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The characteristics of bilateral breast cancer patients

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Introduction. Bilateral breast cancer (BBC) consists of 2–12% all cases of breast carcinoma. In relation to time between the first and second cancer diagnosis, the synchronous (s-BBC) or metachronous (m-BBC) bilateral breast cancer is defined.

Material and methods. The clinicopathologic characteristics of 303 patients treated between 1963 and 2014 for bilateral breast cancer was presented. Synchronous BBC was diagnosed in 70 patients (23.1%) and remaining 233 patients (76.9%) developed metachronous BBC.

Patients with m-BBC in comparison to s-BBC were younger (mean age: 51.4 vs 60.6 years), the positive family cancer history was rare (36.7% vs 48.5%), and more frequently these patients were before menopause (65.7% vs 44.3%). While the lobular type of breast cancer which consisted of 6.6% cases in first breast and 8.9% cases of second carcinomas, more frequently was presented in s-BBC (8.6%) in comparison to m-BBC (6%).

Results. The mean time of follow up was 174 months. The 5- and 10-year overall survival rates were 89.3% and 76.1%, respectively. The presence of s-BBC connected with worse prognosis; the 5- and 10-year overall survival were 93.1% and 82% for m-BBC and 76.4% and 52.1% for s-BBC (p = 0.00244, log-rank test).

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

Introduction

The incidence of bilateral breast cancer affects 2–12% of all breast cancer patients. The risk of developing cancer in the second breast is greater than the risk of developing the original disease in a hitherto healthy person. It is estimated that each year 0.7% of patients with breast cancer develop cancer in their second breast [1–3].

The development of two separate primary breast cancers is the result of genetic predisposition, exposure to specific environmental factors or a combination of independent events [4].

The risk factors for bilateral breast cancer (BBC) include family history of malignant neoplasms, development of breast cancer at an early age, lobular breast cancer, early stage of development, presence of receptor expression and the type of treatment methods used [5–9].

Depending on the time between the diagnosis of BBC in both breasts, synchronous and metachronous bilateral breast cancer can be distinguished [10, 11]. The diagnosis of cancer in both breasts at the same time does not raise any doubts that it is synchronous BBC. However, if the diagnosis of cancer in the second breast takes place after some time since the diagnosis of the first tumor, there is currently no clear time milestone to determine whether it is a synchronous or metachronous disease. The literature data indicate that researchers use the period from 1 month to 1 year as the boundary between classification into synchronous or metachronous BBC [5, 12].

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The aim of this paper is to present the characteristics of a group of patients with bilateral breast cancer, in relation to the time between the diagnosis of breast cancer (synchronous vs metachronous BBC).

Material and methods

Synchronous bilateral breast cancer (s-BBC) was defined as the diagnosis of breast cancer at the same time or up to 6 months, while metachronous bilateral breast cancer (m-BBC) refers to those cases of second breast cancer that were diagnosed after a period longer than 6 months.

Patients

In 303 breast cancer patients treated in the years 1963–2014 in the Maria Skłodowska-Curie Institute — Oncology Center, Branch in Kraków, bilateral breast cancer was diagnosed. These patients were: 0.25% of all (121 209) patients, 1.5% of all (20 004) breast cancer patients and 9.4% of all (3219) multiple cancer patients treated during this period.

The age of patients included in the analysis was on average 53.5 years (range: 19–85 years). Of all patients with bilateral breast cancer, 70 (23.1%) had synchronous and 233 (76.9%) had metachronous BBC.

The time between the diagnosis of cancer in both breasts ranged from 0 to 543 months and was 85 months on average. Figure 1 shows the frequency of diagnosis of second breast cancer depending on the interval between cases (s-BBC vs m-BBC).

The range and mean time between the diagnosis of both cancers depending on the type of BBC was 0–5 months and 0.5 months (in the case of s-BBC) and 7–543 months and 94 months (in the case of m-BBC), respectively.

Tables I and II present the characteristics and methods of treatment applied in the whole group and in relation to the type of bilateral breast cancer.

