VIA MEDICA
ORGINAL PAPER / GYNECOLOGY
Ginekologia Polska
2018, vol. 89, no. 5, 235–239

ISSN 0017–0011
DOI: 10.5603/GP.a2018.0041

Bilateral synchronous breast cancer developed as metachronous malignancy after therapy of other primaries

Michał Kurzyński[1], Jerzy Mituś[2, 3], Marta Kołodziej-Rzepa[3], Beata Sas-Korczyńska[4]

[1]Department of Radiotherapy, Maria Sklodowska-Curie Institute — Oncology Center, Cracow Branch, Poland
[2]Department of Surgical Oncology, Maria Sklodowska-Curie Institute — Oncology Center, Cracow Branch, Poland
[3]Department of Anatomy, Jagiellonian University Medical College, Cracow, Poland
[4]Department of Oncology Clinic, Maria Sklodowska-Curie Institute — Oncology Center, Cracow Branch, Poland

ABSTRACT

Objectives: Cancer morbidity rates have been increasing steadily. A longer lifespan and easier access to modern diagnostic and therapeutic methods are the main reasons for the growing number of cancer survivors. Additionally, some types of oncological treatment, such as radiotherapy or immunosuppression, may also increase the risk of secondary tumors. These factors have resulted in an increased incidence of primary multiple cancers. Multiple primary cancers are generally understood as either synchronous, in which the cancers occur at the same time, or metachronous, in which the cancers follow in sequence (for instance, more than 2 months apart).The results published in other studies show that between 2% and 15.8% of all cancer patients have more primary multiple cancers. Within this group with multiple primary cancers, some have bilateral breast cancer, and our study focuses on patients from this group.

Material and methods: Our study describes 10 patients who were treated for bilateral synchronous breast cancer at the Cracow Branch of the Maria Sklodowska-Curie Institute — Oncology Center during the years 1992–2014 and who developed another primary tumor after their treatment bilateral synchronous breast cancer.

Results: In our discussion we present detailed data on the incidence of metachronous cancers in the 10 patients, including breast cancer, following the treatment of their other primary tumors.

Conclusion: The 10 cases of our study, and clinical experiences and publications in general show how important it is for patients to continue medical follow-up after treatment of primary tumors, not only to detect recurrences as early as possible, but also to diagnose any other malignancies occurring in other sites, including secondary, treatment-related tumors.

Key words: bilateral breast cancer, synchronous breast cancer, primary multiple cancer

Ginekologia Polska 2018; 89, 5: 235–239

INTRODUCTION

Cancer morbidity rates have been increasing steadily in Poland. According to The Polish National Cancer Registry, approximately just under 160,000 new cancer cases were reported in 2014, compared with 34,000 in 1980 [1]. A longer life span and easier access to modern diagnostic and therapeutic methods are the main reasons for the growing number of cancer survivors, which in turn has resulted in an increased incidence of primary multiple cancers. It is worth noting that some types of oncological treatment, such as radiotherapy or immunosuppression, may also increase the risk of secondary tumors [2]. There are two main definitions of multiple primary cancers (MPC). The first is that used by the International Agency for Research on Cancer (IARC) while the second was developed by Surveillance, Epidemiology, and End Results (SEER) [3–6]. They differ in terms of the anatomical distribution of structures in which multiple primary tumors develop. However, the common feature defining primary multiple cancers is the presence of two or more primary tumors (MPC) independently of each

Corresponding author:
Michał Kurzyński
Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Cracow Branch
Garncarska St. 11, 31–115 Cracow, Poland
e-mail: mkurzynski@onet.eu

other's occurrence. This definition has been accepted by the WHO. One specific example of MPC is bilateral breast cancer, which can develop as both as synchronous and metachronous tumors. According to the current definition, synchronous tumors are those detected up to 6 months after the diagnosis of the primary tumor, while metachronous tumors are those diagnosed after this period [7]. Other time intervals have been used in the literature. For example, SEER recommends a 2-month interval as a defining criterion [8]. The data regarding bilateral breast cancer diagnoses is not so clear in this context. A diagnosis of bilateral breast cancer is not unequivocal and is more commonly identified as chronic metastatic cancer [9].

