Bilateral breast cancer

J. Skowronek[1], T. Piotrowski[2]

[1]*Department of Radiotherapy,* [2]*Department of Medical Physics, Greatpoland Cancer Center, 61-866 Poznan, Poland, e-mail: janusko@priv6.onet.pl*

Received June 25, 2001

The aim of this study was to evaluate the clinical and pathological features of breast cancer patients with bilateral breast cancer and to assess the impact of the second breast cancer on their prognosis.

Thirty six breast cancer patients with bilateral (metasynchronous) cancer were treated in Greatpoland Cancer Center from 1983 to 1995. It constituted 4.1% of all breast cancer patients treated in those years. 5-year survival rates were compared with clinical data (age, clinical stage, histological diagnosis), methods of treatment and length of interval between occurring of both tumors.

Five year survival of patients treated for second breast cancer was 55.6% (20/36), disease-free survived – 15/36 (41.7%). 5-year survival rate was greater in group of patients with clinical stage T1 or T2 (69.6%, 16/23) than in group with T3 or T4 (30.8%, 4/13) (p=0.009). In group of 20 patients without nodal involvement (N0) 5 years survived 75.0% of patients (15/20), in group with N1 – 11.1% (1/9) (p=0.01). Length of interval between both breast tumors influenced 5-year survival rate. In group of patients with interval longer than 5 years, 5-year survival rate was 73.9% (17/23), in group of patients with interval shorter than 2 years – 0% (0/6) (p=0.002). No correlations were observed between survival rate and age, histological diagnosis, methods of treatment.

Key words: Bilateral breast cancer, metachronous breast cancer.

Second primary breast cancer occurs in contralateral breast in 1.4% to 12% of all breast cancer patients [19, 33]. Risk of incidence after previous treatment due to breast cancer is estimated from 0.5 to 0.8% yearly and is several times greater than in healthy population [23, 39]. Familiar breast cancer is also an important risk factor for second breast cancer [2, 29, 31]. Higher incidence of second breast cancer was observed in families where breast cancer occurred in first-degree relatives [7, 37].

Some factors have an influence on rising incidence of second breast cancer. First, an increase in overall survival and longer free survival times from the first breast cancer can lead to a rise in the incidence of second cancer. The most common second cancer for breast cancer patients is second breast cancer [17, 25, 26]. Second, more tumors are detected in earlier stages due to better mammographic equipment and more accurate patients care. Other risk factors include nulliparity, younger age at first breast cancer, lobular cancer, coexistence with carcinoma *in situ* and multicentricity of first breast cancer [3, 4, 14, 19].

Prognosis for patients with second breast cancer is worse than for patients with unilateral breast cancer. Prognosis is probably dependent on clinical stage in time of recognition and on length of time between both cancers.

We have analyzed the outcome of bilateral breast cancer patients in comparison with chosen clinical factors.

Material and methods

Thirty-six patients with contralateral breast cancer were treated in Greatpoland Cancer Center between January 1983 and December 1995, what represents 4.1% (36/878) of all breast cancer patients treated in this period.

Median age of patients with primary breast cancer was 46.2 years, that of patients with second breast cancer 52.4 years. Median time between both tumors was 69.4 months, in 23/36 cases (63.9%) was longer than 5 years. Most of patients had the second cancer in clinical stage T2 (n = 17) and T3 or T4 (n = 13) and stage N0 (n = 20). In one case

clinical stage was T2N1M1 due to metastasis in supraclavicular lymph nodes. Histologically they were diagnosed as: solid cancer (n = 14), ductal invasive cancer (n=11), tubular cancer (n = 5), lobular invasive cancer (n = 2).

Patients with primary breast cancer were treated in all cases by mastectomy and, in majority of cases by radiotherapy and/or chemotherapy. They underwent second mastectomy with the exception of two cases with advanced stage. After surgical treatment patients were treated by radiotherapy (in 6 cases) with fraction dose 200 cGy up to total dose 5000 cGy (n = 6). In two inoperable cases whole breast was irradiated up to 5000 cGy.

Chemotherapy was used in 11 cases, usually after mastectomy; CMF schema (6 cycles) or FAC schema were used. In 15 cases hormonotherapy with tamoxifen was used (20 mg daily).

