

Metachronous bilateral breast cancer – a comparison of clinical and histopathological features of the first and of the second primary cancer

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Introduction. Bilateral breast cancer (BBC) is recognised in patients, who develop two primary tumors in both breasts. Cancer metastases to the contralateral breast are not considered as BBC. BBC may be diagnosed as a synchronous or a metachronous disease.

This study compares clinical and histopathological features of the first and the second BBC.

Material and methods. 3646 women with breast cancer were operated upon at the Department of Surgical Oncology, Medical University of Łódź, between 1977 and 1998. BBC was recognised in 139 of them (3.81%), of which 99 (2.71%) were metachronous (MBBC) – i.e. the interval between two diagnoses was at least six months. The final analysis was performed on a group of 74 women with MBBC. The remaining 25 women were excluded from the study due to incomplete data concerning the first cancer.

Results. The interval between the diagnosis of the first and of the second cancer ranged from 7 to 293 months (mean 70.7 months). The mean duration of the symptoms before the diagnosis of the first MBBC (fMBBC) was significantly longer than before the diagnosis of the second MBBC (sMBBC) (5.8 months fMBBC vs 3.0 months sMBBC; $p < 0.05$). The mean diameter of the first tumor (fMBBC) was significantly larger, than that of the second (sMBBC) (4.8 cm fMBBC vs 3.1 cm sMBBC; $p < 0.05$). Local stage (T) of fMBBC was higher than local stage of sMBBC ($p < 0.05$). Regional stage of both cancers (acc. to the clinical TNM scale) was similar. In 28 of the 74 patients (37.8%) the histological type of the first cancer was different from that of the second. In the remaining 46 patients (62.2%) the histologic types of both cancers were the same. There were no in situ cancers among sMBBC. The percentage of fMBBC and sMBBC cases with lymph nodes metastases was the same (43.2%).

Conclusions. (1) In patients with MBBC the second cancers were significantly smaller than the first. The duration of symptoms before the diagnosis of the second cancer was shorter. However, axillary lymph nodes metastases were found in the same percentage of cases of fMBBC and sMBBC. (2) Our observations confirm that routine mammographic screening of contralateral breast in women with diagnosed unilateral breast cancer is of crucial importance. Contralateral mammography should be performed every 12-18 months after breast cancer surgery throughout the patients' life.

Dwuczasy obustronny rak piersi – porównanie cech klinicznych i patologicznych pierwszego i drugiego raka

Wprowadzenie. Obustronny rak piersi (ORP) jest rozpoznawany u kobiet, u których rozwinęły się dwa pierwotne raki w obu piersiach. Przerzuty raka występującego jednostronnie do drugiej piersi nie są uznawane za ORP. ORP może ujawnić się w postaci choroby jednoczasowej lub dwuczasyowej.

Cel. Porównanie cech klinicznych i histopatologicznych pierwszego i drugiego ORP.

Materiał i metody. W latach 1977-1998 w Klinice Chirurgii Onkologicznej Akademii Medycznej w Łodzi operowano 3646 kobiet z powodu raka piersi. U 139 z nich (3,81%) rozpoznano obustronny raka piersi. U 99 (2,71%) choroba miała postać dwuczasyową, to znaczy drugiego raka rozpoznano po upływie co najmniej 6 miesięcy od rozpoznania pierwszego raka. Dane kliniczne i histopatologiczne na temat pierwszego i drugiego raka uzyskano z historii chorób Regionalnego

List of abbreviations:

BBC – bilateral breast cancer

SBBC – synchronous bilateral breast cancer

MBBC – metachronous bilateral breast cancer

fMBBC – first metachronous bilateral breast cancer

sMBBC – second metachronous bilateral breast cancer

Ośrodka Onkologicznego. Badaniami objęto ostatecznie 74 kobiety, które oba zabiegi operacyjne miały wykonane w Klinice. Pozostałe 25 kobiet wyłączone z badań z powodu niepełnej dokumentacji dotyczącej pierwszego raka.

