

ORIGINAL ARTICLE

Comparison of prognosis and clinical features between synchronous bilateral and unilateral breast cancers

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Summary

Purpose: The clinical significance of synchronous bilateral breast cancer (SBBC) is unclear and its influence on prognosis is controversial. Our study objective was to determine the epidemiological features, tumor characteristics, and prognosis of SBBC in comparison with those of unilateral breast cancer (UBC).

Methods: A total of 3675 breast cancer patients diagnosed and treated between 2000 and 2014 were evaluated. Of these patients, 132 (3.6%) had bilateral breast cancer, including 55 patients (1.5%) with SBBC and 77 (2.1%) with metachronous bilateral breast cancer (MBBC). The patient demographic characteristics, including survival data and clinicopathological tumor characteristics, were obtained from medical charts and compared between the patients with SBBC and those with UBC.

Results: The median age in the SBBC group was 51 years (range 32–77). The mastectomy rate was higher in the SBBC group (72.7%) than in the UBC group (66.6%). ($p=0.08$). In both the SBBC and UBC groups, the baseline clinicopathological features and the history of treatment with

radiotherapy and chemotherapy were similar. Infiltrating ductal carcinoma was the most common histology in both groups. Lobular histology was more frequent in the SBBC group (36.3%) than in the UBC group (17.1%; $p<0.001$). Stage IV disease at initial presentation was more frequent in the SBBC group than in the UBC group (34.5 vs 8.7%, $p<0.001$). The 5-year disease-free survival (DFS) rates were 90% and 82% in the SBBC and UBC groups, respectively ($p=0.99$). The 5-year overall survival (OS) rates were 83% and 88%, respectively ($p=0.357$). The multivariate Cox regression analysis, including stage, hormone receptor status, grade, and SBBC, revealed that the presence of SBBC was not associated with OS (hazard ratio 0.929; 95% confidence interval, 0.455–0.1894, $p=0.839$).

Conclusion: Despite the differences in histology, initial stage, and other characteristics, the prognoses of UBC and SBBC were similar.

Key words: prognosis, survival, synchronous bilateral breast cancer

Introduction

Bilateral breast cancer (BBC) is estimated to occur in approximately 7% of women with breast cancer [1-3]. The risk of developing a contralateral breast cancer is 2-6-fold higher in women with breast cancer than in the general population [4]. Other risk factors of bilateral breast cancer include young age, multicentric tumors, lobular histology, radiation exposure, BRCA1 and BRCA2

mutations, and positive family history [5-8]. Bilateral breast cancer can be synchronous or metachronous. SBBC is usually defined as the presentation of secondary breast tumor(s) within 6 months after the primary tumor was diagnosed, whereas MBBC is defined as a second tumor diagnosed 6 months after the diagnosis of the primary tumor [9-12].

The impact of bilateral breast cancer on disease course and survival is still controversial. A recent meta-analysis showed that bilaterality itself was a poor prognostic factor apart from other known prognostic factors, but the quality of the studies included was generally low and sample sizes were small [13].

The aim of this study was to describe patient and tumor characteristics in SBBC cases and analyze the impact of the disease on patient survival in comparison with UBC.

Methods

We evaluated the hospital charts of the patients with breast cancer (n=3675) diagnosed between 2000 and 2014 in the Department of Medical Oncology, Hacettepe University Cancer Institute. All the patients were treated according to local protocols, which are similar to those used in patients with SBBC and UBC in our institution. Annual mammography was performed in all of the patients. Secondary breast cancer diagnosed within 6 months of diagnosis of the primary breast cancer was defined as a synchronous tumor. If the interval was >6 months, it was designated as a metachronous tumor. The study compared patients with synchronous tumors and those with unilateral tumor according to age, body mass index (BMI), menopausal status, tumor histology, lymph node involvement, tumor size, estrogen (ER) and progesterone receptor (PR) status, HER-2, and tumor grade and stage. DFS and OS were also estimated and compared. This study was approved by the institutional ethics committee.

Statistics

Statistical analyses were performed by using SPSS version 21.0 for Windows (SPSS, Chicago, IL). For the comparisons between the groups, the Mann-Whitney U test, chi-square test, and Student's t-test were used. Tumors with missing values were omitted from the analyses. Two-sided p values of <0.05 were considered statistically significant. DFS was defined as the time interval from the time of diagnosis to the first disease recurrence or death from any cause if disease recurrence did not occur. OS was defined as the time interval from diagnosis to death from any cause. Survival rates were estimated by using the Kaplan-Meier analysis and compared with the log-rank test.