5-year survival rate was compared with clinical data (age, clinical stage, histological diagnosis), methods of treatment and length of interval between occuring of both tumors.

Median follow-up was 74 months (6–134).

Statistical analysis was performed using F. Cox test. Survival rates were analyzed using Kaplan-Meier method.

Results

Out of 36 patients treated for second breast cancer 20 survived 5 years (55.6%), disease free 5 years survived 15 patients (41.7%). Histology did not influence survival rates. Prognosis according to TNM staging was analyzed (Tab. 1). In group of patients with T1 all patients (n = 6) survived 5 years, with T2 tumor 5 years survived 58.8% (10/17), with T3 tumor – 25.0% (2/8) and with T4 tumor – 40.0% (2/5). Statistically important difference was observed between patients with T1 or 2 and T3 or 4 (p = 0.009) (Fig. 1).

In the group of 20 patients without nodal involvement (N0) 5 years survived 75.0% patients (15/20), in the group with N1 – 11.1% (1/9), in the group with N2 – 57.1% (4/7). Difference was noted between N0 and N1 group (p = 0.01) (Fig. 2).

Correlation between clinical stage (AJCC classification) and survival rate didn't show any important differences probably due to the small group of examined patients (p = 0.08).

Median age at the time of second breast cancer diagnosis was compared with length of survival. No significant correlation was found (p = 0.38).

Difference in 5-year survival rate was observed when comparing the length of time interval between both breast cancers (Tab. 2). In the group of patients where interval between cancers was longer then 5 years, 5-year survival rate after the end of treatment(of the second cancer) was 73.9% (17/23), in the group of patients with interval shorter than 2 years – 0% (0/6), in the group of patients with interval between 2 and 5 years – 42.9% (3/7). Statistically significant difference was noted between first and second group (p = 0.002) (Fig. 3).

Correlations between 5-year survival rate after the end of treatment of second breast cancer and methods of treat-

Table 1. Clinical stage of second breast cancer and survival rates

Clinical stage according to TNM	N=	<5 years	≥5 years	
			Total	Free of symptoms
T1N0	5	–	5	5
T1N1	1	–	1	1
T2N0 10	–	–	10	8
T2N1	6	6	–	–
T2N1M1	1	1	–	–
T3N0	5	5	–	–
T3N1	1	1	–	–
T3N2	2	–	2	1
T4N2	5	3	2	–

Table 2. Length of interval between both breast cancers and 5-years survival rates

Lenght of interval (month)	N=	<5 years	≥5 years	
			Total	Free of symptoms
<12	–	–	–	–
12–24	6	6	–	–
25–36	3	1	2	1
37–48	2	2	–	–
49–60	2	1	1	1
>60	23	6	17	13
Total	36	16 (44.4%)	20 (55.6%)	15 (41.7%)

Table 3. Features helping in differentiating between second primary breast cancer and metastasis to contralateral breast

Second primary breast cancer	Metastasis to contralateral breast
1. Median time of occuring – 5 years after first primary	1. Median time ofoccuring – 2 years after first primary
2. Lose of metastasis (excluding regional lymph nodes)	2. Presence of other metastasis, sometimes local recurrence
3. Single lesion in breast	3. Multiple lesions in breast (localized in glandular tissue or adipose tissue)
4. Simultaneously carcinoma *in situ*	4. Infiltration in tissue destroying architecture of breast
5. Frequency – about 1%	5. Frequency – about 5%
6. Histology may differ between both breasts	6. Histology usually similar or the same like in another breast

In: Jacek Jassem (ed.) : Rak sutka. Podrecznik dla studentów i lekarzy. Springer PWN, Warszawa 1998, 78.

