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Original article

Synchronous malignancies in patients with breast cancer

Beata Sas-Korczyńska[1], Jerzy W. Mituś[2], Wojciech Kamzol[1], Marta Kołodziej Rzepa[2],
Jerzy Jakubowicz[3], Wojciech M. Wysocki[2]

Introduction. The continuously improving cancer detection at an early stage and improving survival rates have been observed and, therefore, patients are predisposed to detection of multiple primaries. It has been reported that the incidence of multiple primaries in breast cancer patients ranges from of 4% to 17%.

Materials and methods. A group of 112 breast cancer patients with synchronous malignancies was presented. They constituted 0.09% of patients (118,952 cases) who were treated for breast cancer at the same time period, and made up 3.5% of all patients (3,176 cases) with multiple primary cancers, and 21.7% of all patients (517 cases) with breast cancer who developed multiple primaries.

Results. The most frequent type of synchronous primary malignancy was breast cancer (63.4%) and 90.1% of them were diagnosed at the same time or within one month following the first breast cancer diagnosis. Among cases of non-breast synchronous primaries, female genital organ malignancies were predominant (36.6%). Synchronous breast cancer was diagnosed significantly earlier than non-breast cancers (mean time was 0.4 and 1 month, respectively, p = 0.0123). Better results in the group with synchronous contralateral breast cancer in comparison to synchronous breast and non-breast cancer were observed (5-year overall survival rates were 90.9% and 66.3%, respectively, and 5-year disease-free survival rate — 62.5% and 51.3%, respectively).

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Key words: synchronous malignancies, breast cancer, contralateral breast cancer

Introduction

Significant progress has been observed in the prevention, diagnosis and therapy of cancers. Screening programmes and improvements in diagnostic methods result in cancer being detected at an earlier stage and, moreover, the advances in treatment methods yield an increase the overall survival of cancer patients. In consequence, the occurrence of multiple independent primary cancers in the same patient is still growing and ranges from 1% to 18% [1–7].

The definition of multiple primary cancers is based on the classic criteria of Warren and Gates which include: (i) the site of origin, (ii) the morphology and histology of tumours, and (iii) the amount of time passed since the initial diagnosis. This means that tumours arise in other organs than the independent primaries, each tumour has to be histologically distinctive and the possibility of metastasis or recurrence must be excluded [8, 9]. Considering the time of occurrence, multiple primary cancers generally fall into the synchronous or metachronous [8–10]. According to the International Agency for Research on Cancer (IARC), the diagnosis of synchronous primaries is made within an interval of less than 6 months [8].

Multiple primary cancers are categorized according to predominant etiologic influences: treatment-related, syn-

[1]Clinic of Oncology, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Kraków Branch, Poland

[2]Department of Surgical Oncology, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Kraków Branch, Poland

[3]Department of Gynecological Oncology, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Kraków Branch, Poland

dromic and those due to shared etiologic factors [11]. Causal mechanisms of their development include the following: (i) host factors – genetic (BRCA mutations, Li-Fraumeni syndrome), hormonal, prior cancer diagnosis and treatment exposures, (ii) lifestyle factors such as alcohol and tobacco use (risk factors for several cancer types), and (iii) environmental influences – geography (areas of increased radon exposure), pathogens (human papilloma virus or Epstein-Barr virus infections) and occupational factors [1, 3, 8, 10, 12–14].

Breast cancer is the most common cancer in women; in Poland 17,400 new cases of breast cancer (which constituted 21.7% of all cancers in 2014) were diagnosed in [15]. In these patients, continuously improving detection at an early stage and improving survival rates have been observed and, therefore, these patients are predisposed to detection of multiple primaries. It has been reported that the incidence of multiple primaries in breast cancer patients ranges from of 4% to 17% [5, 7, 10, 16].

The risk of developing multiple primary malignancies in breast cancer patients is associated with positive family history, suppressor gene mutation (*BRCA1*, *BRCA2*, *PTEN*, *TP53*), age, body weight, alcohol intake, hormonal replacement therapy and breast cancer therapy (especially for metachronous primaries) [14, 17, 18].

Lee et al. showed that synchronous malignancies developed in 23.8% of breast cancer patients and the most frequent were malignancies located in the thyroid gland (71% cases) and in the gynaecologic tract (9.7%) [8].

