale Hospital, Department of Medical Oncology, Istanbul, Turkey; [6]Istanbul Bilim University, Department of Medical Oncology, Istanbul, Turkey; [7]Istanbul Haseki Training and Research Hospital, Department of Medical Oncology, Istanbul, Turkey; [8]Istanbul Bilim University, Department of Physical Therapy and Rehabilitation, Istanbul, Turkey; [9]Istanbul Bilim University, Faculty of Medicine, Department of Psychiatry, Istanbul, Turkey; [10]Gayrettepe Florence Nightingale Hospital, Department of Radiology, Istanbul, Turkey; [11]Istanbul Florence Nightingale Hospital, Department of Radiology, Istanbul, Turkey; [12]Istanbul Bilim University, Faculty of Medicine, Department of Pathology, Istanbul, Turkey; [13]Istanbul University, Faculty of Medicine, Department of General Surgery, Istanbul, Turkey

Summary

Purpose: *The objective of this study was to assess the demographic, pathologic and survival characteristics of patients who were diagnosed as having bilateral breast cancer.*

Methods: *A review was conducted of the records pertaining to patients who presented to our clinic and were diagnosed as having breast cancer. Any second cancer diagnosed within 12 months of initial diagnosis was defined as synchronous bilateral breast cancer. Assessment included treatments administered to the patients and survival rates, as well as their demographic, reproductive and pathologic features.*

Results: *The total number of patients who were diagnosed as having bilateral breast cancer in the context of the present study was 99. Among the patients with synchronous breast cancer, the median age at the time of initial diagnosis was found as 57 years. The median age of the discovery of first tumor among the patients with metachronous tumor was 52 years and the median age of second tumor detection was 59 years. Family history in metachronous tumor was significantly greater (p=0.041). The median time of metachronous cancer incidence was 96 months. The length of disease-free period among the patients with synchronous tumor was 126.3 months, whereas it was 243.7 months in those with metachronous tumor (p=0.041).*

Conclusion: *The incidence rate of synchronous breast tumors has been rising thanks to growing awareness and the leading-edge imaging methods. The fact that the second tumor developed after more than 5 years among the patients with metachronous cancer gave rise to the increased rate of survival.*

Key words: *breast cancer, bilateral, metachronous, synchronous*

Introduction

Bilateral breast cancer is been increasingly appearing at breast clinics. Heightened awareness and ever developing diagnostic methods allow for early diagnosis, increasing 5-year survival up to 98% with the inclusion of contemporary treatment methods [1]. As a direct result of patients living longer, the incidence of bilateral breast cancer has been increasing. Studies indicate that the frequen-

Correspondence to: Alper Ozturk, MD. Biruni University Hospital, Genereal Surgery Department, Besyol Mah. Eski Londra Asfalti No:10, 34295 Florya, Istanbul, Turkey.
Tel: +90 532 545 04 60, E-mail: alperozturk79@gmail.com
Received: 21/03/2018; Accepted: 25/04/2018

cy of bilateral breast cancer ranges between 1.4 and 11.8% [2-5]. The risk of contralateral breast primary in patients with breast cancer is predicted as 2 to 6 times greater than that of first breast cancer in the general population [6-8].

Some studies suggest that development of cancer in the contralateral breast negatively affects survival, whereas others have shown that it remains unaffected [9,10]. It is also proposed that genetic and hormonal factors and those associated with cancer treatment all play a part in pathogenesis of bilateral breast cancer [11,12]. Risk factors for bilateral breast cancer were found to include good prognosis and better life expectancy, existence of breast cancer in family history, having breast cancer at early age, the initially discovered tumor being lobular carcinoma, having received treatment for the first tumor and not having given birth [5,13-16]. The impact of receiving adjuvant treatment for breast cancer on the incidence of bilateral breast cancer has not yet been fully uncovered. Hartman et al. [17] suggested that adjuvant chemotherapy had a two-way effect on metachronous tumors. Chemotherapy has been considered to reduce the risk of developing bilateral breast cancer, whereas in patients with early-onset metachronous cancer, it has been recognized as a predictor of poor prognosis [17]. On the other hand, hormone therapy reduces the risk of developing bilateral breast cancer at a lower rate than chemotherapy [18,19].

Although metachronous tumors were previously seen in most patients due to extended follow-up periods, this has been gradually decreasing as a result of sophisticated treatment methods. On the contrary, the incidence rate of synchronous breast tumors has been increasing as a result of the growing awareness of breast cancer and the ever-increasing use of modern imaging techniques such as tomosynthesis and magnetic resonance imaging (MRI) [13]. The differences between synchronous and metachronous breast cancer are completely clear. The present study aimed to assess patients diagnosed as having bilateral breast cancer at our clinic for their demographic features, pathologic details of the first and second tumor, the type of surgery performed, disease-free periods, and overall survival rates.