MATERIAL AND METHODS

Out of a total of 12,893 patients treated for breast cancer in the Cracow Branch of the Maria Sklodowska-Curie Institute — Oncology Center in the years 1992–2014, ten (0.08%) were diagnosed with synchronous bilateral breast cancer, which developed between 1 and 35 years after the treatment of another primary tumor. These patients accounted for 0.4% of all patients (2,292) treated for primary multiple cancers during the same period. Table 1 summarizes the clinical characteristics of these patients.

RESULTS

The treatment provided for those cases of breast cancer and other malignancies that occurred prior to the synchronous bilateral breast cancer diagnosis, as referred to in the table, remained consistent with the treatment protocols and recommendations used at that time. It should also be noted that the cases referred to in the table cover a period of more than 40 years. The primary disease in three of the patients in the analyzed group was Hodgkin's lymphoma, in two others the primary cancer was colorectal cancer, and in another two it was ovarian cancer. Of the remaining three patients in the group, one had previously been treated for endometrial cancer, one for kidney cancer and one for laryngeal cancer. Synchronic bilateral breast cancer was diagnosed in women aged between 33 and 86. Four of the women had a positive family history of cancer (two patients had a mother suffering from breast cancer, one patient's father had been treated for cancer of the pharynx, and one patient's father had been diagnosed with a brain tumor). For the women in our study, bilateral radical mastectomy was the most common surgical treatment: the Madden technique was used on five patients, the Patey technique on two, and one-sided mastectomy and breast conservation surgery (BCS) on the other three. Postoperative radiotherapy was performed on one patient following a mastectomy (one side) and in two cases after BCS (one side). Eight patients from the group received adjuvant hormone therapy (tamoxifen-5, anastrozole-3). During a follow-up, two patients developed distant metastases: one to the lung and another to the liver (CB and ZS, respectively). Cancer detected before bilateral synchronous breast cancer occurred at ages ranging between 11 and 74. A complete cure was achieved in nine patients following treatment, while one patient (ED), who had been treated for ovarian cancer, developed a locoregional recurrence prior to developing breast cancer.

It is worth noting in context of our study the case of one patient treated for Hodgkin's Lymphoma. At the age of eleven she underwent chemotherapy and radiotherapy. Twelve years later she was diagnosed with a sarcoma affecting the soft tissue of the neck. The treatment of choice was local resection. One year later due to a recurrence, a resection with adjuvant radiotherapy was performed. During follow-up 21 years later the patient was diagnosed with synchronous bilateral breast cancer, and 12 months after that, skin cancer was detected in three locations (each tumor had a different histological pattern).

DISCUSSION

The research and data analysis set out below demonstrates that cancer survivors have an increased risk of developing other primary tumors. The published results show that between 2% and 15.8% of all cancer patients later develop other primary multiple cancers: 7.2% in Amer [10], 2% in Bulatti, et al. [11], 15.8% in Weir, et al. [12], 6.3 in Rosso, et al. [13], 6.3% in AIRTUM Working Group [14], and 8.17% in Voigt [15]. The differences between these figures is a result of the researchers using diverging definitions of primary tumors (SEER and IARC definitions) and different observation periods. Detailed data on the incidence of metachronous cancers, including breast cancer, following the treatment of other primary tumors is presented below.

Patients treated for Hodgkin's lymphoma (HL), which is often diagnosed at an early age, have a higher risk of developing secondary tumors associated with their treatment (radiotherapy and chemotherapy). After radiotherapy the following are observed with greater frequency: breast cancer, lung cancer, and thyroid cancer [16, 17]; and following chemotherapy: leukemia, lung cancer, gastrointestinal cancer, and sarcoma [18]. In 2006 Franklin, et al. reported that the application of chemotherapy and radiotherapy in the treatment of HL increases the risk of developing secondary tumors [19]. However, according to Conway J.L., et al. the use of modern radiotherapy techniques (e.g., IMRT or VMAT), which reduce the dose to critical organs and the integral dose, reduces the number of secondary tumors (late effects of radiotherapy) [20].