The purpose of this study was (i) to present the characteristics of breast cancer patients with synchronous primaries in relation to the type of synchronous primaries (breast and breast versus breast and non-breast) and (ii) to evaluate the outcomes and the impact of the type of synchronous cancers on survival rate.

Materials and methods

In this paper, synchronous malignancies are defined as primaries diagnosed at the same time or following the diagnosis of breast cancer in a time interval shorter than 6 months.

Patient population

Between 1965 and 2014, synchronous malignancies (in compliance with the above definition) were diagnosed in 112 breast cancer patients who were treated at Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in Kraków. These patients constituted 0.09% of all patients (118,952 cases) who were treated for breast cancer in this time period, and they made up 3.5% of all patients (3,176 cases) with multiple primary cancers and 21.7% of all patients (517 cases) with breast cancer who developed multiple primaries.

Table I presents the types of synchronous malignancies and Figure 1 presents the time interval between the diagnosis of breast cancer and synchronous malignancy in the analysed group of 112 breast cancer patients.

The mean time interval between diagnosis of breast carcinoma and synchronous cancers was 0.6 ± 1.1 month (range: 0–5 months). More than 80% of synchronous malignancies were diagnosed at the same time or during the first month following breast cancer diagnosis.

The most frequent type of synchronous primary malignancy was breast cancer (71 cases — 63.4%). In 64 cases, this type of second synchronous cancer was diagnosed at

Table I. The types of synchronous primary cancers in 112 patients with breast cancer

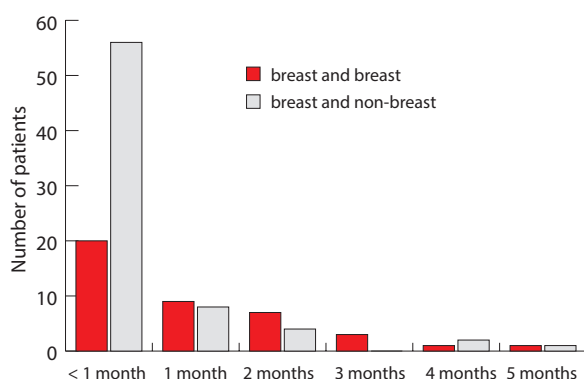| Diagnosis of synchronous cancers	ICD-10 code	No. of cases	%
Total		112	100.0
Breast cancer (in contralateral breast)	C50	71	63.4
Female genital organ cancers:		15	13.4
Cervical uteri cancer	C53	10	8.9
Endometrial cancer	C54	1	0.9
Ovarian cancer	C56	4	3.6
Digestive organ cancers:		2	1.8
Stomach cancer	C16	1	0.9
Rectal cancer	C20	1	0.9
Skin cancer	C44	11	9.8
Lung cancer	C34	1	0.9
Urinary tract cancers:		4	3.6
Kidney cancer	C64	3	2.7
Urinary bladder cancer	C67	1	
Thyroid cancer	C73	3	0.9
Lymphatic tissue neoplasms	C81, C85, C91	4	3.6
Laryngeal cancer	C32	1	0.9

Figure 1. The time interval between the diagnosis of breast cancer and synchronous malignancy in 112 patients

the same time or within one month following first breast cancer diagnosis. Among 41 cases of non-breast synchronous cancers, female genital organ malignancies were predominant (15 cases — 36.6%).

Statistical methods

In the studied population, two groups were distinguished: patients with synchronous bilateral breast cancer and patients with synchronous non-breast cancer. The comparison of these groups was performed in order to assess the relation to frequency of the analysed factors with the use of the Pearson's Chi-square test for independence (for categorized variables) and variance analysis with Student's t-test (for continuous variables). Overall survival rate and disease-free survival rate were evaluated with the Kaplan-Meier method, and the log-rank test was applied to assess the influence of type of synchronous cancers on the evaluated results.

All calculations were performed by STATISTICA v.12 software (StatSoft, Inc. Tulsa, OK, USA) and the significance level at α = 0.05 was adopted for all statistical analyses.

Results
Patient characteristics and comparison

The mean age at diagnosis of breast cancer was 61.5 ± 12.8 years (range: 30 — 85, median: 62 years). Age over 50 years was noted in 90 cases (80.4%). Positive cancer history was found in 47 patients (42%) including 16 cases (34%) with breast cancer history. Synchronous breast cancer appeared in 33 patients with positive family history (70%) and in 11 patients with breast cancer family history (68.8%). Benign breast diseases and/or hormonal disturbances were found in 8 individuals (7.2%).