Family history of cancer was found in 117 (38.6%) patients. Women before menopause (184 — 60.7%), T1–2 cancer (78.9% in the first and 91.4% in the second breast cancer) and less frequent lymphadenopathy (69.3% in the second disease) dominated in the analyzed group. Surgical treatment with mastectomy dominated in all patients (88.4% in the first and 70.3% in the second breast cancer). In 170 patients (55.7%) radiotherapy was performed — in 35% on one side and in 21.1% on both sides. Adjuvant chemotherapy was applied in 169 patients (55.8%) and hormone therapy in 210 patients (69.3%).

Comparison of m-BBC and s-BBC subgroups shows significant differences in age, family history, menopause, histological type of breast cancer, frequency of lymph node metastases and treatment methods used (surgery, hormone therapy). In the case of m-BBC, compared to s-BBC, patients were younger (mean age: 51.4 years vs 60.6 years), less frequent was family history of cancer (36.7% vs 48.5%), more often were before menopause (65.7% vs 44.3%). In contrast, lobular breast cancer represented 6.6% of first and 8.9% of second breast cancers and was significantly more

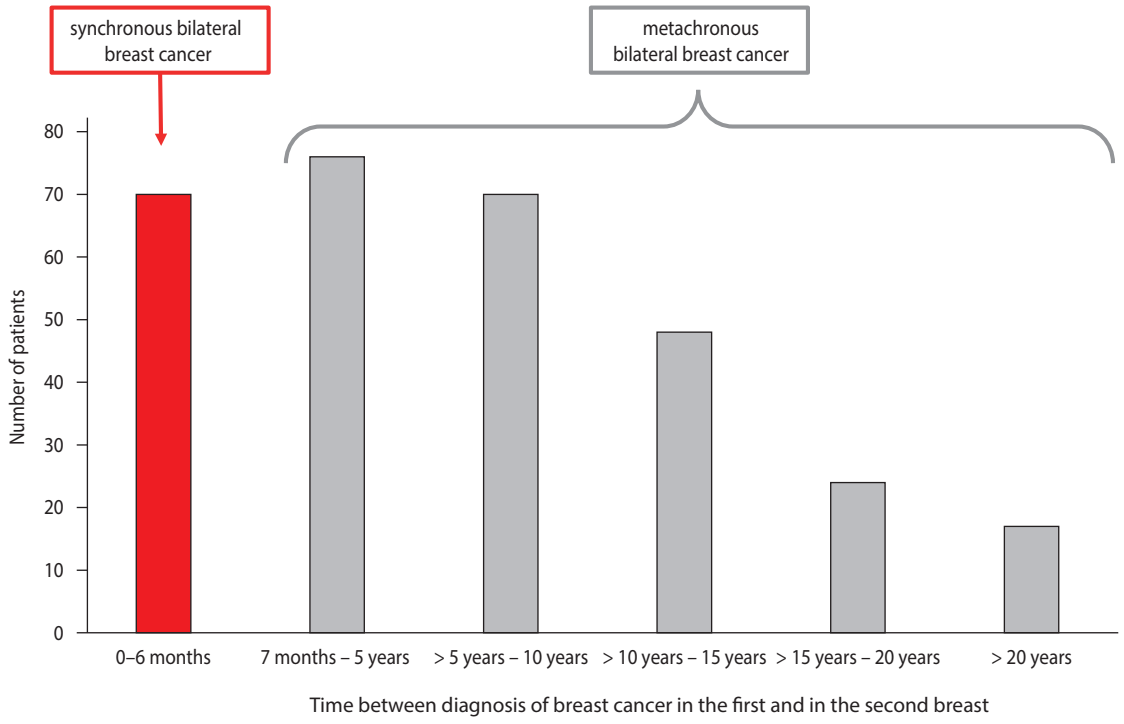

Figure 1. Bilateral breast cancer frequency depending on the time between the first breast cancer diagnosis and the cancer diagnosis in the second breast

Table I. Characteristics of a group of 303 patients treated for bilateral breast cancer (BBC)