The incidence of breast cancer and ovarian cancer is often defined as hereditary breast-ovarian cancer (HBOC). The incidence results from a group of factors based on

Table 1. The characteristics of patients treated for synchronous breast cancer as metachronous malignancy

No	Patient	The first diagnosed primary malignancy			Synchronous bilateral breast cancer			
		Year	Cancer	Treatment and follow-up	Year	Age	Therapy	Follow-up
1	DT	1974	Hodgkin's Lymphoma	Chemotherapy + radiotherapy — free of disease	2009	46	Bilateral modified radical mastectomy (Madden) hormonotherapy — tamoxifen	84 months disease free, 3 skin cancers reported
		1988	Sarcoma of the soft tissue (Neck)	Surgical resection, after 1 year due to local recurrence surgical resection and adjuvant radiotherapy-free of disease				
2	JSN	2001	Hodgkin's Lymphoma	Chemotherapy + radiotherapy — free of disease	2011	33	Bilateral lumpectomy, thereafter bilateral modified radical mastectomy (Madden) due to patient's refusal of adjuvant radiotherapy	36 months disease free
3	BC	2003	Hodgkin's Lymphoma	Chemiotherapy — free of disease	2012	73	Bilateral modified radical mastectomy (Madden), adjuvant chemotherapy (FAC) radiotherapy (left), hormonotherapy (tamoxifen)	54 months free of disease
4	CB	1991	Ovarian cancer (Carcinoma endometroides)	Hysterectomy with bilateral oophorectomy — free of disease	2012	70	Bilateral modified radical mastectomy (Madden), disqualified from chemotherapy, refusal of radiotherapy, hormonotherapy (anastrozole)	After 47 months metastatic spread to the lungs
5	ED	1990	Ovarian cancer (adenocarcinoma endometroidale)	Hysterectomy with bilateral oophorectomy, adjuvant radiotherapy — local recurrence after 84 months	1992	54	Bilateral modified radical mastectomy (Patey)	63 months free of disease
6	JF	70's	Colorectal cancer-histopathological result no available	Abdominoperineal resection of the rectum — free of disease	2008	83	Lumpectomy thereafter modified radical mastectomy (Madden) — right, simple mastectomy — left. Disqualified from chemotherapy and radiotherapy, hormonotherapy — tamoxifen	53 months free of disease
7	MR	1989	Colorectal cancer (Adenocarcinoma cylindrocellulare	Right hemicolectomy — free of disease	2000	86	Bilateral modified radical mastectomy (Patey), hormonotherapy (anastrozole)	55 months free of disease
8	ZZ	2012	Uterine cancer (Carcinoma endometroides)	Hysterectomy + brachytherapy HDR — free of disease	2014	74	Lumpectomy — right, simple mastectomy — left, hormonotherapy (tamoxifen)	66 months free of disease
9	MKR	2009	Renal cell cancer (Carcinoma pappilare)	Nefrectomy — free of disease	2009	67	Lumpectomy-right, simple mastectomy — left, hormonotherapy (anastrozole) Radiotherapy — right	67 months free of disease
10	ZS	2006	Laryngeal cancer (Carcinoma planoepitheliale)	Radiotherapy — free of disease	2010	74	Modified radical mastectomy (Madden) — right, lumpectomy — left, radiotherapy — left. hormonotherapy (tamoxifen)	After 47 months metastatic spread to the liver

a different etiology which predisposes an individual to the development of these cancers. The most common causes of breast cancer and ovarian cancer include mutations in the BRCA1 and BRCA2 genes. Gabai, et al. reports that women with the mutation of the above gene have an 83% risk of breast cancer and a 76% risk of ovarian cancer before they reach the age of 80 [21]. The risk of developing breast cancer in BRCA mutation carriers, 10 years after an ovarian cancer diagnosis, is low, i.e. within a range of 7.8–11% [22, 23]. This can be explained using chemotherapy for OC (platinum-based) as a treatment, which is also effective in patients with BRCA associated BC by reducing the risk of consecutive BC