Wyniki. Odstęp czasowy między wystąpieniem pierwszego i drugiego raka wahał się od 7 do 293 miesięcy; średnio 70,7 miesiąca. Średni czas trwania objawów chorobowych przed rozpoznaniem pierwszego dwuczaskowego obustronnego raka piersi (pDORP) była znacząco dłuższa od średniego czasu trwania objawów przed rozpoznaniem drugiego dwuczaskowego obustronnego raka piersi (dDORP) (5,8 miesiąca pDORP w porównaniu do 3,0 miesięcy dDORP; $p < 0,05$). Średnia średnica pierwszego raka (pDORP) była znacząco większa niż średnia średnica drugiego raka (dDORP) (4,8 cm pDORP w porównaniu do 3,1 cm dDORP; $p < 0,05$). Stan zaawansowania regionalnego (w skali TNM) obu raków był podobny. U 28 spośród 74 chorych (37,8%) typ histologiczny pierwszego raka różnił się od typu drugiego raka. U pozostałych 46 chorych (62,2%) typ histologiczny obu raków był taki sam. Wśród dDORP nie stwierdzono żadnego raka *in situ*. Przerzuty do węzłów chłonnych rozpoznano u takiego samego odsetka chorych na pDORP, jak i dDORP (43,2%).

Wnioski. 1. Raki drugiej piersi u kobiet chorych na dwuczaskowego obustronnego raka piersi były znacząco mniejsze niż pierwsze raki. Czas trwania objawów chorobowych przed rozpoznaniem drugiego raka był krótszy niż przed rozpoznaniem pierwszego raka. Mimo to, przerzuty w pachowych węzłach chłonnych stwierdzono u takiego samego odsetka chorych przy rozpoznaniu pierwszego raka, jak i przy rozpoznaniu drugiego raka. 2. Nasze obserwacje potwierdziły, iż rutynowe wykonywanie mammografii drugiej piersi u kobiet chorych na jednostronnego raka piersi ma znaczenie podstawowe. W ramach pooperalcyjnych badań kontrolnych kobiet chorych na raka piersi, mammografię drugiej piersi powinno się wykonywać co 12-18 miesięcy przez całe życie chorych.

Key words: metachronous, bilateral, breast cancer

Słowa kluczowe: dwuczaskowy, obustronny, rak piersi

Introduction

Breast cancer is the most common malignancy in women in developed countries [1]. It may develop as a unilateral or a bilateral disease. Bilateral breast cancer (BBC) is recognised in women, in whom two primary tumors are diagnosed in both breasts. Cancer metastases to the contralateral breast are not classified as BBC. The first case of bilateral breast cancer was reported as early as in 1800 by William Nisbet [3]. The revolution in breast cancer therapy occurred almost one hundred years later, when in 1882 Halsted resected a cancerous breast *en block* with both pectoral muscles and axillary lymph nodes [4]. This led to a significant increase of survival – in the 1920s five-year survival reached 30%. However a number of survivors developed new primary cancer in the contralateral breast. The first major paper on bilateral breast cancer was published in 1921 [5].

Bilateral breast cancer may be diagnosed as a synchronous or a metachronous disease. Synchronous BBC is recognised when the second, contralateral tumor is not found later than six months after the diagnosis of the first cancer. Metachronous cancer is diagnosed when the period between the diagnosis of the first and the second cancer exceeds 6 months [6-9]. It should be noted that these terms are not biological, but purely clinical, while the classification bases only upon the time interval between the diagnoses of the first and the second cancer. As the natural history of breast cancer may exceed 10 years before the tumour reaches the volume of 1 cm³ [10], one should be aware that clinically metachronous cancers may, in fact, be biologically synchronous. The development of imaging techniques, especially the introduction of routine contralateral mammography in the 1980s, increased the incidence of metachronous BBC 5-fold [11].