Factor n = 303		Whole group	m-BBC*	s-BBC**	p
		n = 233	n = 70		
Age	(mean ± SD)	53.3 ± 12.3	51.4 ± 11.2	60.6 ± 13.1	< 0.00001
Family history:					
negative		186 (61.4%)	150 (64.4%)	36 (51.4%)	
breast cancer		55 (18.2%)	43 (18.5%)	12 (17.1%)	0.03220
other cancer		62 (20.5%)	40 (17.2%)	22 (31.4%)	
Menopause					
no		184 (60.7%)	153 (65.7%)	31 (44.3%)	
yes		119 (39.3%)	80 (34.3%)	39 (55.7%)	0.00132
Histopathological type – first breast cancer:					
ductal		219 (72.3%)	162 (69.5%)	57 (81.4%)	
lobular		20 (6.6%)	14 (6%)	6 (8.6%)	0.03141
other		64 (21.1%)	57 (24.5%)	7 (10%)	
– second breast cancer					
ductal		237 (78.2%)	184 (79%)	53 (75.7%)	
lobular		27 (8.9%)	20 (8.6%)	7 (10%)	0.84552
other		39 (12.9%)	29 (12.5%)	10 (14.3%)	
T parameter – first breast cancer					
T1–2		239 (78.9%)	278 (76.4%)	61 (87.1%)	
T3–4		64 (22.1%)	55 (23.6%)	9 (12.9%)	0.05337
– second breast cancer					
T1–2		277 (91.4%)	211 (90.6%)	66 (94.3%)	
T3–4		26 (8.6%)	22 (9.4%)	4 (5.7%)	0.32882
pN parameter – first breast cancer					
pN0		150 (49.5%)	112 (48.1%)	38 (54.3%)	
pN+		153 (50.5%)	121 (51.9%)	32 (45.7%)	0.36161
– second breast cancer					
pN0		211 (69.3%)	151 (64.8%)	60 (85.7%)	
pN+		92 (30.4%)	82 (35.2%)	10 (14.3%)	0.00085

*m-BBC — metachronous bilateral breast cancer
**s-BBC — synchronous bilateral breast cancer

common in s-BBC (8.6%) compared to m-BBC (6%) in the first breast cancer. Surgical procedures with breast saving were more frequent in the treatment of the second breast (29.7% vs 11.6%), especially visible differences concerned m--BBC (7.3% in the first breast vs 25.8% in the second breast).

Statistical methods

The criterion for results evaluation in the whole group and in relation to the type of bilateral breast cancer (s-BBCvs m-BBC) was adopted for 5- and 10-year survival rates estimated with the Kaplan-Meier method, and the results were compared with the log-rank test. In comparison of s-BBC and m-BBC groups the chi^2 test (step values) or variance analysis (continuous values) were applied. All statistical analyses were carried out using Statistica v.13.3 TIBCO Software Inc. package, assuming a significance level of $p \leq 0.05$.

Results

In the analyzed group the observation time (calculated from the diagnosis of cancer in the second breast) was 2–558 months (mean: 174.3 months, median: 159 months). At that time 160 patients (52.8%) died of: breast cancer (66 patients — 21.8%), other cancer (5 patients — 1.7%), non-cancer diseases (82 patients — 27.1%).

Figure 2 shows the survival probability curves for the whole group (a) and depending on the type of BBC (b).

Table II. Treatment methods used in 303 patients with bilateral breast cancer (BBC)

Factor	Whole group	m-BBC*	s-BBC**	p
	n = 303	n = 233	n = 70	
Surgery	303 (100%)	233 (100%)	70 (100%)	
– first breast cancer				
BCS	35 (11.6%)	17 (7.3%)	18 (25.7%)	
mastectomy	268 (88.4%)	216 (92.7%)	52 (74.3%)	0.00002
– second breast cancer				
BCS	90 (29.7%)	60 (25.8%)	30 (42.9%)	
mastectomy	213 (70.3%)	173 (74.3%)	40 (57.1%)	0.00602
Radiotherapy				
none	133 (44.3%)	104 (44.6%)	29 (41.4%)	
unilateral	106 (35%)	86 (36.9%)	20 (28.6%)	0.10063
bilateral	64 (21.1%)	43 (18.5%)	21 (30%)	
Chemotherapy	169 (55.8%)	131 (56.2%)	38 (54.3%)	0.77472
Hormone therapy	210 (69.3%)	152 (65.2%)	58 (82.9%)	0.00506
Tamoxifen	197 (65%)	140 (60.1%)	57 (81.4%)	0.00103

*m-BBC — metachronous bilateral breast cancer
**s-BBC — synchronous bilateral breast cancer