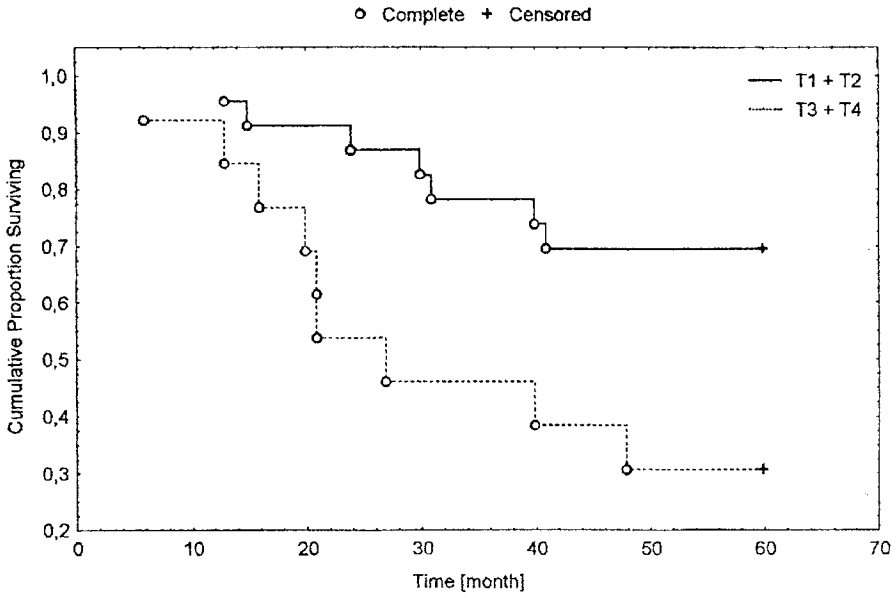

Figure 1. Cumulative proportion surviving (Kaplan-Meier) for summed groups T1 and T2 and summed groups T3 and T4. F Cox test (p=0.009).

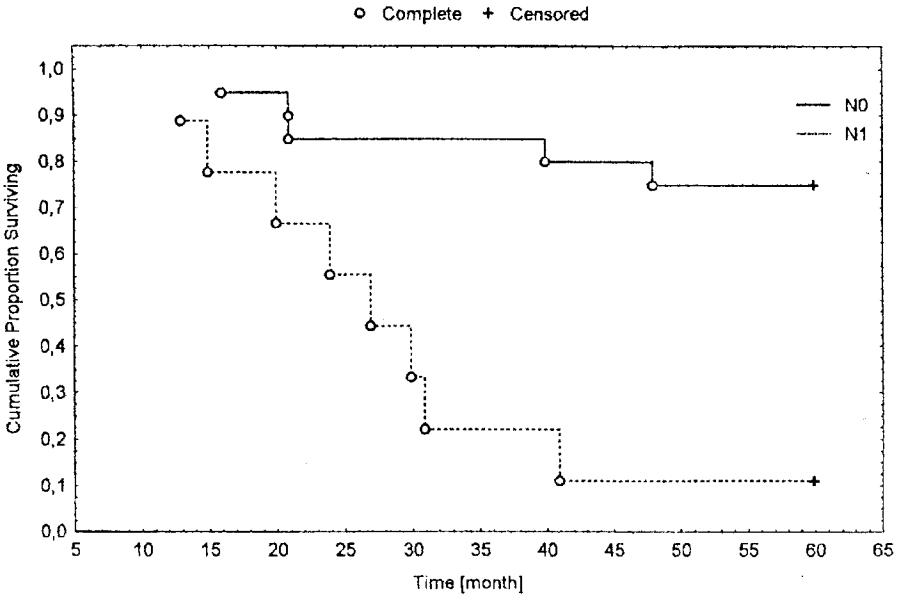

Figure 2. Cumulative proportion surviving (Kaplan-Meier) for group N0 and N1. F Cox test (p = 0.002).

ment were analyzed. Patients were divided into three groups. First group contained 17 patients treated surgically only (mastectomy) – 5-year survival rate in this group was 52.9% (9/17). Second group contained 6 patients treated surgically and then irradiated – 5-year survival rate was 33.3% (2/6). Third group contained 11 patients treated surgically and then with chemotherapy – 5-year survival rate in this group was 81.8% (9/11). Two patients disqualified for mastectomy survived, respectively 30 and 41 months. Differences between all analyzed groups were statistically not significant (p = 0.18).