The diagnosis of a malignant tumor in the breast of a patient previously treated for cancer of the contralateral breast raises a fundamental question: is the diagnosed lesion a new primary cancer, or is it a metastatic tumor from the contralateral breast? The answer is crucial, as it implies the type of treatment to be introduced. Clinical and pathological criteria for diagnosing second primary cancer that have been outlined by Robbins and Berg (1964) [12], Haagensen (1971) [13] and Chaudary (1984) [11] are important. When combined and considered, they are a useful clinical tool, and allow for the correct selection of women with two primary cancers in both breasts. These criteria may be presented as follows: (1) due to a typical spread of cancer across the midline to the second breast, it can well be expected that metastatic lesions are predominantly located in the inner quadrants of the contralateral breast. (2) metastatic lesions are usually multiple. Generally, the second primary cancers are solitary. (3) when cancer spreads to the second breast distant metastases are usually present. They are usually absent if the tumor in the contralateral breast is a new primary cancer. (4) the typical location of metastatic tumors is in the fat surrounding the breast parenchyma. New primaries are located within the parenchyma. (5) New cancers infiltrate the surrounding tissues; metastases expand them. (6) The tumour in the second breast is a new primary cancer if carcinoma *in situ* is discerned. (7) The tumor of the contralateral breast is a new primary if its histologic type is different from that of the first breast cancer. (8) The cancer in the second breast is to be considered a new primary if its degree of histological differentiation is distinctly greater than that of the lesion in the first breast. (9) If these criteria are not met, the second tumor can be considered the new primary provided there is no evidence of local, regional or distant metastases from the cancer of the ipsilateral breast.

Our study material was qualified according to these criteria

Aim of the study

To compare the clinical and pathologic features of the first and the second cancer in women with metachronous bilateral breast cancer.

Material and methods

Between 1977 and 1998 3646 women underwent surgical treatment for breast cancer at the Clinical Department of Surgical Oncology of the Medical University of Łódź. Bilateral breast cancer was diagnosed in 139 cases (3.81%). In 99 cases (2.71%) the disease was metachronous, i.e. the second cancer was not diagnosed earlier than six months after the first. Clinical and histologic data concerning both breasts was obtained from the patients' files at the Regional Oncologic Center. Data analysis comprised: (1) the age at the diagnosis of the first and the second breast cancer; (2) the duration of symptoms; (3) the interval between the diagnosis of each lesion of the pair; (4) the clinical features of the tumours (diameter, TNM-staging, location); (5) the pathology of the tumors (histologic type, grade, multicentricity, nodal status). A retrospective review of the files provided complete clinical and pathological data of 74 women. The remaining 25 women with metachronous BBC underwent initial surgery outside our Department and, unfortunately, the data concerning the first tumour was incomplete. These 25 patients were excluded from further study. Statistical analysis was performed using the Student t test and χ^2 test; p values less than 0.05 were considered to be significant.

Results

The age of the patients, duration of symptoms before diagnosis, location, size and stage (TNM) of the first and the second cancers are presented in Table I. Pathological features of the tumours are listed in Table II. Data concerning diagnostic and surgical procedures is presented in Table III.

The time interval between the diagnosis of the first and the second cancer ranged between 7 and 293 months (mean 70.7 months (SD 60.1; median 49.5)). (Fig. 1) The mean duration of symptoms before the diagnosis of the first MBBC (fMBBC) was significantly longer than before the diagnosis of the second MBBC (sMBBC) (5.8 months fMBBC vs 3.0 months sMBBC; $p < 0.05$). The mean diameter of the first tumor was significantly greater than the mean diameter of the second tumor (4.8 cm fMBBC vs 3.1 cm sMBBC; $p < 0.05$). There were no significant differences in the location of the first and the second tumors (side, quadrants). The local stage (T) of fMBBC was higher than the local stage of sMBBC. The difference was statistically significant. The regional stage of the cancers (according to the TNM scale) was similar.