Methods

Data pertaining to patients diagnosed as having and treated for bilateral breast cancer from January 1990 to February 2016 at the Florence Nightingale Hospital, Department of Breast Diseases, were reviewed retrospectively. To that end, development of cancer in the contralateral breast within 12 months of initial diagnosis was defined as synchronous breast tumor, and any second tumor found in the contralateral breast after 12 months was defined as metachronous breast cancer. In the context of synchronous breast tumors, the tumor with the larger diameter was identified as the dominant tumor. Age at first and second tumor, the time elapsed between development of two tumors, state of menopause, family history, the type of surgery performed, axillary intervention, histopathologic type and diameter of tumor, levels of estrogen, progesterone and HER-2 receptors and histologic grade (Bloom Richardson) were recorded. Estrogen, progesterone and HER-2 receptors were evaluated using immunohistochemical methods. Fluorescence *in situ* hybridization (FISH) was used for patients with suspicious HER-2 levels. Surgical procedures performed to the patients were classified into three categories: breast-conserving surgery, mastectomy and subcutaneous mastectomy+reconstruction. Overall survival, disease-free survival, local-recurrence-free survival, and metastasis-free survival rates were calculated. Overall survival time was described as the period between the date of diagnosis of the first tumor and the last medical assessment.

Statistics

Statistical analyses were performed using SPSS software version 17. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests) to determine whether they were normally distributed. Descriptive analyses are presented using means and standard deviations for normally distributed variables. Parametric variables were analyzed using the one-way ANOVA test, and non-parametric variables were investigated using the Mann-Whitney *U* test. Where appropriate, either the chi-square test or Fisher's exact test (when chi-square assumptions did not hold due to low expected cell counts) were used to assess proportions of nominal/ordinal variables in different groups. The overall 5-year survival rate was calculated from the date of diagnosis to the date of the last follow-up or death for any reason, using Kaplan-Meier survival analysis. The univariate difference between the curves was assessed using the log rank test. A p value of less than or equal to 0.05 was accepted as statistically significant.

Results

Of the 5143 patients who were treated and followed up for breast cancer between January 1990 and February 2016, 99 (1.92%) were diagnosed as having bilateral breast cancer. Sixty-two (62.6%) and 37 (37.4%) of these patients had synchronous and metachronous breast tumors, respectively.

With regard to metachronous tumors, patient characteristics and tumor-related factors are shown in Table 1. The median age at the discovery of the first tumor in patients with metachronous tumor was 52 years (range, 37-76), and 75.7% were postmenopausal. Thirteen (35.1%) patients had a his-

tory of breast cancer in their family. The most common surgical intervention was breast-conserving surgery, and the kind of surgical intervention for the first and second tumors remained unchanged. Axillary dissection was performed on 24 (64.8%) patients at discovery of the first tumor and on 10 (27%) patients when the second tumor was found (p=0.001). The most common histologic type in both tumors was invasive ductal carcinoma. The mean tumor diameter was 22.3±13 mm in the first tumor, and 14.3±11.5 mm in the second tumor (p=0.008). No statistically significant difference

Table 1. Patient and disease characteristics in metachronous tumors (n=37)

Characteristics	*First tumor n (%)*	*Second tumor n (%)*	*p value**
Median age, years (range)	52 (37-76)	59 (40-81)	
Menopausal status			
Premenopausal	9 (24.3)	3 (8.1)	
Postmenopausal	28 (75.7)	34 (91.9)	
Family history	13 (35.1)	13 (35.1)	
Type of surgery			0.267
Breast-conserving surgery	24 (64.8)	29 (78.4)	
Subcutaneous mastectomy +reconstruction	0	1 (2.7)	
Mastectomy	13 (35.2)	7 (18.9)	
Axillary dissection	24 (64.8)	10 (27)	0.001
Tumor diameter (mm), mean±SD	22.3±13	14.3±11.5	0.008
Multifocal tumor	3 (8.1)	2 (5.4)	0.999
Tumor pathology			>0.05
IDC	29 (78.3)	28 (75.6)	
ILC	1 (2.7)	1 (2.7)	
DCIS	1 (2.7)	5 (13.5)	
IDC+ILC	6 (16.2)	3 (8.1)	
Number of tumor foci			0.388
Single focus	51 (82.2)	55 (88.7)	
More than one focus	11 (17.8)	7 (11.3)	
Histological grade			0.999
I	9 (24.3)	8 (21.6)	
II	12 (32.4)	13 (35.1)	
III	5 (13.5)	10 (27.0)	
Unknown	11 (29.7)	6 (16.2)	
Estrogen receptor			0.999
Positive	18 (48.6)	20 (54)	
Negative	11 (29.7)	7 (18.9)	
Unknown	8 (21.6)	10 (27.0)	
Progesterone receptor			0.999
Positive	17 (45.9)	18 (48.6)	
Negative	10 (27)	14 (37.8)	
Unknown	10 (27)	5 (13.5)	
HER2			0.999
Positive	3 (8.1)	4 (10.8)	
Negative	24 (64.8)	25 (67.5)	
Unknown	10 (27.0)	8 (21.6)	
Lymphovascular invasion			0.250
Positive	8 (21.6)	6 (16.2)	
Negative	18 (48.6)	25 (67.5)	
Unknown	11 (29.7)	5 (13.5)	
Median time of metachronous cancer occurrence, months (range)	96 (12-191)		