Because patients with breast cancer and synchronous cancers were managed over a period of 49 years, the diagnostic methods and the spectra of treatment changed along with the indications. Nevertheless, surgery was the primary treatment modality of breast cancer. Because in the presented group of 112 patients with breast cancer

and synchronous cancers in 71 cases synchronous bilateral breast cancer was diagnosed, therefore, in our material in 112 patients 183 breast primary tumours were found. Radical mastectomy was performed in 131 breast tumours (71.6%), whereas 52 tumours (28.4%) underwent breast-conserving surgery. The following adjuvant therapy was applied: postoperative radiotherapy (77 breast tumours — 42.1% in 55 patients — 49.1%), chemotherapy (51 patients — 45.5%) and hormonotherapy (87 patients — 77.7%), which in 85 patients (75.9%) was combined with tamoxifen. In some cases, multimodal treatment was performed in an adjuvant setting.

Table II presents the characteristics of 112 patients with breast cancer and synchronous primary malignancies and their comparison in relation to the type of synchronous primary cancers: breast and breast cancers versus breast and non-breast cancers.

Synchronous breast cancer was diagnosed significantly earlier than non-breast cancers; mean time was 0.4 and 1 month, respectively (p = 0.0123) after first breast cancer.

There were no significant differences between the two analysed patients' groups (synchronous primaries: breast and breast cancer versus breast and non-breast cancer) in relation to epidemiological, clinical and pathological features.

Survival and outcomes

The follow-up period after the diagnosis of breast cancer ranged from 2 to 371 months with a mean value of 78.2 ± 72 months and a median of 56.5 months. Table III presents the outcomes which developed during clinical observation. The mean time of these outcomes was as follows: 14.9 ± 13.9 months (for locoregional recurrence), 46.6 ± 44.2 months (for distant metastases) and 41.1 ± 33.5 months (for metachronous carcinomas) after diagnosis of breast cancer. Patients with synchronous contralateral breast cancer had a tendency to more frequent development of distant metastases (32.4% patients vs 13.8% patients with synchronous breast and non-breast cancer, p = 0.07776, Chi^2 test). However, there were no significant differences (p > 0.05, Chi^2 test) between the two analysed groups in relation to the development of locoregional recurrences or metachronous (third and fourth) primaries.

During the follow-up period 28 patients (25%) died, and the causes of death were as follows: breast cancer (13 cases), non-breast primaries (6 cases), coexistent non-cancer internal disease (3 cases), and unknown (6 cases).

The estimated 5-year and 10-year survival rates were 81% and 65.3% (for overall survival) and 58.3% and 44.9% (for disease-free survival).

Figure 2 shows the probability of overall survival (a) and disease-free survival (b) in relation to the type of synchronous primaries (synchronous contralateral breast cancer versus breast and non-breast cancer).

Table II. The characteristics of 112 patients with breast cancer and synchronous malignancies and its comparison in relation to the type of synchronous primary cancers: breast and breast cancers versus breast and non-breast cancers