The results of cytological examination revealed the presence of cancer cells in a similar percentage of cases in both groups. Suspected cells were found in a higher percentage of cytology specimens obtained from patients

Tab. I. First and second metachronous bilateral breast cancer – clinical data

	fMBBC	sMBBC
Age (years)	49.3±12.1	55.0±11.6
Duration of symptoms (months)	5.8±8.2	3.0±2.7
Localization of cancer on side: (%)		
- left	35 (47.3)	39 (52.7)
- right	39 (52.7)	35 (47.3)
Localization of cancer in quadrant (%)		
- upper-outer	25 (33.8)	23 (31.1)
- upper quadrants' border	11 (14.9)	14 (18.9)
- central	10 (13.5)	10 (13.5)
- outer quadrants' border	10 (13.5)	13 (17.6)
- upper-inner	5 (6.8)	4 (5.5)
- lower quadrants' border	5 (6.8)	6 (8.1)
- lower-outer	4 (5.4)	1 (1.3)
- lower-inner	3 (4.0)	2 (2.7)
- inner quadrants' border	1 (1.3)	1 (1.3)
Tumor's diameter (cm)	4.8±2.5	3.1±1.5
Stage of primary tumor classified clinically – T (%)		
- T0	0 (0)	3 (4.1)
- T1	8 (10.8)	16 (21.6)
- T2	35 (47.3)	45 (60.8)
- T3	17 (23.0)	4 (5.4)
- T4	14 (18.9)	6 (8.1)
Stage of regional lymph nodes (clinically) – N (%)		
- N0	35 (47.3)	44 (59.5)
- N1	30 (40.5)	24 (32.4)
- N2	9 (12.2)	6 (8.1)

Data are presented as: mean value ± standard deviation; number of patients (percentage). fMBBC means: first metachronous bilateral breast cancer; sMBBC means: second metachronous bilateral breast cancer

Tab. II. First and second metachronous bilateral breast cancer – results of pathologic examination

	fMBBC	sMBBC
Type of cancer (%)		
- ductal invasive	62 (83.8)	54 (73.0)
Grade 1 – Bloom and Richardson scale	3 (4.1)	4 (5.4)
Grade 2 – Bloom and Richardson scale	16 (21.6)	10 (13.5)
Grade 3 – Bloom and Richardson scale	24 (32.4)	31 (41.9)
Grade was not evaluated due to damage of cancer cells after chemotherapy	14 (18.9)	2 (2.7)
- lobular invasive	8 (10.8)	20 (27.0)
- ductal cancer in situ	2 (2.7)	0 (0)
- lobular cancer in situ	0 (0)	0 (0)
- mixed type	2 (2.7)	0 (0)
Mean number of cancer-positive axillary lymph nodes	2.1±4.1	1.9±3.9
Metastases in axillary lymph nodes (%)	32 (43.2)	32 (43.2)
Infiltration of node's capsule (%)	10 (13.5)	17 (23.0)
Emboli of cancer cells (%)	8 (10.8)	9 (12.1)
Multifocality/multicentricity (%)	7 (9.5)	5 (6.8)

Data are presented as: mean value ± standard deviation; number of patients (percentage). fMBBC means: first metachronous bilateral breast cancer; sMBBC means: second metachronous bilateral breast cancer

Tab. III. Diagnostic procedures, adjuvant therapy and type of surgery in patients with first and second metachronous bilateral breast cancer

	fMBBC	sMBBC
Results of cytological examination (%)		
- cancer cells	63 (85.1)	60 (81.1)
- suspected cells	6 (8.1)	13 (17.6)
- normal cells	5 (6.8)	1 (1.3)
Frozen section examination	11 (14.9)	14 (18.9)
Preoperative chemotherapy	18 (24.3)	4 (5.4)
Type of surgery		
- modified radical mastectomy – Madden type	69 (93.3)	71 (96.0)
- radical mastectomy – Halsted type	1 (1.3)	0 (0)
- quadrantectomy	2 (2.7)	1 (1.3)
- total (simple) mastectomy	2 (2.7)	2 (2.7)
Mean number of removed lymph nodes	10.0±4.6	11.1±4.1