*McNemar/ Wilcoxon test

was detected between the first and second tumors in terms of estrogen, progesterone, and HER-2 receptors.

Concerning synchronous tumors, patient characteristics and tumor-related factors are shown in Table 2. Some 67.7% of the patients were postmenopausal, with a median age of 57 years (range, 31-84). The percentage of patients with a positive family history was calculated as 17.7%. Breast-conserving surgery was the most common surgical intervention performed to both breasts. Axillary dissection was performed at a significantly lower

Table 2. Patient and disease characteristics in synchronous tumors (n=62)

Characteristics	*Dominant tumor n (%)*	*Contralateral tumor n (%)*	*p value**
Median age, years (range)			>0.05
	57 (31-84)	57 (31-84)	
Menopausal status			>0.05
Premenopausal	20 (32.3)	20 (32.3)	
Postmenopausal	42 (67.7)	42 (67.7)	
Family history	11 (17.7)	11 (17.7)	>0.05
Type of surgery			0.062
Breast-conserving surgery	35 (56.4)	38 (61.2)	
Subcutaneous mastectomy + reconstruction	9 (14.5)	13 (20.9)	
Mastectomy	18 (29.0)	11 (17.7)	
Axillary dissection	34 (54.8)	9 (14.5)	<0.001
Mean tumor diameter, mm	21.5±13.3	12.0±8.3	<0.001
Multifocal tumor	11 (17.8)	7 (11.3)	0.388
Tumor pathology			>0.05
IDC	42 (67.7)	28 (45.1)	
ILC	9 (14.5)	9 (14.5)	
DCIS	-	19 (30.6)	
IDC+ILC	11 (17.7)	6 (9.6)	
Number of tumor foci			0.388
Single focus	51 (82.2)	55 (88.7)	
More than one focus	11 (17.8)	7 (11.3)	
Grade			0.350
I	9 (14.5)	11 (17.7)	
II	25 (40.3)	15 (24.1)	
III	16 (25.8)	8 (12.9)	
Unknown	12 (29.3)	18 (29)	
Estrogen receptor			0.250
Positive	48 (77.4)	34 (54.8)	
Negative	9 (14.5)	6 (9.6)	
Unknown	5 (8)	22 (35.4)	
Progesterone receptor			0.999
Positive	43 (69.3)	32 (51.6)	
Negative	14 (22.5)	8 (12.9)	
Unknown	5 (8)	22 (35.4)	
HER2			0.999
Positive	13 (8.1)	6 (10.8)	
Negative	43 (64.8)	31 (67 5)	
Unknown	6 (27.0)	25 (21.6)	
Lymphovascular invasion			0.791
Positive	10 (16.2)	12 (19.3)	
Negative	35 (56.3)	33 (53.2)	
Unknown	17 (27.5)	17 (27.5)	

*McNemar/Wilcoxon test

rate than that to the contralateral breast (p<0.001). The median tumor diameter was therefore significantly greater in the dominant breast (p<0.001). There was no statistically significant difference between the two tumors in terms of estrogen, progesterone, and HER-2 receptors. Estrogen receptor was positive in the dominant breast among 77.4% of the patients, and in 54.8% of the patients in the contralateral breast (p=0.25). In 19 patients, one breast had invasive cancer and the other had DCIS.