[24]. In the same study (Gabai, et al.), the authors showed that death before the age of 80 due to BC can be reduced by less than 1% with an MRI and by less than 2% with a mastectomy. For this reason, preventive mastectomy or MRI screening is not warranted, except in patients with early--stage ovarian cancer and for those who have survived OC for ten years without recurrence. The average risk of breast cancer is low in BRCA mutation carriers and individuals diagnosed with OC. Most cases of BC can be detected by means of mammography in its early stages [25].

There are no published studies showing an increased incidence of breast cancer in patients treated for colorectal cancer. Instead, in this group, and especially after the administration of radiotherapy, uterine cancer, bladder cancer and leukemia are diagnosed more often [26]. Several publications, including Evans, et al., reported that women who have had colorectal cancer before the age of 65 have a greater risk of developing uterine cancer, bladder cancer and leukemia [27].

Zhu, et al. demonstrated an increased risk of throat, stomach and lung cancer in patients who had undergone treatment for esophageal cancer. Also, the use of radiotherapy during treatment statistically increases the incidence of laryngeal and thyroid cancer [28].

According to Jones, et al., among patients successfully treated for head and neck cancer the rate of occurrence of another cancer is estimated at 9.1% over a period of 372 months after treatment [29]. The most common diagnoses were squamous cell carcinoma in another location in the upper airway mucosa, and lung cancer. Interestingly, in the Jones, et al., study, no association was found between the onset of another tumor and the use of radiotherapy. Available publications also show that head and neck tumors and lung cancer are one of the most common combinations of MPC (together with bilateral metachronous and synchronous breast cancer) [30]. This is probably related to environmental factors (pollution) and lifestyle (smoking) [31]. Another very important factor conducive to the development of head and neck cancer, cervical cancer, and rectal cancers is the human papillomavirus (HPV). Neuman, et al., reported that patients diagnosed with HPV-associated cancer have a higher risk of being diagnosed with another cancer associated with this virus [32].

The incidence of subsequent cancers among patients treated for lung cancer is estimated to range between 13.4% (Rosso, et al. [33]) and 22% (Sanchez, et al. [34]). The most common scenario is a diagnosis of another lung cancer with a different histological pattern. According to Baskarl, et al. [35], the histological results of the second tumor of the lung are as follows: adenomatous carcinoma (29.9% of all tumors), squamous cell carcinoma (27.1%), and small cell carcinoma (7.9%). The principal cause of multiple primary tumors of the lung is smoking; and radiotherapy does not have a major impact on the incidence of secondary lung cancer [34].

The above cases, clinical experiences and publications show how important it is for patients to continue follow-ups after treatment not only to detect recurrences as fast as possible, but also to diagnose other malignancies in other sites, including secondary treatment-related tumors. Secondary cancers are usually diagnosed at an earlier clinical stage, which results in a better prognosis. In the case of post-treatment follow-up, it is important to note any history of tumors in other family members. On the other hand, changes in life habits such as smoking cessation, alcohol abstinence or increased physical activity also play an important role in early cancer prevention [18].