Results

Among the 3675 patients evaluated, 132 (3.6%) had bilateral breast cancer. Fifty-five patients (1.5%) presented with SBBC and 77 (2.1%) presented with MBBC. The patient characteristics are shown in Table 1, and the tumor features are

Table 1. Patient characteristics

Characteristics	SBBC	UBC	p value
Age, years (range)	51 (32-77)	48 (18-92)	0.37
Age at menarche, years (range)	13.5 (10-17)	13.27 (8-24)	0.63
Age at first gestation, years (range)	24 (16-47)	23 (16-55)	0.53
Smoking, n (%)	10 (18.2)	737 (20.4)	0.69
Menopausal status, n (%)			0.770
Pre	27 (50)	1920 (53.4)	
Post	27 (50)	1678 (46.6)	
BMI, kg/m ² , n (%)			0.127
>25	40 (78.4)	2171 (65.7)	
<25	11 (21.6)	1163 (34.9)	
Surgery, n (%)			0.08
BCS	10 (22.7)	1104 (32.4)	
MRM	32 (72.7)	2260 (66.6)	
No surgery	2 (4.5)	31 (0.9)	
Chemotherapy, n (%)	37 (68.5)	2706 (76.6)	0.23

BMI: body mass index, BCS: breast-conserving surgery, MRM: modified radical mastectomy, SBBC: synchronous bilateral breast cancer, UBC: unilateral breast cancer

shown in Table 2. The median ages was 51 years (range 32–77) in the SBBC group and 48 years (range 18–92) in the UBC group (p=0.37). Fewer patients underwent breast-conserving surgery in the SBBC group compared to the UBC group (32 vs 23%; p=0.08).

Invasive ductal carcinoma (IDC) was the most frequent subtype in both groups. The prevalence of lobular carcinoma (pure or mixed) was higher in the SBBC group than in the UBC group (36.3 vs 17.1%, respectively; p<0.001). More patients in the UBC group had grade III disease compared to the SBBC group (42 vs 28%; p=0.029). The frequency of ER and PR positivity was higher in the SBBC group than in the UBC group. Moreover, more patients in the SBBC group had stage IV disease compared to the UBC group (34.5 vs 8.7%; p<0.001).

The 5-year OS survival rate was 83% in the SBBC group and 88% in the UBC group (p=0.357). Among the patients with non-metastatic disease, those with synchronous and unilateral tumors, respectively, had 5-year OS rates of 92 and 91% (p=0.901, Figure 2) and 5-year DFS rates of 90 and 82% (p=0.99, Figure 1).

Multivariate Cox regression analysis including stage, hormone receptor negativity, grade and SBBS revealed that the presence of SBBC was not associated with OS but the remaining covariates were (Table 3)

Table 2. Tumor characteristics

Characteristics	SBBC n (%)	UBC n (%)	p value
Histology			<0.001
Ductal	26 (47.3)	2633 (73.4)	
Lobular	2 (3.6)	186 (5.2)	
Mixed type (ductal + lobular)	18 (32.7)	427 (11.9)	
Other	9 (16.4)	342 (9.5)	
Lymph node involvement			0.745
N (-)	18 (40)	1541 (44.4)	
N (+)	27 (60)	1929 (55.6)	
T stage			0.345
T1-2	41 (80.4)	2827 (81.1)	
T3-4	10 (19.6)	657 (18.9)	
Lymphovascular invasion			0.712
(-)	40 (72.7)	2619 (72.3)	
(+)	15 (27.3)	1001 (27.3)	
Perineural invasion			0.761
(-)	48 (87.5)	3220 (89.0)	
(+)	7 (12.7)	400 (11)	
Grade			0.029
I/II	33 (72.7)	1827 (58.1)	
III	13 (28.3)	1318 (41.9)	
Estrogen receptor status			0.022
(-)	8 (15.4)	877 (25.1)	
(+)	44 (84.6)	2615 (74.9)	
Progesterone receptor status			0.014
(-)	11 (21.6)	1000 (28.9)	
(+)	40 (78.4)	2455 (71.1)	
HER-2 status			0.278
(-)	45 (81.8)	2874 (79.4)	
(+)	10 (18.2)	746 (20.6)	
Stage			<0.001
I	12 (21.8)	778 (22)	
II	18 (32.7)	1523 (43.1)	
III	6 (10.9)	929 (26.3)	
IV	19 (34.5)	307 (8.7)	

