Bilateral breast cancer

Incidence, diagnosis and histological patterns

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ABSTRACT

Objective: Bilateral breast cancer is uncommon (1-2.6% of all patients with breast carcinoma). There are conflicting reports and inadequate data regarding the incidence and survival of such patients. This study examined the frequency, mode of detection, therapeutic modalities and histological features among the 2 breasts.

Methods: Medical records of patients who were treated for breast cancer were reviewed at Khartoum Teaching Hospital, Sudan during a 5-year period of 1994 to 1999. Data of patients found to have bilateral breast cancer was analyzed focusing on the demographic information, family history, menstrual status, surgical therapy, chemoradiation, staging and histopathological characteristics.

Results: Of 521 patients treated for breast cancer, 90 (17.2%) were reported to have advanced breast carcinoma (stage III, IV) and 7 (1.3%) revealed bilateral cancer: 5 (0.9%) synchronous and 2 (0.4%)

metachronous breast cancer. The median age was 47.3 years (range, 24-81 years). Four (57.1%) patients had positive family history for breast cancer. First breast cancer was detected by mammogram in 2 cases while second cancer was diagnosed by the same study in 5 patients. Five (71.5%) underwent mastectomy and 2 (28.5%) were treated by lumpectomy and axillary dissection. Six patients presented with stage III and one with stage IV breast cancer. Invasive ductal carcinoma was reported to be the most common type found in 10 (71.5%) breasts. Grade III breast carcinoma was revealed in 9 and Grade I cancer in 3 specimens.

Conclusion: Bilateral breast cancer is invariably advanced when diagnosed. Mammogram is a valuable tool in early detection. Whether synchronous or metachronous, both breasts often share the same histological type.

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The incidence of bilateral breast cancer (BBC) avaries from 1-3.2%^{1,3} Such a wide range is partly attributed to the different time spans applied to define synchronous and metachronous breast cancers. The incidence of BBC is expected to rise as a direct result of improved diagnostic techniques and longer survival times.^{4,5} The best management of patients with BBC is still not known.⁶ Patients with unilateral breast cancer are not routinely offered a risk-reduction intervention for the second breast and controversy still prevails regarding the proper management. The purpose of this study is to present our experience in patients with BBC over a 5-year period.

Methods. This retrospective study comprised a consecutive series of 521 female patients who

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received treatment for breast cancer at Khartoum Teaching Hospital, Sudan during a 5-year period of 1994 through 1999. Charts of those patients found to have BBC were further analyzed regarding patients' characteristics (age, pre/postmenopausal status, family history of cancer in general and any evidence of cancer family syndrome), mode of detection, treatment and histological features among the 2 breasts. Synchronous breast cancer (SBC) was defined as cancer diagnosed in both breasts simultaneously or within 3 months of diagnosis of Metachronous breast cancer the first tumor.7 (MBC) was defined as the one diagnosed in the contra lateral breast more than 3 months after the diagnosis of the tumor in the first breast. Patients were coded as premenopausal if they were having menstrual periods at the time of diagnosis and as postmenopausal if they had either natural or surgically induced menopause.8 A family history of breast carcinoma was considered positive when the patient had at least one first-degree relative with the same disease 8 Complete tumor excision was accomplished by wide local excision or mastectomy with axillary clearance (level I, II). The radiotherapy regime comprised 45 grays (Gy) in fractionated doses followed by 15 Gy booster to the tumor bed using 4- or 6- mV linear accelerator over 6 weeks (median dose, 65.0 Gy). All premenopausal patients nodes were with positive lymph given chemotherapy. For the postmenopausal women with positive lymph nodes, adjuvant hormonal therapy was administered. Neoadiuvant therapy comprised 3-4 cycles of Adriamycin and Cyclophosphamide 3 weeks apart while adjuvant therapy included 3-4

cycles of Docetracel. Histological features along with a grade of differentiation were recorded for each patient. Estrogen and progesterone receptor positivity were defined as at least 10% cellular staining. All patients were followed up every 3 months for the first 2-3 years and twice a year thereafter. During follow up, locoregional recurrence, distant metastasis and disease free survival were recorded.