Data are presented as: mean value ± standard deviation; number of patients (percentage). fMBBC means: first metachronous bilateral breast cancer; sMBBC means: second metachronous bilateral breast cancer

with sMBBC than from patients with fMBBC (fMBBC 8.1% vs sMBBC 17.6%; $p < 0.05$). The examined cells were considered normal in a significantly higher percentage of fMBBC specimens, than sMBBC specimens (fMBBC 6.8% vs sMBBC 1.3%; $p < 0.05$).

Preoperative chemotherapy was given in a higher percentage of the first MBBC than of the second MBBC (fMBBC 24.3% vs sMBBC 5.4%; $p < 0.05$). Frozen section examination was performed in a similar percentage of cancers. Surgical treatment was similar in both cancers.

The percentages of invasive ductal, lobular *in situ* and ductal in situ cancers were similar both groups. Invasive lobular cancer was more rare among the first MBBC than among the second MBBC patients (I MBBC 10.8% vs II MBBC 27.0%; $p < 0.05$).

The grade of invasive cancers was not compared between the groups, as changes after chemotherapy precluded grading in a majority of cases.

In 28 of 74 patients (37.8%) the histologic type of the first cancer was different from the type of the second cancer. In the remaining 46 patients (62.2%) the histologic type of both cancers was the same. The difference between the mean number of removed lymph nodes was not significant. Similarly, there was no significant difference between the mean number of cancer-positive nodes in both groups. The percentage of the first MBBC cases with cancer-positive nodes was the same as the percentage of the second MBBC cases (43.2%). Infiltration of node capsule, cancer cells emboli and multifocality/multicentricity was observed in a similar percentage of patients in both groups ($p > 0.05$).

Discussion

The analysis of our material revealed 139 cases (3.81%) of bilateral breast cancer. In 40 of these cases (1.1%) contralateral cancer was found synchronously with the first cancer (SBBC), i.e. the diagnosis of both cancers was made simultaneously, or the second cancer was not diagnosed later than 6 months after the first one. In the remaining 99 cases (2.71%) metachronous bilateral breast cancer was recognised (MBBC). Patients with synchronous BBC comprised 29.6% and patients with metachronous BBC 70.4% of all BBC patients.

Literature reports varying results. The percentage of BBC patients ranges, among all breast cancer patients, between 2.4% and 20% [8, 14-26]. This percentage depends mainly on the duration of the follow-up after surgery. The longer this period, the higher the number of contralateral cancers may develop in the studied population of unilateral breast cancer patients. The proportion of metachronous cancers to synchronous cancers also changes: the shorter the follow-up period, the higher the percentage of metachronous cancers [27]. Synchronous BBC is recognised in 0.3-3% of patients with breast cancer [6-8, 11, 14, 15, 19, 20, 28-31]; metachronous BBC is recognised in 2.6%-11.8% of breast cancer patients [8, 14, 15, 17, 22]. The presented incidence of BBC cancers was observed in patients in whom contralateral cancers were detected mammographically or during physical examination. In patients in whom contralateral breast biopsies or prophylactic contralateral mastectomies were performed, the incidence of synchronous BBC detected in histopathologic examination, was even as high as 50% [32-40]. However, the majority of such contralateral neoplasms are ductal *in situ* or lobular *in situ* cancers. Invasive cancers do not exceed 7.7% of all synchronous BBC [32-40]. The percentage of contralateral cancers found in patients after prophylactic mastectomies and in some autopsy studies [41], substantially exceeds the incidence found in clinical studies [42]. It seems that at least some contralateral cancers regress or, during a patient's lifetime, do not reach sizes allowing for their clinical or mammographical detection [11, 41].