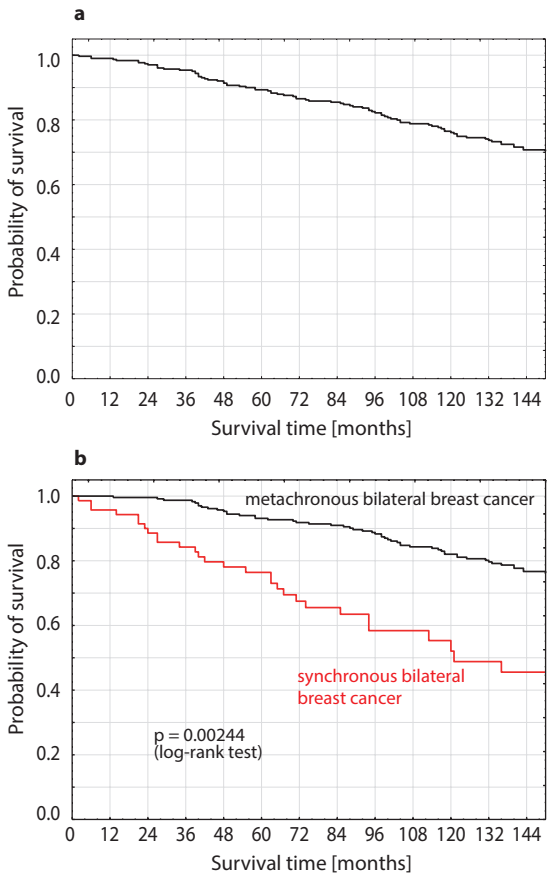

Figure 2. Probability of overall survival (**a**) in the whole group and (**b**) in depending on the type of bilateral breast cancer (metachronous vs synchronous)

The percentage of 5- and 10-year total survival in the whole group was 89.3% and 76.1%, respectively, while in relation to the analysed subgroups m-BBC and s-BBC were as follows: 93.1% and 76.4% (5-year-old) and 82% and 52.1% (10-year); these differences were statistically significant (p = 0.00244, log-rank test).

During the follow-up 47 patients (15.5%) had a relapse, which was most often located on the chest wall or in the breast (85.1%). In 78 patients (25.7%) the development of distant metastases was observed, the most frequent localization of which were bones (60.3%).

Table III summarizes the treatment failures that occurred in patients with bilateral breast cancer.

In the s-BBC subgroup, in comparison with the m-BBC, the development of distant metastases took place significantly earlier (mean time of development: 59.2 months vs 114.2 months).

Discussion

In the material presented, bilateral breast cancer (BBC) affected 1.5% of all patients with breast cancer, 23.1% of whom synchronous BBC was diagnosed and 76.9% of patients with metachronous BBC. The frequency of these types of bilateral breast cancer presented in the literature is 30–48% for s-BBC and 52–70% for m-BBC [1, 11, 13–15].

In the case of bilateral breast cancer, the two primary cancers located in both breasts may develop simultaneously or after a period of time. This development may be the result of genetic predisposition, exposure to environmental factors or the co-participation of two independent events. The development of s-BBC, which resembles unilateral breast cancer, indicates an accumulation of the effects of exposure to environmental carcinogens, while the high risk of m-BBC development in young women indicates the role of genetic predisposition [13, 14, 16].

One of the factors conducive to the development of BBC is family history of cancer [8, 12, 17–21]. In the presented material 38.7% of patients were diagnosed with cancer in the family, which significantly more often concerned patients with s-BBC than patients with m-BBC (48.5% vs 35.7%).

Other authors indicate that despite the relationship between family history of cancer and development of BBC, only 5% of patients with BBC are diagnosed with *BRCA1/BRCA2* gene mutations [8]. Moreover, there are data in the literature which do not confirm the correlation between the family history of cancer and the development of bilateral breast cancer [22, 23].