The Statistical Package for Social Sciences 10.0 software package (SPSS Inc., Chicago, IL) was used for statistical analysis. The Chi-squared test was employed for analysis of the statistical differences with regards to histological characteristics, tumor grading and receptor status. A p value of 0.05 was considered to be statistically significant.

Results. During the period 1994 to 1999. a total of 521 patients were treated for breast carcinoma. Out of these, 90 (17.2%) patients were found to have advanced breast cancer (stage III, IV) and 7 (1.3%) cases had BBC; 5 (0.9%) SBC and 2 (0.4%) MBC. The median age of patients with BBC was 47.3 years (range, 24-81 years). Four (57.1%) subjects revealed a positive family history of breast cancer, 5 (71.4%) patients were premenopausal and 2 (28.6%) in postmenopausal status. First cancer was detected by mammogram in only 2 (28.5%) patients while second cancer was diagnosed by this study in 5 (71.5%) cases. Among the patients with BBC, 5 (71.5%) underwent bilateral mastectomy and 2 (28.5%) lumpectomy with axillary dissection (Table 1). The most common type of breast cancer recorded in this series was primary invasive ductal

Table 1 - Case presentations of patients with bilateral breast cancer (N=7).

Case	Age (years)	Menopausal status	Family history	Surgical treatment and adjuvant therapy			Histology		DFI
				Mastectomy	Wide local excision	Chemoradio therapy	Index breast	Wide local excision	
1	39	Premenopausal	Positive	Index breast	Second breast	Second breast	Index breast	Second breast	84
2	57	Postmenopausal	Negative	Both breasts*	-		Both breasts	-	11†
3	46	Premenopausal	Negative	Second breast	Index breast	Index breast	Second breast	Index breast	23‡
4	48	Premenopausal	Positive	Index breast*	Second breast	Second breast	Index breast	Second breast	72
5	24	Premenopausal	Positive	Both breasts	-		Both breasts	-	29**
6	43	Premenopausal	Positive	Second breast	Index breast	Index breast	Second breast	Index breast	67
7	81	Postmenopausal	Negative	Second breast§	Index breast	Index breast	Second breast	Index breast	6††

*metachronous breast cancer, †developed pleural effusion,

‡developed liver metastasis, **patient died due to cerebral metastasis, §toile mastectomy, ††patient died due to cachexia, bilateral pleural effusion, DFI - disease free interval in months. IDC - invasive ductal carcinoma, ILC - invasive lobular carcinoma, DCIS - ductal carcinoma in svitu, DLC - ductal/obular carcinoma, carcinoma found in 10 (71.5%) breasts followed by primary invasive lobular type reported in 2 (14.2%) breasts (**Table 2**). Four patients with SBC and both cases with MBC showed regional axillary lymph nodes metastasis. One patient with a stage IV SBC presented 2 months after initial bilateral mastectomy with dyspnea and cough. She was found to have massive bilateral pleural effusion which reaccumulated rapidly after aspiration and pleurodesis, and the patient died during the same admission.

Discussion. Bilateral breast carcinoma represents a very small proportion of all breast carcinoma cases. The incidence of BBC reported in this series is similar to the published data $(1.1-2.4\%)^{9-12}$ This incidence, of course, is significantly influenced by the conflicting cut off times for synchronous and metachronous lesions. These ambiguous criteria range from one month to 2 years and make meaningful comparisons difficult. The definition of SBC used in our study is in accordance with that used by The Radiation Oncology Advisory Group and other groups.8,13 The history of breast cancer increases the risk of subsequent breast cancer in the contra lateral breast. Kollias et al14 have demonstrated that there was a mean annual incidence of 6.5 per thousand women per year for the development of MBC. Family history5,15 and early age of onset (40 years)6 of breast carcinoma have been reported to be the