The proportion of synchronous to metachronous BBC depends mainly on the type of contralateral breast

screening in patients with unilateral disease. Studies conducted before the 1980s studies comprised patients in whom mammography was practically not performed. In those studied the percentage of synchronous BBC did not exceed 15% of all BBC patients [12, 13, 25]. Routine mammographic screening of the contralateral breast, introduced in late 1970s, allowed to detect a majority of nonpalpable breast cancers. Had mammography not been performed, these contralateral cancers would have been detected clinically during the first 3 years of follow-up after the first surgery, and therefore, be pronounced as metachronous. With the introduction of mammography as a non-obligatory part of contralateral breast screening, the percentage of synchronous BBC reached 25%-30% [8, 26, 43, 44]. Nowadays, when mammography of the contralateral breast is a routine diagnostic procedure, the proportion of synchronous to metachronous BBC approaches one [9, 14, 16, 27, 45]. However, it must be stressed that although routine mammographic screening of the contralateral breast has increased the detectability of synchronous BBC, the total detectability of bilateral breast cancer has remained stable [15].

The percentage of synchronous BBC patients among all BBC patients treated in our Clinic (29.6%) is nearest to the observations of Yeatman et al. (29.3%) [44], Schell et al. (30.9%) [43] and studies performed by Senofsky et al. between 1976 and 1984 (28%) [25]. Also, Kułakowski et al. observed that synchronous BBC comprised 32.3% of all BBC patients [26]. However, in studies by Kułakowski, synchronous BBC was recognised when both cancers were diagnosed within a 3-month time interval (in our study this interval was set at 6 months).

In our study, a majority of the first metachronous BBCs were diagnosed in the fifth decade of life (40-49 y.a.). The mean age at the time of the diagnosis of the first MBBC was 49.3. The diagnosis of the second MBBC was most prevalent in the sixth decade of life (50-59 y.a.). The mean age at the diagnosis of the second MBBC was 55.0 (Fig. 2). Our observations resemble those of other authors. The mean age of patients at the time of diagnosis of the first MBBC is generally reported to be less than 50 [6, 11, 46, 47], while in the case of the second MBBC the usual age is over 50 years [46, 47].

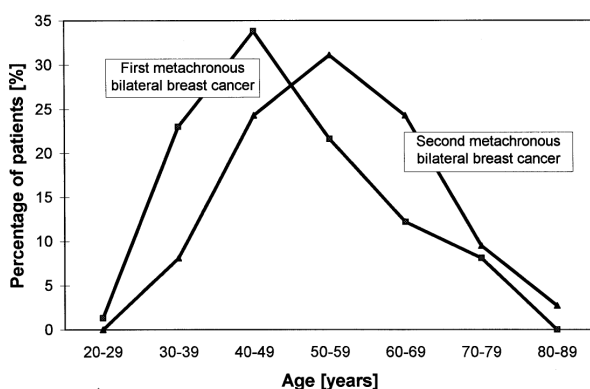


Fig. 1. Age of patients at the time of diagnosis of the first and second metachronous bilateral breast cancer

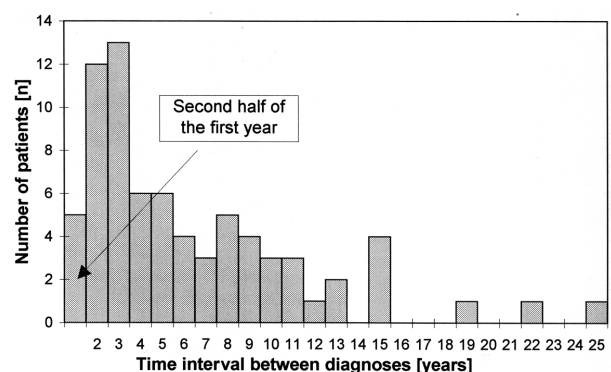


Fig. 2. Time interval between diagnoses of the first and second bilateral breast cancer