Parameters		Group N = 112 (100%)	Synchronous cancers		p
			breast and breast N = 71 (100%)	breast and non-breast N = 41 (100%)	
mean time between breast and synchronous cancers [months]		0.6 ± 1.1	0.4 ± 0.9	1.0 ± 1.3	0.0123[a]
Age:	mean value [years]	61.5 ± 12.8	60.8 ± 12.9	62.6 ± 12.7	0.4909[a]
	≤ 50	22 (19.6%)	15 (21.1%)	7 (17.1%)	0.6030
	> 50	90 (80.4%)	56 (78.9%)	34 (82.9%)	
Menopausal status:					
	premenopausal	47 (42%)	31 (43.7%)	16 (39%)	0.6319
	postmenopausal	65 (58%)	40 (56.3%)	25 (61%)	
Family history of cancers:					
	negative	65 (58%)	38 (53.5%)	27 (65.9%)	
	breast cancers	16 (14.3%)	11 (15.5%)	5 (12.2%)	0.4392
	other cancers	31 (27.7%)	22 (31%)	9 (22%)	
Breast disease and other symptoms:					
	none	102 (91.2%)	65 (91.6%)	37 (90.2%)	
	benign breast disease	2 (1.8%)	1 (1.4%)	1 (2.4%)	
	hormonal disturbances	6 (5.4%)	3 (4.2%)	3 (7.3%)	0.61970
	BRCA1/2 mutation	2 (1.8%)	2 (2.8%)	0	
Histological type:					
	ductal	84 (75%)[b]	57 (80.3%)[b]	27 (65.9%)	
	lobular	8 (7.1%)[b]	6 (8.5%)[b]	2 (4.9%)	0.0573
	other*	20 (17.9%)[b]	8 (11.3%)[b]	12 (29.3%)	
Stage breast cancer:					
	pT1-2	89 (79,5%)[b]	59 (83.1%)[b]	30 (73.2%)	0.2102
	pT3-4	23 (20.5%)[b]	12 (16.9%)[b]	11 (26.8%)	
	pN0	60 (53.6%)[b]	38 (53.5%)[b]	22 (53.6%)	0.9888
	pN+	52 (46.4%)[b]	33 (46.5%)[b]	19 (46.3%)	
Mean number of pN+		5.7 ± 6.0	5.3 ± 5.8	6.2 ± 6.4	0.6047[a]
Treatment methods:					
	radiotherapy	55 (49.1%)[b]	40 (56.3%)[b]	15 (36.6%)	0.0440
	chemotherapy	51 (45.5%)	36 (50.7%)	15 (36.6%)	0.1484
	tamoxifen	85 (75.9%)	57 (80.3%)	28 (68.3%)	0.1530

*other types of breast cancer: medullary, mucinous, metaplastic, apocrine, tubular, inflammatory, Paget's disease of the nipple, papillary; [a] p value from t-Student test, other p for chi-square test; [b] presence of the parameter in one breast cancer at least (patients with synchronous bilateral breast cancer)

Better results in the group with synchronous contralateral breast cancer in comparison to synchronous breast and non-breast cancer were observed (5-year overall survival rates were 90.9% and 66.3%, respectively, and 5-year disease-free survival rate — 62.5% and 51.3%, respectively), but these observations were statistically nonsignificant.

Discussion

Published data indicate that 4–17% of breast cancer patients develop multiple primary malignancies and, according to Lee et al., synchronous primaries were diagnosed in 24% of cases [5, 7, 8, 10, 16]. The group of 112 patients with breast cancer and synchronous malignancies presented in this study constituted 21.7% of all patients with breast cancer who developed other primaries in the analysed period. It is interesting that 11 (9.8%) of our breast cancer patients with synchronous malignancies developed metachronous malignancies during the follow-up period, in comparison to 2.8% observed in patients analysed by Lee at al. [8].

Our observation showed that the most frequent synchronous neoplasms were contralateral breast cancer (71 cases — 63.4%) and genital organ cancer (15 cases — 13.5%), of which cervical uterine cancer was predominant (8.9%).

Some literature data showed that a lobular component of breast carcinoma was associated with an almost 2-fold increase in the risk of developing contralateral breast cancer, especially synchronous bilateral breast cancer [19–21].
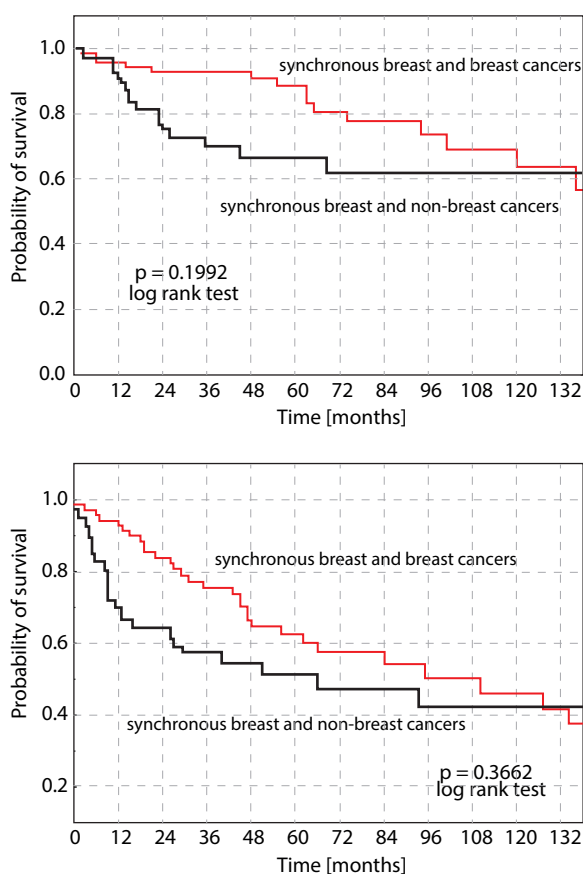
Figure 2. The probability of overall (a) and disease-free (b) survival rates in relation to type of synchronous malignancy in 112 patients treated for breast cancer