haracteristics	Ν	(%)
listonathology (n=14)		
Both primary invasive ductal	10	(71.5)
Both primary invasive lobular	2	(14.2)
Primary mixed ductal/lobular*	ĩ	(7.1)
DCIS†	i	(7.1)
istological Grade (n=14)		
I (well differentiated)	3	(21.4)
II (moderately differentiated)	2	(14.2)
III (poorly differentiated)	9	(64.4)
trogen-recentor $(n=9)$		
Positive [†]	8	(88.8)
Negative	1	(11.2)
ngesterone-recentor $(n=5)$		
Positive	3	(60)
Negative	2	(40)
i vogativo	2	(-0)

*Reported in first breast of a patient with metachronous breast cancer, †All found in synchronous breast cancer, DCIS - ductal carcinoma in situ found in second breast of the patient with metachronous breast cancer established risk factors in the development of BBC. We demonstrated 57.1% incidence of positive family history for breast cancer. Kinoshita et al¹⁷ have demonstrated that the percentage of patients with a p53 gene abnormality and positive family history was higher for those with bilateral than unilateral breast cancer. At the same time, the increased mortality of patients with bilateral synchronous breast carcinoma may be due to the higher incidence of HER-21neu overexpression.18 As illustrated in a retrospective review⁸ of patients with BBC, contra lateral breast cancers were diagnosed at an earlier stage than carcinomas of the index breast. Aggressive cancer screening with high-quality mammography has contributed towards this early detection and improved survival of patients with BBC. Other published reports19,20 also emphasized the need of careful screening with mammogram of the contra lateral breast. In the study, first breast cancer was present mammographically confirmed in 2 patients whereas 5 cases were found to have second breast cancer by the same study. All patients in this series presented with various breast cancer-related affections and since there were no established breast cancer screening practice in our region, mammography was employed to confirm the clinical findings or to exclude malignancy in the same or contralateral breast. There is a significant tendency for contralateral breast carcinoma to have similar mammographic features to those of the initial tumor which is likely to be explained by the similar histological grades and mammographic background patterns seen in bilateral cancers.21 The current study showed that BBC manifested at an advanced stage: 6 (85.7%) cases had stage III and 1 (14.3%) had a stage IV breast carcinoma. Similarly, the histological type of breast cancer was the same in 2 breasts in 71.5% cases, a finding consistent with most of the existing literature.22 Conversely, Hall et al21 mentioned that second breast cancer often shares the same histological grade but different histological type. Present series reported Grade III in 9 and Grade I in 3 breast specimens. This is strikingly disparate but failed to reach statistical significance, possibly due to the relatively small sample size $(p \ 0.05)$. Estrogen-receptor positivity has been reported to be predictive of bilateral breast disease hv Coradini et al.23 who reviewed the hormone-receptor status of bilateral breast carcinoma patients. The present study showed 57.1% cases of BBC with estrogen-receptor positivity (p 0.05). This observation reaffirms the premise that the receptor positivity is one manifestation of a "field effect" of hormonal sensitivity that promotes a neoplastic process. The complex interplay of various prognostic factors which influence survival of patients with BBC includes tumor stage, interval between the first and second primaries and histological grade of primary tumor.^{34,25} Jobsen et al⁶ have demonstrated that the patients with BBC had a significantly higher distant metastasis rate than those with unilateral breast carcinoma (30.8% versus 15.1%, *p*=0.028). The aggressive nature of BBC lesions was also documented in a study which concluded that recurrence was almost twice as high for bilateral than unilateral cases (29% versus 16%).²⁶ Such findings further substantiate the notion that patients with BBC require more aggressive treatment and careful screening.

Based on this small study group, we conclude that the patients with BBC present at an advanced stage with worse histological grade. Second breast cancer is more frequently detected by mammogram which should be routinely used for follow up and screening purpose. There is no significant difference in histological characteristics between the 2 breasts of patients with BBC.

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