Concerning the comparison of synchronous and metachronous tumors, there was no significant difference in terms of age at initial diagnosis and menopausal status (p=0.199, p=0.418, respectively). In the metachronous breast cancer group, on the other hand, family history was found significantly greater (p=0.041). When comparing the dominant side of synchronous tumors with the first tumor of metachronous tumors, there were no statistically significant differences in terms of the type of surgery performed, axillary involvement, breast pathology, tumor diameter, and hormone receptors. When the non-dominant side of synchronous tumors was compared with second tumors of metachronous tumors, a statistically significant difference was discovered in terms of tumor pathology (p=0.024) and progesterone receptor (p=0.030)

Table 3. Comparison of synchronous and metachronous tumors

Characteristics	*Synchronous Dominant n (%)*	*Metachronous First tumor n (%)*	*p value**	*Synchronous Contralateral n (%)*	*Metachronous Second tumor n (%)*	*p value**
Type of surgery			0.055			0.065
Breast-conserving surgery	35 (56.4)	24 (64.8)		38 (61.2)	29 (78.3)	
Subcutaneous mastectomy+reconstruction	9 (14.5)	0		13 (20.9)	1 (2.7)	
Mastectomy	18 (29.0)	12 (35.1)		11 (17.7)	7 (18.9)	
Axillary dissection	34 (54.8)	24 (64.8)	0.337	9 (14.5)		
Mean tumor diameter (mm), mean±SD	21.5±13.3	22.3±13	0.707	12.0±8.3	14.3±11.5	0.405
Multifocal tumor	7 (11.2)	3 (8.1)		9 (14.5)	2 (5.4)	0.343
Tumor pathology			>0.05			0.024
IDC	42 (67.7)	29 (78.3)		28 (45.1)	28 (75.6)	
ILC	9 (14.5)	1 (2.7)		9 (14.5)	1 (2.7)	
DCIS	-	1 (2.7)		19 (30.6)	5 (13.5)	
IDC+ILC	11 (17.7)	6 (16.2)		6 (9.6)	3 (8.1)	
Histologic grade			0.217			0.704
I	9 (14.5)	9 (24.3)		11 (17.7)	8 (21.6)	
II	25 (40.3)	12 (32.4)		15 (24.1)	13.(35.1)	
III	16 (25.8)	5 (13.5)		8 (12.9)	10 (27.0)	
Unknown	12 (29.3)	11 (29.7)		18 (29)	6 (16.2)	
Estrogen receptor			0.269			0.173
Positive	48 (77.4)	18 (48.6)		34 (54.8)	20 (54)	
Negative	9 (14.5)	11 (29.7)		6 (9.6)	7 (18.9)	
Unknown	5 (8)	8 (21.6)		22 (35.4)	10 (27.0)	
Progesterone receptor			0.237			0.030
Positive	43 (69.3)	17 (45.9)		32 (51.6)	18 (48.6)	
Negative	14 (22.5)	10 (27)		8 (12.9)	14 (37.8)	
Unknown	5 (8)	10 (27)		22 (35.4)	5 (13.5)	
HER2			0.190			
Positive	13 (8.1)	3 (8.1)		6 (10.8)	4 (10.8)	
Negative	43 (64.8)	24 (64.8)		31 (67 5)	25 (67.5)	
Unknown	6 (27.0)	10 (27.0)		25 (21.6)	8 (21.6)	
Lymphovascular invasion			0.120			0.971
Positive	10 (16.2)	8 (21.6)		12 (19.3)	6 (16.2)	
Negative	35 (56.3)	18 (48.6)		33 (53.2)	25 (67.5)	
Unknown	17 (27.5)	11 (29.7)		17 (27.5)	5 (13.5)	

*McNemar/Wilcoxon test

(Table 3). There was no statistically significant difference between the two groups in terms of local recurrence and distant metastasis (Table 4).

In the context of survival analysis, synchronous and metachronous groups were compared in terms of overall survival, disease-free survival, local-recurrence-free survival, and distant-metastasis-free survival. Disease-free survival was 126.3 months and 243.7 months in synchronous and metachronous tumors, respectively; the difference between these groups was statistically significant (p=0.041) (Table 5).

Development of second tumor in the metachronous cancer group was also compared by time, i.e., <5 years vs. >5 years, and it was determined that second tumors that developed after more than 5 years gave rise to longer overall survival (p<0.001) (Table 6).

Table 4. Local recurrence and distant metastasis

		Synchronous tumor	*Metachronous tumor*	*Total*	*p value*
Primary disease	Non-metastatic	60	37	97	0.511
	Metastatic	2	0	2	
Local recurrence	Non-existent	58	34	92	0.744
	Existent	4	3	7	
Metastasis	Non-existent	55	31	86	0.449
	Existent	7	6	13	
	Dead	4	6	10	0.159
	Alive	48	28	76	

Table 5. Univariate survival analysis

	Estimated mean (months)	*95% Confidence interval*		*p**	*5-year survival (%)*	*10-year survival (%)*
		Lower limit	*Upper limit*			
Overall survival				0.407		
Synchronous	207.0	185.6	228.4		96.9	207.0
Metachronous	258.1	229.2	287.0		96.9	258.1
Overall	251.9	225.2	278.6		96.7	251.9
Disease-free survival				0.041		
Synchronous	126.3	110.2	142.4		83.4	126.3
Metachronous	243.7	210.1	277.2		91.4	243.7
Overall	223.9	193.9	253.9		86.9	223.9
Distant-recurrence-free survival				0.124		
Synchronous	159.5	134.4	184.7		87.8	159.5
Metachronous	258.4	228.6	288.2		97.2	258.4
Overall	244.9	217.6	272.2		92.4	244.9
Local-recurrence-free survival				0.286		
Synchronous	142.6	128.4	156.9		92.6	142.6
Metachronous	278.2	254.6	301.7		94.2	278.2
Overall	269.0	241.1	291.0		92.9	269.0