T: tumor, HER-2 status: human epidermal growth factor receptor 2, SBBC: synchronous bilateral breast cancer, UBC: unilateral breast cancer

Table 3. Multivariate Cox regression analysis of overall survival

Variables	Hazard ratio	95% confidence interval	p value
Synchronicity	0.929	0.455-1.894	0.839
Grade			0.001
II vs I	1.390	0.894-2.161	0.143
III vs I	1.934	1.241-3.013	0.004
Hormone receptor negative	1.686	1.270-2.238	<0.001
Stage			<0.001
II vs I	2.415	1.397-4.172	0.002
III vs I	6.727	3.950-11.456	<0.001
IV vs I	26.918	15.493-46.766	<0.001

Discussion

In this study, we found that the prognosis of

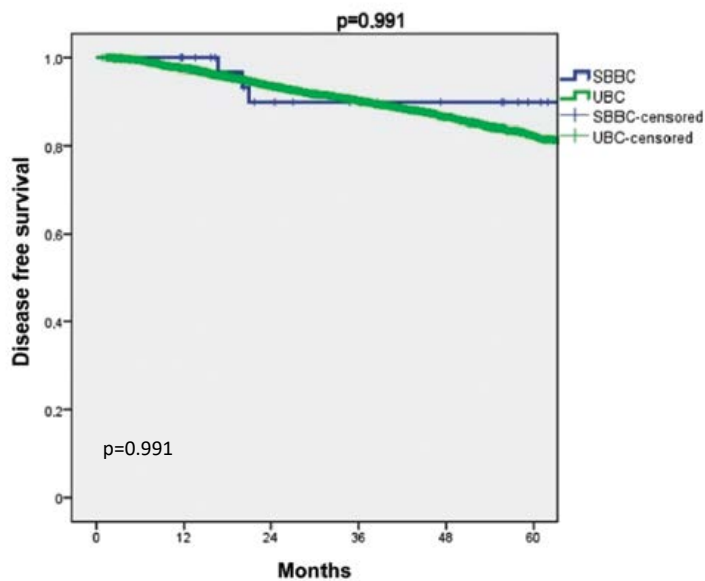


Figure 1. Kaplan-Meier time-to-event curves. Disease-free survival.

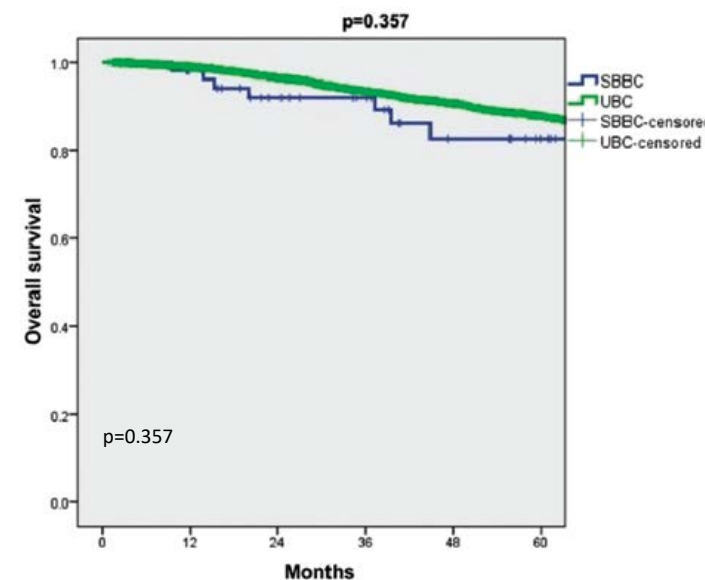


Figure 2. Kaplan-Meier time-to-event curves. Overall survival.

SBBC was similar to that of UBC. Although the patients with SBBC were diagnosed at more advanced stages than those with UBC, this may have been counterbalanced with the higher rates of hormone receptor positivity and lower tumor grade in the SBBC group, resulting in similar outcomes with the UBC group in terms of DFS and OS.