The mean interval between the diagnosis of the first and the second metachronous BBC in patients treated in our Clinic was 5 years and 11 months (70.7 months). The reported time intervals between these two diagnoses ranges between 4.5 years to 9.7 years [8, 26, 27, 46-48]. Egan et al. observed that 85% of contralateral cancers were recognised within 6 years from the diagnosis of the first cancer [46]. We have observed similar results, as 78% of contralateral cancers in our BBC patients were recognised during the first 6 years of follow-up after the first diagnosis, while the longest time interval between the two diagnoses was 26 years. In the studies of Egan et al. the longest time interval between the two diagnoses was similar, reaching 27 years [46].

In our patients we have observed a peak of incidence of the second metachronous BBC during the first three years of follow-up (Fig. 2). The morbidity caused by of contralateral cancer was twice as high during the second and third year of follow-up as during all next years of follow-up. Similar observations were reported in studies performed before 1980. Those studies had shown that the morbidity caused by contralateral cancer during the second year [17], the second and third year [12, 49], and the second, third and fourth year [30] after the diagnosis of the first cancer was twice as high, as the morbidity caused by contralateral cancer during all the next years. A majority of contralateral cancers would have been diagnosed synchronously with the first breast cancer, had mammography of the contralateral breast been performed at the time of the diagnosis of the first cancer.

We did not observe any statistically significant difference between the percentage of the first cancers located in the left or in the right breast. In a majority of cases both the tumours were located in the upper-outer quadrant and centrally in the subareolar tissue. There were no statistically significant differences between the groups concerning the anatomical location of the tumour.

The mean diameter of the first metachronous tumor was significantly larger than the mean diameter of the second tumor (4.8 cm vs 3.1 cm). Therefore, the local stage (T – in TNM scale) of the first cancer was higher, than that of the second cancer. However, locoregional stage of the first cancer was similar to that of the second cancer. In both groups the axillary lymph nodes were palpable in a similar percentage of patients. Clinical observation was confirmed by histopathology. In both groups metastases were found in an identical percentage of patients (i.e. 32/74; 43.2%).

There was no difference between the groups as to the mean number of cancer-positive lymph nodes (first metachronous BBC 2.1 vs second metachronous BBC 1.9). In conclusion, although the first tumors were larger than the second tumors, the regional stage of the first and the second BBC was the same.

Other authors report varying data concerning the stage of the first and the second metachronous cancers. Some of the authors have found that the stages of the

first and the second BBC were the same [8, 17, 50-53]. We have paid special attention to the results of Fisher et al. [17]. In their population of metachronous BBC patients, contralateral tumors were smaller than the first tumors, but the percentage of cases with metastases in axillary lymph nodes was the same in both groups. We have found that our results are closest to those of Fisher et al. Other authors have reported different results; for instance the second cancers were less advanced than the first ones [12, 14, 25, 27, 46, 48, 54]. Senofsky et al. [25] performed a comparison of two consecutive groups of patients with BBC, the main difference lying in the fact that the first group was treated a decade earlier than the second. Senofsky has reported, that the diagnosis of the second cancer at an earlier stage than the first cancer, had not been possible before the introduction of routine mammographic screening of the contralateral breast. However, the observations of Robbins and Berg published in 1964 negate such a conclusion [12] stressing that the second cancers were less advanced than the first ones, although mammography was not performed in their BBC patients. Robinson et al. [48] have shown that in patients in whom follow-up contained a thorough and regular physical examination, the second cancers were significantly smaller and metastases to axillary lymph nodes were significantly more rare than in the case of patients who did not undergo regular examination. It may, therefore, be surprising, that the survival was similar in both groups. It seems that palpation of the contralateral breast is not sufficient as a follow-up procedure in order to decrease the mortality in patients with metachronous BBC. Introducing mammography into routine practice has decreased the mortality of patients with unilateral breast cancer. It is suggested that mammography screening of the contralateral breast of breast cancer patients will decrease the mortality of women with metachronous BBC [48].