*Kaplan-Meier, Log Rank

Table 6. Time elapsed between development of two tumors in the metachronous group

Time elapsed between development of two tumors	*Estimated mean (months)*	*95% Confidence interval*		*p value**
		Lower limit	*Upper limit*	
<5 years	106.500	75.423	137.577	
>5 years	199.417	178.087	220.747	<0.001
Overall	182.370	159.669	205.071	

*Kaplan-Meier, Log Rank

Discussion

The second most common malignancy seen in patients with a history breast cancer is the development of cancer in the contralateral breast [7]. Several criteria exist to define synchronous and metachronous tumors. Synchronous breast tumor was defined as development of cancer within 1 month of initial diagnosis by Gollamoid et al., 3 months of initial diagnosis by Hartman, Diaz et al., and 1 year of initial diagnosis by Kheirelseid, Chen, Heron et al. [13,17,20-23]. In the present study, development of cancer in the contralateral breast within 1 year of initial diagnosis was defined as synchronous breast tumor, and any second tumor found in the contralateral breast after 1 year was defined as metachronous breast cancer.

The risk of contralateral breast primary in patients with breast cancer is 2 to 6-fold greater than that of first breast cancer in the general population [5]. Prolonged life expectancy among patients with breast cancer as a direct result of current treatment methods contributes to increasing the incidence of bilateral breast cancer. Various studies report the incidence of second primary cancer development in contralateral breast ranging from 1.4% up to 12%, whereas in our series, this rate was calculated as 1.92% [2-5]. According to the current literature, the annual incidence of metachronous breast cancer ranges from 0.3% to 1%; the majority of cases occur 5 years after the initial diagnosis. In our series, on the other hand, this period was found as 8 years (median time) [11]. The incidence rate of synchronous breast cancer was reported to be less than 2% according to the existing literature [12]. However, the present study found an incidence rate of 0.72% for metachronous breast cancer, and 1.20% for synchronous breast cancer.

Risk factors for bilateral breast cancer are reported to include the existence of breast cancer in family history, having breast cancer at an early age, not having given birth, the initially discovered tumor being lobular carcinoma (histologic type), and the first tumor being multicentric [24,25]. Family history plays an important role in bilateral breast cancer. Patients whose first-degree relatives have had breast cancer at early age are at greater risk in terms of bilateral breast cancer development [26].

In the present study, the median age at the time of initial discovery of metachronous cancers was lower than that of synchronous cancers. Among patients with synchronous breast cancer, the median age at the time of initial diagnosis was 57 years (range, 31-84), and 42 (42%) patients were in the postmenopausal period. On the other hand, the median age at the discovery of the first tumor in the metachronous group was 52 years (range, 37-76), and the median age at the second tumor detection was 59 years (range, 40-81). This finding is in keeping with the existing literature; i.e., the median age at initial diagnosis in the metachronous group was found as 51 years by Diaz et al., 52 years by Kheirelseid et al., and 46 years by Liang et al. [21,22,27]. Similarly, all these studies found that the mean age at the time of initial discovery of metachronous cancers was significantly lower than that of synchronous cancers.

Considering the impact of family history of breast cancer on synchronous and metachronous breast cancer, Liang et al. found the rate of positive family history as 28.5% and 34.2% in the synchronous and metachronous groups, respectively, while Diaz et al. found this proportion as 27.6% and 24.2% for the same groups, respectively [21,27]. Although both of these studies found no significant difference in terms of family history, the present study showed that the rate of positive family history was significantly greater in the metachronous group. In other words, this rate was 17.7% and 35.1% in the synchronous and metachronous groups, respectively (p=0.041).