Discussion

Bilateral breast cancer represents relatively small proportion of all breast cancer cases. According to different authors it has a cumulative incidence of 1.4% to 12% in patients with primary operable breast cancer [1, 13, 24, 27]. Second primary breast cancer in the opposite breast can be either synchronous or metachronous, the majority are metachronous. The incidence of synchronous bilateral cancer (both cancers diagnosed within six months) is approximately 1% to 2% and of metachronous cancer 5% to 10% [10, 11]. The incidence of bilateral breast cancer is expected to rise as a direct result of improved detection capabilities and longer survival times [21, 34].

The risk of developing a contralateral breast cancer is influenced by the age of the patient, the presence of *in situ* disease, lobular histology of this new lesion, multicentricity, exposure to certain types ionizing irradiation, and of family history of breast cancer [8, 11, 12, 13, 16]. Genetic background in the majority of cases of bilateral breast cancer coud not be proved [9].

It is important for clinician to differentiate between second primary breast cancer and metastases from primary breast lesion. In the first case patient should be treated radically, in the second in most of cases – palliatively only.

In the Table 3 histopathological criteria which could help to differentiate between second cancer and metastasis are presented. In case of doubts without signs of disseminated disease, tumor in second breast should be concerned as second primary.

Early detection remains the cornerstone of effective breast cancer treatment. Optimal treatment remains controversial.

Treatment of second breast cancer is similar to treatment

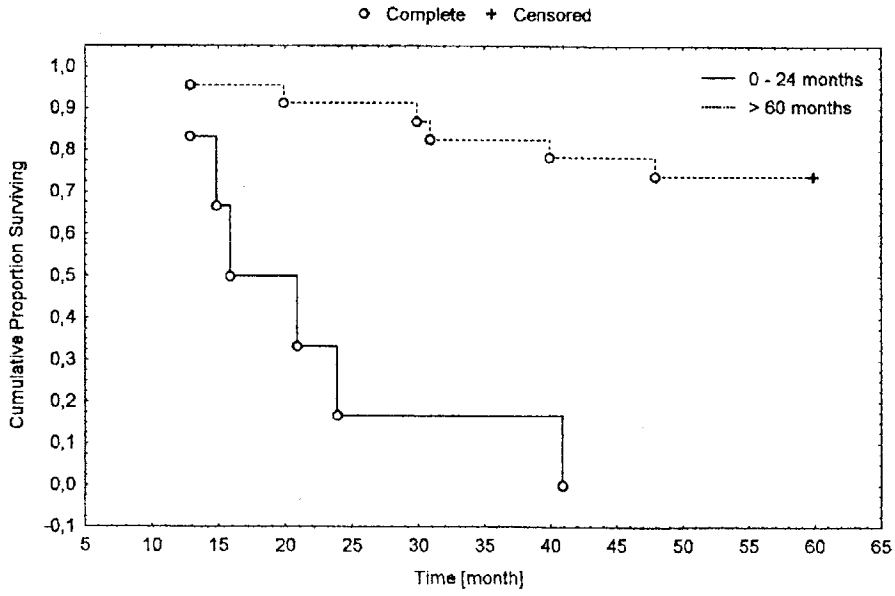

Figure 3. Cumulative proportion surviving (Kaplan-Meier) for group of patients with interval between cancers longer then 5 years (60 months) and 2 years (24 months). F Cox test (p = 0.0006).

of first tumor. Treatment should be appropriate for the stage of disease. Relatively rare tumorectomy or quadrantectomy is used because of preceding radiotherapy and worse prognosis in this group. Some authors [10, 15, 18, 38] are of the opinion that bilateral conservative treatment is feasible with acceptable cosmetic results and toxicity by using carefully designed radiotherapy techniques. Indications for complementary systemic treatment or radiotherapy are the same in first and second breast cancer [8, 19].

In the past, when breast cancer occurred, even prophylactic mastectomy of second breast was recommended. Expansion of mammography and earlier detection of tumor resulted in the change of this recommendation [19].

Due to more frequently performed mammography second breast cancer is recently diagnosed in earlier clinical stage [22]. It seems, however, that even yearly done mammography may not have influence on survival in this group of patients [6, 23]. Another point of view presented Robinson et al [34], based on a group of 167 patients with conclusion that yearly mammography of the contralateral breast in patients with previous breast tumors must be performed in order to increase the cure rate of contralateral breast cancer.