Our own observations indicate that BBC was more frequent in premenopausal patients (60.7% vs 39.3%), and after taking into account the type of BBC, s-BBC was more frequent in postmenopausal patients (55.7%), while m-BBC was more frequent in premenopausal patients (65.7%). The dependence of s-BBC on age is also confirmed by differences in mean age, which indicate that patients with s-BBC are older than those with m-BBC (60.6 years vs 51.4 years). Different observations were published by Hartman et al., who found that older women were more often diagnosed with m-BBC [12]. However, it should be noted that in the categorisation of synchronous — metachronous BBC the authors have adopted a period of 3 months.

Others, such as Intra et al. [23] and Wadasadawala et al. [20], found that s-BBC occurred in older patients after menopause and was more often associated with lobular breast cancer. Similar observations are made by the authors: lobular carcinoma was significantly more frequent in patients with s-BBC and this referred both the first (8.6% vs 6%) and the second (10% vs 8.6%) breast cancer.

Literature data indicate that s-BBC in comparison to m-BBC is characterized by worse prognosis [3, 5, 7, 12–14, 16, 20, 21, 24–30]. In the material presented by Ibrahim et al. [14], the percentage of 5-year experiences for s-BBC and m-BBC is 60% and 78.7%, respectively. The results by Vuota et al. are similar: [5]: 63.3% (s-BBC) and 94.6% (m-BBC). In the material presented by Heron et al., in turn, [7] this percentage is: 83.1% (s-BBC) and 97.8% (m-BBC). Sim et al. [21] point out that although s-BBC is a more favourable type of breast cancer in terms of prognosis (the presence of hormonal receptor expression and lack of HER-1 expression), it is nevertheless associated with significantly worse prognosis compared to m-BBC, which is explained by the existence of additional biological and genetic factors.

According to Barreta et al. [24] this is associated with a more frequent lack of hormonal receptor expression in patients with s-BBC, which is a recognized negative prognostic factor. Moreover, the authors point out that the change of receptor status (from the presence of expression to the lack of expression) in the case of m-BBC is an independent predictive factor [24].

Our own results confirm that s-BBC, compared to m-BBC, is associated with worse prognosis. The percentage of 5-year

Table III. Treatment failures in patients with bilateral breast cancer (BBC)

Factor	Whole group	m-BBC*	s-BBC**	p
	n = 303	n = 233	n = 70	
Relapse	47 (15.5%)	38 (16.3%)	9 (12.9%)	0.48419
Average development time (months)	47.9	49.1	42.8	0.76582
Location:				
chest wall/breast	40 (85.1%)	32 (82.1%)	8 (88.9%)	
lymph nodes	5 (10.6%)	4 (10.3%)	1 (11.1%)	0.69127
chest wall/breast + lymph nodes	2 (4.3%)	2 (5.1%)	–	
Distant metastases	78 (25.7%)	56 (24%)	22 (31.4%)	0.21468
Average development time (months)	98.7	114.2	59.2	0.00001
Location:				
bones	47 (60.3%)	33 (58.9%)	14 (63.6%)	
lymph nodes	14 (17.9%)	12 (21.4%)	2 (9.1%)	
lungs	12 (15.4%)	9 (16.1%)	3 (13.6%)	0.58033
liver	12 (15.4%)	6 (10.7%)	6 (27.3%)	
brain	11 (14.1%)	9 (16.1%)	2 (9.1%)	
skin	1 (1.3%)	1 (1.8%)	–	
peritoneum	1 (1.3%)	1 (1.8%)	–	
Other cancer	33 (10.9%)	28 (12%)	5 (7%)	0.25099
Average development time (months)	133.7	151.4	34.4	0.00008

*m-BBC — metachronous bilateral breast cancer
**s-BBC — synchronous bilateral breast cancer

survival was: 76.4% vs 93.1% respectively. Moreover, the development of distant metastases was observed in patients with s-BBC significantly earlier than in patients with m-BBC.

Summary

Our own observations and literature data indicate that although bilateral breast cancer is relatively rare, given the incidence of breast cancer and the associated risk of developing breast cancer in the other breast, it should be borne in mind and taken into account during diagnostics and post-treatment follow-up. Diagnosis of synchronous bilateral breast cancer is a prognostic factor influencing the deterioration of prognosis in breast cancer patients, whereas the occurrence of long-term risk of metachronistic development of bilateral breast cancer indicates the need for careful clinical follow-up and the role of mammographic screening in patients with diagnosed breast cancer.

Conflict of interest: none declared

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