To evaluate patients in terms of tumor diameters, Kheirelseid et al. calculated the median dominant tumor diameter as 24 mm (range, 1-130) and the median contralateral tumor diameter as 12 mm (range, 1-140) in synchronous tumors; the median first and second tumor diameters in metachronous tumors were 20 mm (range, 1-100) and 15 mm (range, 1-82), respectively [22]. These authors found a statistically significant difference between the dominant and contralateral breast solely in synchronous tumors [22]. Diaz et al. estimated the median diameter of dominant tumors as 37 mm (range, 0.5-70) and the median diameter of contralateral tumors as 14 mm (range, 0.3-60) in synchronous tumors; the median diameters of the first and second tumors in metachronous tumors were 27 mm and 20 mm, respectively. The difference of diameters between metachronous tumors was found statistically significant (p=0.003) [21]. In our study, the mean tumor diameter was calculated as 21.5±13.3 mm in the dominant tumor and 12±8.3 mm in the contralateral breast in the context of synchronous tumors. In the metachronous group, the mean tumor diameter was 22.3±13 mm in the first tumor and 14.3±11.5 mm in the second tumor. A statistically significant difference was detected between synchronous and metachronous groups in terms of first and second tumor diameters (p<0.001, p=0.008, respectively). In our study, as a direct result of close follow-up of the patients with breast cancer, the second tumor in the metachronous

group was detected with smaller diameters. In both groups, the most common type of tumor was invasive ductal carcinoma, in harmony with the existing literature.

The selection of surgical operation in cases of bilateral breast cancer remains a controversial issue. Previous studies have shown that breast-conserving surgery does not negatively affect survival in patients with early synchronous and metachronous breast cancer [28]. However, it remains contentious as to whether breast-conserving surgery accompanied by radiotherapy increases the risk of tumor development in the contralateral breast. Bedrosian et al. [29] showed that contralateral prophylactic mastectomy positively affected, albeit a little, 5-year survival, notably in young patients with ER(-) stage 1-2 disease. However, most previous studies reported that performing prophylactic mastectomy to the contralateral breast had no effect on survival, with the exception of selected cases [30,31]. Apart from having no positive effect on survival, contralateral prophylactic mastectomy was found to cause morbidity and unfavorable psychological impacts [32,33].

Breast-conserving surgery was defined as an effective and reliable procedure in the treatment of early breast cancer [20,28,34,35]. According to Yamauchi et al. [35], a 95-month median follow-up resulted in non-existence of distant metastasis and local recurrence in patients who underwent bilateral breast-conserving surgery. On the other hand, the study conducted by Lee et al. reported no difference between patients who had unilateral and bilateral breast-conserving surgery in terms of survival [28]. According to another study by Rochefordiere et al. in which 51 patients with synchronous breast cancer treated by bilateral breast-conserving surgery were compared with patients who underwent bilateral mastectomy or unilateral breast-conserving surgery, no significant difference was found between the two groups in terms of survival [34]. Kheirelseid et al. found no association between receiving radiotherapy for the first tumor and development of cancer in the contralateral breast [22].

To sum up, even though many studies confirmed that breast-conserving surgery followed by radiotherapy did not increase the risk of contralateral breast cancer, other studies that employed former techniques with longer-term follow-up asserted the contrary [24,36,38]. In the present study, breast-conserving surgery was performed to suitable patients, and no statistically significant difference was determined between the breast-conserving surgery and mastectomy groups in terms of development of tumor in the contralateral breast. In the study of Kheirelseid et al., breast-conserving surgery was performed to 6.1% of dominant and 14.3% of contralateral breasts in the synchronous group, and to 25.9% of patients with first tumor and 19% of patients with second tumor in the metachronous group [22]. In the scope of the study conducted by Diaz et al., breast-conserving surgery was performed to 20.7% of dominant and 55.2% of contralateral breasts in the synchronous group, and to 26.4% of patients with first tumor and 36.3% of patients with second tumor in the metachronous group [21]. In the study of Liang et al., breast-conserving surgery was performed to 6% of dominant and 9.5% of contralateral breasts in the synchronous group, and to 1.9% of patients with first tumor and 6.7% of patients with second tumor in the metachronous group [27]. In our study, on the other hand, breast-conserving surgery was more common as compared with the above mentioned studies; it was performed to 56.4% of dominant and 61.2% of contralateral breasts in the synchronous group, and to 64.8% of patients with first tumor, and 78.4% of patients with second tumor in the metachronous group.

A review of the literature by Diaz et al. about the use of axillary dissection revealed that axillary dissection was used in the synchronous group for the treatment of dominant and collateral breasts rates in 82.8% and 55.2%, respectively, whereas it was performed for the first tumors in 91.2%, and for the second tumors in 77.3% in the metachronous group [21]. In the study of Kheirelseid et al., axillary dissection was performed to 45% of dominant and 15.7% of contralateral breasts in the synchronous group, and to 46.7% of first tumors and 25% of second tumors in the metachronous group [22]. In our study, on the other hand, axillary lymph node dissection was performed in the synchronous group to 54.8% of dominant breasts and 14.5% of collateral breasts, whereas it was performed to 64.8% of first tumors and 27% of second tumors in the metachronous group. As a result of close follow-up of patients, second tumors were diagnosed earlier, and therefore axillary dissection was used at a lower rate, in a similar way to the current literature.