REFERENCES

1. U. Wojciechowska, P. Olasek .K. Czauderna, et al. Nowotwory złośliwe w Polsce.
2. Travis LB. The epidemiology of second primary cancers. Cancer Epidemiol Biomarkers Prev. 2006; 15(11): 2020–2026, doi: 10.1158/1055-9965.EPI-06-0414, indexed in Pubmed: 17057028.
3. IARC/ENCR/IACR Working Group: International rules for multiple primary cancers. Asian Pacific J Cancer Prev. 2005; 6: 104–106.
4. International Agency for Research on Cancer: International Rules for Multiple Primary Cancers (ICD-O Third Edition). Internal Report No. 2004/02. Lyon: IARC, 2004.
5. Błaszczyk J, Hudziec P. Nowotwory pierwotne mnogie (Multiple Primary Cancer) w populacji dolnośląskiej w latach 1984–2009.
6. Coyte A, Morrison DS, McLoone P. Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014; 14: 272, doi: 10.1186/1471-2407-14-272, indexed in Pubmed: 24742063.
7. Rochefordiere Ad, Asselain B, Scholl S, et al. Simultaneous bilateral breast carcinomas: A retrospective review of 149 cases. International Journal of Radiation Oncology*Biology*Physics. 1994; 30(1): 35–41, doi: 10.1016/0360-3016(94)90516-9.
8. Johnson CH, Peace S, Adamo P, et al. The 2007 Multiple Primary and Histology Coding Rules. National Cancer Institute, Surveillance, Epidemiology and End Results Program. Bethesda, MD. ; 2007.
9. Chen Y, Thompson W, Semenciw R, et al. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev. 1999; 8(10): 855–861, indexed in Pubmed: 10548312.
10. Amer MH. Multiple neoplasms, single primaries, and patient survival. Cancer Manag Res. 2014; 6: 119–134, doi: 10.2147/CMAR.S57378, indexed in Pubmed: 24623992.
11. Buiatti E, Crocetti E, Acciai S, et al. Incidence of second primary cancers in three Italian population-based cancer registries. Eur J Cancer. 1997; 33(11): 1829–1834, doi: 10.1016/s0959-8049(97)00173-1, indexed in Pubmed: 9470841.
12. Weir HK, Johnson CJ, Thompson TD. The effect of multiple primary rules on population-based cancer survival. Cancer Causes Control. 2013; 24(6): 1231–1242, doi: 10.1007/s10552-013-0203-3, indexed in Pubmed: 23558444.
13. Rosso S, De Angelis R, Ciccolallo L, et al. EUROCARE Working Group. Multiple tumours in survival estimates. Eur J Cancer. 2009; 45(6): 1080–1094, doi: 10.1016/j.ejca.2008.11.030, indexed in Pubmed: 19121933.
14. AIRTUM Working Group, AIRTUM Working Group, CCM, AIEOP Working Group, AIRTUM Working Group. [Italian cancer figures, report 2010: Cancer prevalence in Italy. Patients living with cancer, long-term survivors and cured patients]. Epidemiol Prev. 2010; 34(5-6 Suppl 2): 1–188, indexed in Pubmed: 21220827.
15. Vogt A, Schmid S, Heinimann K, et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017; 2(2): e000172, doi: 10.1136/esmoopen-2017-000172, indexed in Pubmed: 28761745.
16. Bhuller KS, Zhang Y, Li D, et al. Late mortality, secondary malignancy and hospitalisation in teenage and young adult survivors of Hodgkin lym-