Prognosis of bilateral breast cancer depend mainly on clinical stage and on length of interval between first and second cancer [5, 11, 19, 28, 32, 34]. The longer the women survived after the first cancer diagnosis, the greater is the likelihood of her developing a second cancer; the longer is the interval between the diagnosis of the two cancers, the better is the survival rate [27].

Results presented by Holmberg et al [21] suggest that two different breast tumors contribute independently to the patient's prognosis and thus occur as two seemingly biologically unrelated events with respect to the tumour-host relationship and metastatic behavior.

Mose et al [28] observed in a group of 36 patients 56% 5-year survival rate and bilateral breast cancer was observed in contained 7.2% (36/498) of all analyzed breast cancer patients.

Boice et al [5] observed greater probability of second breast cancer incidence in patients younger than 45 and treated with mastectomy and radiotherapy. Similar observations were made by Hislop et al [20]. They concluded that only in a small group of patients (3%) second breast cancer may be induced by irradiation. This may appear when tangential fields cover another breast.

Schell et al [36] compared in group of 126 patients 20-years disease-free survival rates. They didn't observe significant differences between patients with unilateral tumors and those with bilateral synchronous or metachronous tumors. They concluded that the doses of radiation given in the management of the first breast cancer were not conducive to the development of a cancer in the remaining breast.

Hislop et al [20] found two important risk factors for bilateral cancer within 1 year of the first primary – histologic diagnosis of lobular carcinoma and absence of pathologic involvement of axillary nodes, after 1 year of the first primary one risk factor was found - family history of breast cancer.

Solin et al [38] presented results of treatment of 30 women with bilateral breast cancer. They were definitively irradiated following breast conserving surgery. 5-year survival rate following treatment of the first breast cancer was 79%, relapse free survival rate – 72%. Results show that radicaly irradiation following breast-conserving surgery for patients with bilateral breast cancer can technically be delivered with low complication rates and with acceptable survival and local control rates.

Abdalla et al [1] compared two groups – patients with bilateral breast cancer (n=132) and patients with unilateral breast cancer (n=2004). Patients with bilateral breast cancer were slightly younger than patients with unilateral cancer (51 years vs 54 years). No other significant differences were observed. The development of second breast cancer was associated with worse survival. On multivariate analysis, factors that decreased survival in patients with bilateral

breast cancer were a higher number of positive lymph nodes of the first and second cancers, a larger size of the second cancer, and a shorter interval between the two primaries.

HEATON et al [18] found positive family history in 29% of patients with bilateral breast cancer. They concluded that breast conserving therapy is an acceptable and desirable option for appropriately selected patients with metachronous or synchronous bilateral breast cancer.

FUNG et al [15] determined whether patients with early-stage bilateral breast cancer can be treated with definitive irradiation following breast-conserving surgery with acceptable survival, local control, complications and cosmetic. For the overall group of 55 patients, the 5- and 10-year overall survival rates were 96% and 94%, respectively, after treatment of the first cancer, and 96% and 92%, respectively, after treatment of the second cancer. They concluded that bilateral definitive breast irradiation after breast-conservation surgery should be considered an acceptable alternative treatment to bilateral mastectomy for selected patients with concurrent or sequential early-stage bilateral breast cancer.

GOGAS et al [16] described a group of 78 patients with contralateral breast cancer (4.2% of all breast cancers). The mean interval between metachronous cancers was 117 months. The risk of developing a contralateral breast cancer was related to the patient's age, family history of breast cancer and lobular histology of the tumor.

BRENNER et al [6] described a group of 251 patients with contralateral breast cancer (2.6% of all patients). They were considerably younger at the time of diagnosis of the first breast cancer than the total group of patients with breast cancer (mean age 55.7 years vs 60.5 years). The survival rates after diagnosis of the second breast cancer were much worse than the survival rates after the first breast cancer diagnosis. Tumor spread at diagnosis of the second cancer was the most important predictor of survival among patients with bilateral breast cancer.

HUNGNESS et al [22] based on a group of 51 patients concluded that bilateral breast cancer is often detected by mammography and is frequently of the same histologic type as the first cancer. The overall 10-year survival rate was 63%.