The time for the second tumor to emerge in metachronous cancers may differ. The median time for occurrence of second tumor was reported as 91 months (range, 12-448) by Diaz et al., 46.8 months by Kheirelseid et al., and 67 months (range, 14-432) by Liang et al. [21,22,27]. In the present study, the median time of metachronous cancer occurrence was found as 96 months (range, 12-191).

Studies comparing bilateral breast cancer with unilateral breast cancer in terms of survival found quite divergent results. Some studies suggested

that bilateral breast cancer incorporated poor prognosis [9,39,40], whereas others argued that prognosis remained unchanged [10,12,13,14,41]. Such divergences might be dependent on the number of patients included, age, treatment regimens, follow-up, and differences in calculation of survival time for synchronous and metachronous tumors. The study performed by Kheirelseid et al. revealed no difference between bilateral and unilateral breast cancer in terms of overall survival, but it reported a better rate of overall survival in the metachronous cancer group as a consequence of a comparison between metachronous and synchronous tumors. The median time of survival for synchronous and metachronous tumors was found as 62 months and 148 months, respectively. For disease-free survival, the median time of overall survival was calculated as 52 months for synchronous tumors and 148 months for metachronous tumors (p=0.013) [22]. The study by Diaz et al. found no difference between synchronous and metachronous tumors in terms of overall survival. The median survival time was estimated as 100 months for synchronous tumors and 136 months for metachronous tumors [21]. This study also revealed that the median survival was clearly poorer among patients in whom metachronous tumor occurred within less than 5 years (the median survival for patients with less than 5 years was 145 months, whereas it was 394 months for those with more than 5 years; p=0.001). In a mortality analysis on 123,757 patients with breast cancer recorded in Sweden's cancer database, Hartmann et al. discovered that if metachronous tumor had been diagnosed after more than 10 years, the risk of mortality due to breast cancer would have been similar to the risk of mortality due to unilateral breast cancer. In that study, it was also underlined that chemotherapy gave a positive contribution to prognosis in cases where the use of adjuvant chemotherapy impeded the development of tumor in the contralateral breast, prolonging the median time, whereas it acted as a negative factor unfavorably predicting survival in cases where early tumor developed in the contralateral breast, despite chemotherapy [17].

In our series, there was no statistically significant difference between the two groups in terms of overall survival, local-recurrence-free survival, and distant-metastasis-free survival. However, the metachronous cancer group displayed better prognosis in terms of disease-free survival; disease-free survival was found as 126.3 months and 243.7 months in synchronous and metachronous tumors, respectively (p=0.041). In metachronous tumors, as the time between discovery of two tumors exceeded 5 years, the overall survival rate was significantly higher. The median overall survival time was found as 106.5 months for patients who had a second metachronous tumor within 5 years, whereas it was 199.4 months for those who developed a metachronous tumor after more than 5 years (p<0.001).

Conclusion

In the present study, among patients with metachronous tumors, the second tumor was diagnosed earlier as a result of close follow-up. The rate of positive family history was found greater in the metachronous cancer group. Disease-free survival was longer in the metachronous group, and survival was better among patients in whom metachronous tumors developed after more than 5 years.

Acknowledgements

The authors would like to thank Mr. David Chapman for his meticulous editing of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

References

1. Ries LAG, Eisner MP, Kosary CL et al. (Eds): SEER cancer statistics review, 1975-2002, National Cancer Institute. Bethesda, MD: 2005. http://seer.cancer.org/csr/1975_2002/, base on November 2004 SEER data submission, pasted to the SEER web site 2005.
2. Donovan AJ. Bilateral breast cancer. Surg Clin N Am 1990;70:1141-9.
3. Michowitz M, Noy S, Lazebnik N, Aladjem D. Bilateral breast cancer. J Surg Oncol 1985;30:109-12.
4. Gogas J, Markopoulos C, Skandalakis P, Gogas H. Bilateral breast cancer. Am Surg 1993;59:733-5.
5. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomark Prev 1999;8:855-61.
6. Chaudary MA, Millis RR, Hoskins EO et al. Bilateral primary breast cancer: a prospective study of disease incidence. Br J Surg 1984;71:711-4.
7. Soerjomataram I, Louwman WJ, Lemmens VE et al.

Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972-2001. Eur J Cancer 2005;41:2331-7.
8. Lu W, Schaapveld M, Jansen L et al. The value of surveillance mammography of the contralateral breast in patients with a history of breast cancer. Eur J Cancer 2009;45:3000-7.
9. Jobsen JJ, Jvd Palen, Ong F, Meerwaldt JH. Synchronous, bilateral breast cancer: prognostic value and incidence. Breast 2003;12:83-8.
10. Verkooijen HM, Chatelain V, Fioretta G et al. Survival after bilateral breast cancer: results from a population-based study. Breast Cancer Res Treat 2007;105:347-57.
11. Healey EA, Cook EF, Oraj EJ et al. Contralateral breast cancer: clinical characteristics and impact on prognosis. J Clin Oncol 1993;11:1545-52.
12. Irvine T, Allen DS, Gillett C, Hamed H, Fentiman IS. Prognosis of synchronous bilateral breast cancer. Br J Surg 2009;96:376-80.
13. Heron DE, Komarnicky LT, Hyslop T, Schwartz GF, Mansfield CM. Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. Cancer 2000;88:2739-50.
14. Newman LA, Sahin AA, Cunningham JE et al. A case-control study of unilateral and bilateral breast carcinoma patients. Cancer 2001;91:1845-53.
15. Mertens WC, Hilbert V, Makari-Judson G. Contralateral breast cancer: factors associated with stage and size at presentation. Breast J 2004;10:304-12.
16. Hartman M, Czene K, Reilly M et al. Genetic implications of bilateral breast cancer: a population based cohort study. Lancet Oncol 2005;6:377-82.
17. Hartman M, Czene K, Reilly M et al. Incidence and prognosis of synchronous and metachronous bilateral breast cancer. J Clin Oncol 2007;25:4210-6.
18. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451-67.
19. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930-45.
20. Gollamudi SV, Gelman RS, Peiro G et al. Breast-conserving therapy for stage I-II synchronous bilateral breast carcinoma. Cancer 1997;79:1362-9.
21. Díaz R, Munárriz B, Santaballa A, Palomar L, Montalar J. Synchronous and metachronous bilateral breast cancer: a long-term single-institution experience. Med Oncol 2012;29:16-24.
22. Kheirelseid EA, Jumustafa H, Miller N et al. Bilateral breast cancer: analysis of incidence, outcome, survival and disease characteristics. Breast Cancer Res Treat 2011;126:131-40.
23. Chen JJ, Huang NS, Xue JY et al. Surgical management for early-stage bilateral breast cancer patients in China. PLoS One 2015;10:e0122692.
24. Bernstein JL, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am J Epidemiol 1992;136:925-36.
25. Li CI, Malone KE, Porter PL, Daling JR. Epidemiologic and molecular risk factors for contralateral breast cancer among young women. Br J Cancer 2003;89:513-8.
26. Malone KE, Daling JR, Weiss NS et al. Family history of young women with invasive breast carcinoma. Cancer 1996;78:1417-25.
27. Liang X, Li D, Geng W, Cao X, Xiao C. The prognosis of synchronous and metachronous bilateral breast cancer in Chinese patients. Tumour Biol 2013;34:995 1004.
28. Lee MM, Heimann R, Powers C, Weichselbaum RR, Chen LM. Efficacy of breast conservation therapy in early stage bilateral breast cancer. Breast J 1999;5:36-41.
29. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst 2010;102:401-9.
30. Quan G, Pommier SJ, Pommier RF. Incidence and outcomes of contralateral breast cancers. Am J Surg 2008;195:645-50.
31. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg 2000;180:439-45.
32. Zion SM, Slezak JM, Sellers TA et al. Reoperations after prophylactic mastectomy with or without implant reconstruction. Cancer 2003;98:2152-60.
33. Frost MH, Slezak JM, Tran NV et al. Satisfaction after contralateral prophylactic mastectomy: the significance of mastectomy type, reconstructive complications, and body appearance. J Clin Oncol 2005;23:7849-56.
34. de la Rochefordiere A, Asselain B, Scholl S et al. Simultaneous bilateral breast carcinoma: a retrospective review of 149 cases. Int J Radiat Oncol Biol Phys 1994;30:35-41.
35. Yamauchi C, Mitsumori M, Nagata Y et al. Bilateral breast-conserving therapy for bilateral breast cancer: results and consideration of radiation technique. Breast Cancer 2005;12:135-9.
36. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-41.
37. Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992;326:781-5.
38. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. Int J Radiat Oncol Biol Phys 2003;56:1038-45.
39. Abdalla I, Thisted RA, Heinmann R. The impact of contralateral breast cancer on the outcome of breast cancer patients treated by mastectomy. Cancer 2000;6:266-72.
40. Gajalakshmi CK, Shanta V, Hakama M. Survival from contralateral breast cancer. Breast Cancer Res Treat 1999;58:115-22.
41. Takahashi H, Watanabe K, Takahashi M, Taguchi K, Sasaki F, Todo S. The impact of bilateral breast cancer on the prognosis of breast cancer: a comparative study with unilateral breast cancer. Breast Cancer 2005;12:196-202.