phoma: report of the Childhood/Adolescent/Young Adult Cancer Survivors Research Program and the BC Cancer Agency Centre for Lymphoid Cancer. Br J Haematol. 2016; 172(5): 757–768, doi: 10.1111/bjh.13903, indexed in Pubmed: 26727959.
17. Lisik-Habib M, Czernek U, Dębska-Szmich S, et al. Secondary cancer in a survivor of Hodgkin's lymphoma: A case report and review of the literature. Oncol Lett. 2015; 9(2): 964–966, doi: 10.3892/ol.2014.2799, indexed in Pubmed: 25621073.
18. Wood ME, Vogel V, Ng A, et al. Second malignant neoplasms: assessment and strategies for risk reduction. J Clin Oncol. 2012; 30(30): 3734–3745, doi: 10.1200/JCO.2012.41.8681, indexed in Pubmed: 23008293.
19. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. Ann Oncol. 2006; 17(12): 1749–1760, doi: 10.1093/annonc/mdl302, indexed in Pubmed: 16984979.
20. Conway JL, Connors JM, Tyldesley S, et al. Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma. Int J Radiat Oncol Biol Phys. 2017; 97(1): 35–41, doi: 10.1016/j.ijrobp.2016.10.004, indexed in Pubmed: 27979454.
21. Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci U S A. 2014; 111(39): 14205–14210, doi: 10.1073/pnas.1415979111, indexed in Pubmed: 25192939.
22. Vencken PM, Kriege M, Hooning M, et al. The risk of primary and contralateral breast cancer after ovarian cancer in BRCA1/BRCA2 mutation carriers: Implications for counseling. Cancer. 2013; 119(5): 955–962, doi: 10.1002/cncr.27839, indexed in Pubmed: 23165859.
23. 2017; 145(2): 346–351.
24. Nathanson KL, Domchek SM. Therapeutic approaches for women predisposed to breast cancer. Annu Rev Med. 2011; 62: 295–306, doi: 10.1146/annurev-med-010910-110221, indexed in Pubmed: 21034216.
25. Gangi A, Cass I, Paik D, et al. Breast cancer following ovarian cancer in BRCA mutation carriers. JAMA Surg. 2014; 149(12): 1306–1313, doi: 10.1001/jamasurg.2014.1081, indexed in Pubmed: 25372568.
26. Warschkow R, Güller U, Cerny T, et al. Secondary malignancies after rectal cancer resection with and without radiation therapy: A propensity-adjusted, population-based SEER analysis. Radiother Oncol. 2017; 123(1): 139–146, doi: 10.1016/j.radonc.2017.02.007, indexed in Pubmed: 28285840.
27. Evans HS, Møller H, Robinson D, et al. The risk of subsequent primary cancers after colorectal cancer in southeast England. Gut. 2002; 50(5): 647–652, doi: 10.1136/gut.50.5.647, indexed in Pubmed: 11950810.
28. Zhu G, Chen Y, Zhu Z, et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. Dis Esophagus. 2012; 25(6): 505–511, doi: 10.1111/j.1442-2050.2011.01273.x, indexed in Pubmed: 22067063.
29. Jones AS, Morar P, Phillips DE, et al. Second primary tumors in patients with head and neck squamous cell carcinoma. Cancer. 1995; 75(6): 1343–1353, doi: 10.1002/1097-0142(19950315)75:6<1343::aid-cncr2820750617>3.0.co;2-t, indexed in Pubmed: 7882285.
30. Aydiner A, Karadeniz A, Uygun K, et al. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol. 2000; 23(4): 364–370, doi: 10.1097/00000421-200008000-00011, indexed in Pubmed: 10955865.
31. Jégu J, Binder-Foucard F, Borel C, et al. Trends over three decades of the risk of second primary cancer among patients with head and neck cancer. Oral Oncol. 2013; 49(1): 9–14, doi: 10.1016/j.oraloncology.2012.06.018, indexed in Pubmed: 22840787.
32. Neumann F, Jégu J, Mougin C, et al. Risk of second primary cancer after a first potentially-human papillomavirus-related cancer: A population-based study. Prev Med. 2016; 90: 52–58, doi: 10.1016/j.ypmed.2016.06.041, indexed in Pubmed: 27370167.
33. Rosso S, De Angelis R, Ciccolallo L, et al. EUROCARE Working Group. Multiple tumours in survival estimates. Eur J Cancer. 2009; 45(6): 1080–1094, doi: 10.1016/j.ejca.2008.11.030, indexed in Pubmed: 19121933.
34. Sánchez de Cos Escuín J, Rodríguez López DP, Utrabo Delgado I, et al. Disease Recurrence and Second Tumors in Long-term Survivors of Lung Cancer. Arch Bronconeumol. 2016; 52(4): 183–188, doi: 10.1016/j.arbres.2015.07.013, indexed in Pubmed: 26558321.
35. Bhaskarla A, Tang PC, Mashtare T, et al. Analysis of second primary lung cancers in the SEER database. J Surg Res. 2010; 162(1): 1–6, doi: 10.1016/j.jss.2009.12.030, indexed in Pubmed: 20400118.