NAYFIELD et al [30] and RUTOVIST et al [35] observed lower risk of second breast cancer in patients treated complementary with Tamoxifen. Risk was lower in both observations at about 35%.

In presented group of 36 patients with bilateral breast cancer treated in Greatpoland Cancer Center we noted 55.6% 5-years survival rate, in most of patients disease free. Prognosis was correlated with clinical stage (tumor size – T and locoregional lymph node involvement – N). Differences between 5-year survival rate were observed according to length of interval between both breast cancers. Longer intervals between two primaries were correlated with longer survival. Our results were similar to those achieved by other authors. We didn't observed strong influence of methods of treatment on survival. Relatively small group of patients was qualified for irradiation after mastectomy, perhaps due to advanced age and earlier irradiation after first primary.

References

[1] ABDALLA I, THISTED RA, HEIMANN R. The impact of contralateral breast cancer on the outcome of breast cancer patients treated by mastectomy. Cancer J Sci Am 2000; 6: 266–272.

[2] ANDERSON D, BADZIOCH M. Bilaterality in familial breast cancer patients. Cancer 1985; 56: 2092–2098.

[3] BELLER FK, NIENHAUS H, NIEDNER W, HOLZGREVE W. Bilateral breast cancer: the frequency of undiagnosed cancers. Am J Obstet Gynecol 1986; 155: 247–255.

[4] 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: 925–936.

[5] 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: 781–785.

[6] BRENNER H, ENGELSMANN B, STEGMAIER C, ZIEGLER H. Clinical epidemiology of bilateral breast cancer. Cancer 1993; 72: 3629–3635.

[7] CLAUS EB, RISCH NJ, THOMPSON WD. Age at onset as an indicator of familial risk of breast cancer. Am J Epidemiol 1989; 131: 961–972.

[8] DAWSON LA, CHOW E, GOSS PE. Evolving perspectives in contralateral breast cancer. Eur J Cancer 1998; 34: 2000–2009.

[9] DAWSON PJ, MALONEY T, GIMOTTY P, JUNEAU P, OWNBY H, WOLMAN SR. Bilateral breast cancer: one disease or two? Breast Cancer Res Treat 1991; 19: 233–244.

[10] DE LA ROCHEFORDIERE A, ASSELAIN B, SCHOLL S, CAMPANA F, UCLA L, VILCOQ JR, DURA JC, POUILLART P, FOURQUET A. Simultaneous bilateral breast carcinomas: a retrospective review of 149 cases. Int J Radiat Oncol Biol Phys 1994; 30: 35–41.

[11] DONOVAN AJ. Bilateral Breast cancer. Surg Clin North Am 1990; 70: 1141–1149.

[12] ENGIN K. Prognostic factors in bilateral breast cancer. Neoplasma 1994; 41: 353–357.

[13] FRACCHIA AA, BORGEN PI. Bilateral breast cancer. Semin Surg Oncol 1991; 7: 300–305.

[14] FRACCHIA AA, ROBINSON D, LEGASPI A, GREENALL MJ, KINNE DW, GROSHEN S. Survival in bilateral breast cancer. Cancer 1991; 55: 1414–1421..

[15] FUNG MC, SCHULTZ DJ, SOLIN SJ. Early-stage bilateral breast cancer treated with breast-conservating surgery and definitive irradiation: the University of Pennsylvania experience. Int J Radiat Oncol Biol Phys 1997; 38: 959–967.

[16] GOGAS J, MARKOPOULOS C, SKANDALAKIS P, GOGAS H. Bilateral breast cancer. Am Surg 1993; 59: 733–735.

[17] HARVEY EB, BRINTON LA. Second cancer following cancer of the breast in Connecticut, 1935–1982. Natl Cancer Inst Monogr 1985; 68: 99–112.

[18] Heaton KM, Peoples GE, Singletary SE, Feig BW, Ross MI, Ames FC, Buchholz TA, Strom EA, McNeese MD, Hunt KK. Feasibility of breast conservation therapy in metachronous or synchronous bilateral breast cancer. Ann Surg Oncol 1999; 6: 102–108.