The stages of the first and the second BBC corresponded with the duration of symptoms before diagnosis. The mean duration of symptoms in patients with the first metachronous cancer was 5.8 months. Contralateral cancers were diagnosed earlier. The mean duration of symptoms was 3.0 months. It seems that women treated for unilateral breast cancer were more aware of the symptoms of the disease. Moreover, some contralateral cancers were diagnosed during follow-up examinations.

In our patients contralateral cancers were smaller than the first cancers and the symptoms lasted shorter before the diagnosis of contralateral cancers. However, the regional stage of both cancers was the same. Our observations confirm that regular mammographic follow-up performed every 12-18 months is necessary for earlier diagnosis of contralateral breast cancer in women with unilateral cancers

The number of patients with the second metachronous BBC who had received preoperative chemotherapy (5.4%) was lower than the number of chemotherapy patients with the first cancer (24.3%). It may be presumed that the reasons for this were: (1) the second tumors were significantly smaller than the first tumors; consequen-

tly chemotherapy was not necessary as often as before the first surgery; (2) many patients had already been given chemotherapy before or after the first surgery. The mode of surgical treatment of the first and contralateral cancers was similar (difference of no statistical significance).

Cytological examination results revealed the presence of cancer cells in a similar percentage of cases in both groups (the first MBBC – 85.1%; second MBBC – 81.1%). Consequently, in a similar percentage of patients, the diagnosis of cancer was made during frozen section examination following wide local resection of the suspected tumor (first MBBC 14.9%; second MBBC 18.9%). It may be worth stressing that suspected cells were found in higher percentage of cytology specimens of patients with second MBBC than patients with the first MBBC (first MBBC 8.1%; second MBBC 17.6%). It is likely that cytologists were aware of elevated risk of contralateral cancer in women previously treated for unilateral disease, and, therefore, cells were referred to as suspected even if only slight abnormalities were observed.

In 37.8% of our patients with metachronous bilateral breast cancer, the histologic type of the first and the second cancers differed. A similar percentage was reported by Gogas et al. – 37.2% [8]. Lesser values were observed by Khafagy et al. (25%) [52].

The percentage of invasive lobular cancers among the first metachronous BBC in our patients (10.8%) is similar to that reported in literature (7.6%-8.5%) [52, 55]. Khafagy et al. [52] have observed that the percentage of lobular cancers among the second metachronous BBC (13.4%) is higher than among the first cancers (8.5%). This correlates with our results. However, in our patients the percentage of invasive lobular cancers among the second MBBC is surprisingly high. It was also surprising that not once did we find lobular *in situ* cancers. Neither did we find intraductal cancers among the second metachronous cancers (0%). Some authors have reported that when physical examination is used, intraductal cancers comprise 4-5% of all the second metachronous BBC [7, 56], while if mammography is also used in some cases, this percentage increases to about 20% [57]. Routine contralateral screening allows for further increase of this value. Roubidoux et al. [57] have found that intraductal cancers comprise 41% of all contralateral metachronous cancers. Among all contralateral metachronous BBC detected by mammography, *in situ* cancers comprised 56%. These facts strongly indicate that the follow-up of our patients with unilateral cancer was not sufficient.

Conclusions

1. Second cancers of the breast in women with metachronous bilateral breast cancer were significantly smaller than the first ones. The duration of symptoms before the diagnosis of the second cancer was shorter than before the diagnosis of the first ones. Nevertheless, metastases in axillary lymph nodes were found in the

same percentage of women with the first breast cancer as women with the second breast cancer.

2. Our observations confirm that routine mammographic screening of the contralateral breast in women with diagnosed unilateral breast cancer is of crucial importance. Patients treated for breast cancer should undergo contralateral mammography every 12-18 months throughout their life.

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