The incidence of SBBC is relatively low, accounting for 0.7–3% of all cases of breast cancer in the literature [9,11,12,14] and 1.5% of the cases in our study. The definition of synchronous differs in various studies, but a recent large series showed that the definition of SBBC did not significantly

affect the incidence of SBBC [15]. Previous studies identified younger age at first diagnosis, history of lobular carcinoma of the breast, and family history of breast cancer [16-18] to be associated with an increased risk of BBC. However, the results of the studies are not entirely consistent. Some studies reported that older age [14,19,20] predicted the development of SBBC, whereas other studies did not find any association with age [21,22] or family history [20,22]. We could not find any differences in patient demographic characteristics, including age, menopausal status, menarche age, age of first gestation, number of children, and smoking. More patients with SBBC were overweight compared to those with UBC, although the difference was not statistically significant (78 vs 66%; $p=0.127$).

More patients with SBBC had stage IV disease at diagnosis. This might have a biological rationale, that is, a more aggressive disease course. On the other hand, it may simply reflect selection bias because patients with stage IV disease might also have contralateral breast metastases. We did not perform any further analysis (histological subtype and presence of in situ disease) to discriminate whether the contralateral tumor is primary or metastatic. In one study, stage distribution was found to be similar between SBBC and UBC when patients with stage IV disease were excluded [15].

The pathological features associated with SBBC were reported to be lobular histology [9,20,21,23], hormone receptor positivity [19,24,25], and presence of sclerosing adenosis [15]. We found that patients with SBBC had lower tumor grade, more frequent ER and PR positivity, and higher rate of pure/mixed lobular histology. Our findings are consistent with most of the above-mentioned studies. Lobular histology is characterized with higher frequency of hormone receptor positivity, bilaterality and multicentricity, and better differentiation compared to ductal carcinomas.

Finally, genetic risk factors, including BRCA positivity [26], as well as Peutz Jeghers [27], Li-Fraumeni [28], and Cowden syndromes [29] may be associated with higher risk of bilateral breast cancer, but none of our patients were evaluated for the presence of any of these syndromes.

The prognosis of SBBC is also controversial. Many small retrospective series reported similar or poorer survival compared with UBC [11,30-32]. However, the main limitation of these studies were the lack of a multivariate analysis or, if a multivariate analysis was performed, the use of

different covariates. A recent meta-analysis of 17 studies that included 8050 SBBC patients from 11 different countries showed that bilaterality itself was associated with 37% increased risk of breast cancer mortality [13]. We found similar DFS and OS in the SBBC patients. The main predictors of survival were disease stage, histological grade, and hormone receptor positivity. Lower histological grade and higher frequency of hormone receptor positivity might have counterbalanced the ominous effect of more advanced stage in patients with SBBC than in those with UBC. The greater likelihood of undergoing mastectomy as a more radical treatment protocol in the SBBC group than in the UBC group (72.7 vs 66.6%) might also have a role, despite evidence suggesting that conservative treatment is equally effective for BBC [33].

The limitations of our study include its retrospective design and small number of patients with SBBC. As the study period was long, treatment modalities, particularly chemotherapy and targeted therapies, have evolved within this period, resulting in heterogeneity in breast cancer care. Similarly, the more frequent use of breast magnetic resonance imaging might have also revealed more cases with SBBC that were previously undetected. Genetic testing for BRCA mutations and other mutations would provide data on the association with tumor features and prognosis of SBBC; however, it could not be performed. The follow-up period for the SBBC patients was relatively short (31 months), and longer follow-up may yield different results. Finally, chemotherapy details were not available for evaluation as a confounding factor of prognosis.

In conclusion, SBBC does not seem to portend poorer prognosis compared to UBC. DFS and OS curves nearly overlapped, particularly for the patients with stage I-III disease. Synchronicity may affect local treatment choice, but systemic treatment decisions should be made based on classical predictive and prognostic factors, including tumor stage, grade, hormone receptor status, and molecular markers such as Oncotype DX, as well as individual patient characteristics. Randomized trials are difficult to conduct in SBBC patients owing to the low incidence of the disease. Therefore, results of meta-analyses of contemporary series with multivariate analyses may provide insights for optimum risk assessment and treatment protocols.

Conflict of interests

The authors declare no conflict of interests.

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