[19] 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; 12: 2739–2749.

[20] Hislop TG, Elwood JM, Coldman AJ, Spinelli JJ, Worth AJ, Ellison LG. Second primary cancers of the breast: incidence and risk factors. Br J Cancer 1984; 49: 79–85.

[21] Holmberg L, Adami HO, Ekbom A, Bergstrom R, Sandstrom A, Lindgren A. Prognosis in bilateral breast cancer. Effects of time interval between first and second primary tumours. Br J Cancer 1988; 58: 191–194.

[22] Hungness ES, Safa M, Shaughnessy EA, Aron BS, Gazder PA, Hawkins HH, Lov EE, Seeskin C, Yassin RS, Hasselgren PO. Bilateral synchronous breast cancer: mode of detection and comparison of histologic features between the 2 breasts. Surgery 2000; 128: 702–707.

[23] Jassem J, editor. Rak sutka. Springer-PWN, Warszawa 1998; 78, 363.

[24] Kułakowski A, Różycki-Gerlach W, AL-Jassaf H. Bilateral breast cancer. A clinical problem. Nowotwory 1984; 34: 125–133.

[25] Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. Contralateral breast cancer and other second malignancies in patients treated by breast conserving therapy with radiation. Int J Radiat Oncol Biol Phys 1988; 15: 277–284.

[26] McCredie JA, Inch WR, Anderson M. Consecutive primary carcinomas of the breast. Cancer 1975; 35: 1472–1477.

[27] Michowitz M, Noy S, Lazebnik N, Aladjem D. Bilateral breast cancer. J Surg Oncol 1985; 30: 109–112.

[28] Mose S, Adamietz IA, Thilmann C, Saran F, Bernhard M, Pahnke R, Botther H. Bilateral breast carcinoma versus unilateral disease. Review of 498 patients. Am J Clin Oncol 1997; 20: 541–545.

[29] Muhonen T, Eerola H, Vehmanen P, Nevanlinna H, Aktan K, Blomqvist C, Kaariainen H, Pyrhonen S. Breast cancer risk estimation in families with history of breast cancer. Br J Cancer 1997; 76: 1228–1231.

[30] Nayfield SG, Karp JE, Ford LG, Dorr FA, Kramer BS. Potential role of tamoksifen in prevention of breast cancer. J Natl Cancer Inst 1991; 83: 1450–1459.

[31] Ottman R, Pike M, King MC, Henderson BE. Practical guide for estimating risk for familial breast cancer. Lancet 1983; 2: 556–558.

[32] Peters GN. Bilaterality and recurrence rates for lobular breast cancer: considerations for treatment. Ann Surg Oncol 1997; 4: 198–202.

[33] Pomerantz RA, Murand T, Hines JR. Bilateral breast cancer. Am Surg 1989; 55: 441.

[34] Robinson E, Rennert G, Bar-Deroma R, Dori DL, Neugut AI. The pattern of diagnosis of a second primary tumor in the breast. Breast Cancer Res Treat 1993; 25: 211–215.

[35] Rutqvist LE, Cedermark B, Glas U, Mattsson A, Skoog L, Somell A, Theve T, Wilking N, Askergren J, Hjalmar ML. Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoksifen therapy. J Natl Cancer Inst 1991; 83: 1299–1306.

[36] Schell SR, Montague ED, Spanos WJ, Tapley ND, Fletcher GH, Oswald MJ. Bilateral breast cancer in patients with initial stage I and II disease. Cancer 1982; 50: 1191–1194.

[37] Schwartz AG, King MC, Belle SH. Risk of breast cancer to relatives of young breast cancer patients. J Natl Cancer Inst 1985; 75: 665–668.

[38] Solin SJ, Fowble BL, Schultz DJ, Goodman RL. Bilateral breast carcinoma treated with definitive irradiation. Int J Radiat Oncol Biol Phys 1989; 17: 263–271.

[39] Yeatman TJ, Lyman GH, Smith SK, Reitner DS, Cantor AB, Cox CE. Bilaterality and recurrence rates for lobular breast cancer: considerations for treatment. Ann Surg Oncol 1997; 4: 198–202.