Outcomes	No. of patients	%
Recurrence at chest wall	10	8.9
Distant metastases	30	26.8
bones	13	11.6
liver	7	6.3
lungs	5	4.5
lymph nodes	4	3.6
brain	3	2.7
skin	1	0.9
Metachronous cancers	11	9.8
breast cancer	1	0.9
endometrial cancer	2	1.8
ovarian cancer	1	0.9
skin cancer	2	1.8
kidney cancer	1	0.9
bladder cancer*	1*	0.9*
Hodgkin's lymphoma	1	0.9
ocular melanoma	1	0.9
biliary tract cancer*	1*	0.9*

*as 4th cancers, and remain – as 3rd morbidity

Our observations confirmed the tendency of developing synchronous contralateral breast cancer in lobular breast carcinoma patients; in 75% of cases of lobular breast carcinoma, synchronous contralateral breast cancer developed. Claus et al. observed that patients with lobular breast carcinoma were 2.6 times more likely to be diagnosed with synchronous contralateral breast cancer than patients with ductal breast carcinoma [22].

Published data indicate that age as well as menopausal status at breast cancer diagnosis are risk factors for development of second cancer [18, 19, 21, 23–27]. Lv et al. showed that 84.6% patients with synchronous malignancies were over 50 years old [27]. In our patients, 80% of patients (90 of 112 cases) were over 50 years old and most of them (65 cases — 58%) were in postmenopausal status. The comparison to breast cancer patients who developed metachronous malignancies confirmed that patients with synchronous malignancies were significantly older and in postmenopausal status (p = 0.00001 and p = 0.00275, respectively).

The occurrence of a second primary is associated with a significantly increased risk of death and significantly worse survival [8, 28, 29]. Particularly, this regards synchronous cancers [27–30]. Results published by Carmichael et al. showed that significantly worse overall survival is observed among patients with synchronous contralateral breast cancer in comparison to metachronous or unilateral breast cancer [31]. Quan et al published that the 5-year survival rate was 80.3% for synchronous breast cancer and 90.5% for metachronous breast cancer [32]. Our results were similar and 5-year survival reached 81% in all breast cancer patients with synchronous malignancies and 90.9% in the synchronous contralateral breast cancer subgroup. The five-year survival rate evaluated in breast cancer patients with metachronous malignancies (presented in our earlier publication) was 91.8% (all breast cancer patients and metachronous malignancies) and 92.9% in patients with metachronous contralateral breast cancer [33]. However, these results were not statistically significant (p = 0.27772, log rank test).

The occurrence of multiple synchronous primaries is challenging and often causes a therapeutic dilemma in daily clinical practice. Therapeutic strategy for patients with synchronous malignancies should be discussed in a multidisciplinary team. The main focus in the therapeutic decision-making process should be placed on (i) evaluation of the prognosis and (ii) the chance of a curative or palliative approach [10].

Conclusions

1. The most frequent type of synchronous malignancy in patients with breast cancer is contralateral breast cancer (63.3% of cases) followed by female genital organ cancer (13.4% of cases).
2. The possibility of development of synchronous primary cancer in breast cancer patients indicates the necessity

of conducting precise diagnostic procedures, because detection of coexistent cancers influences the choice of optimal treatment strategy.

Conflict of interest: none declared

Beata Sas-Korczyńska, MD, PhD
Maria Skłodowska-Curie Memorial Cancer Centre
and Institute of Oncology
Kraków Branch
Clinic of Oncology
ul. Garncarska 11
31-115 Kraków, Poland
e-mail: z5korczy@cyf-kr.edu.pl

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