

Original Article

Bilateral Breast Cancer in Tripoli/Libya

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ABSTRACT

Aims of study. To investigate the characteristics and outcome of BBC in comparison to unilateral breast cancer. **Methods:** Retrospective study of BBC patients who were registered in Tripoli medical Center in the period between Jan 2005 and Dec 2012. BBC is considered synchronous if it occurs within 3 months from the first breast cancer BC and metachronous if it occurs after 3 months.

Results: 437 breast cancer BC patients registered and included in the study. Their median age was 46 years. 25 (5.7%) patients of them developed BBC. 11 (2.5%) of them were synchronous and 14 (3.2%) were metachronous BC. Median age of those patients who had BBC was 41 years. 76% of them were premenopausal. Median time for development of metachronous breast cancer was 22.3 months. Compared to unilateral BC, the BBC group had a younger age ($p=0.02$) They also had a more advanced stage according to TNM classification 56% vs. 37.9% ($p=0.038$) and had more negative hormone receptor status 66.7% vs. 38% ($p=0.007$). Overall survival in unilateral BC, synchronous BBC and metachronous BBC was 166.8 months, 89 months, 72 months respectively. There was no significant difference in overall survival of patients with unilateral and synchronous BBC $p=0.355$. However, patients with unilateral BC had better overall survival in comparison to metachronous BBC $p=0.003$ and there was no significant difference between synchronous and metachronous BBC $p=0.554$.

Conclusion: Patients with BBC were younger and presented with a more advanced tumor size and were more likely to have Estrogen receptor (ER) and Progesterone receptor (PR) negative receptor status. Patients with metachronous BBC had shorter survival.

INTRODUCTION

Breast cancer is the most common malignancy among females and is a major cause of cancer related deaths among women in the world. However, the epidemiology of bilateral breast cancer BBC remains unclear. The incidence of BBC is reported to range from 1.4% to 11.8%. (1-2) On average, the annual risk of contralateral BC is approximately 0.5% , but increases to 3% in carriers of a BRCA 1or BRCA 2 mutation. (3) It remains controversial whether BBC represents increased susceptibility to breast cancer or is simply a second occurrence of breast cancer. Increased risk could be related to early age at first diagnosis, history of lobular carcinoma of breast and A positive family history of breast cancer. (4)

Women diagnosed with breast cancer are at increased risk of developing BBC. This represents a two to six times greater relative risk than developing a first breast cancer in the general population. (5). Contralateral breast cancer is either a metastatic lesion or a second primary cancer, and occurs synchronously or metachronously (Chauday et al).(5) Metachronous disease was much more common among younger patients but the incidence has declined steadily since approximately 1980 most likely due to the expanding use of adjuvant systemic therapy (6). The reported survival rate for women with Bilateral Breast Cancer BBC compared to women with unilateral breast cancer has varied considerably. (7)

The aim of this study is to evaluate the clinicopathological characteristics, outcome and survival of BBC in comparison to unilateral Breast Cancer BC.

MATERIAL AND METHODS

This Retrospective study included histopathologically confirmed female breast cancer patients at the oncology Department in Tripoli Medical Center from Jan 2005 to Dec. 2012.

This study was approved by the scientific committee in the medical Oncology Department in Tripoli Medical Center. 437 patients were registered in this period, of whom 25 patients later developed BBC. Collected data included age, family history, tumor stage (tumor size, lymph node status and distant metastases), histological type, grade, hormone receptor status and HER+2 status, treatment given (chemotherapy, radiotherapy and hormonal therapy), and the time between the first and second tumor in BBC.

First breast cancer is defined as the breast cancer which was initially diagnosed while the second breast cancer the tumor which developed in the contralateral breast. BBCs were categorized as synchronous when the contralateral breast cancer was diagnosed within 3 months from the first tumor, and as Metachronous when the contralateral breast cancer was diagnosed after 3 months from the initial tumor diagnosis according to the Radiation Oncology Advisory Group and Australasian college of surgeons. (8)

Radiotherapy was given to all patients who had a tumor size more than 5 cm, more than 3 positive lymph or patients had breast conserving surgery. Hormonal therapy was given to patients who were hormone receptor positive in the form of Tamoxifen 20mg/d for premenopausal women and an aromatase inhibitor for postmenopausal women.

Overall survival was defined as the time from randomization to death from any cause, it is a direct measure of clinical outcome for patients. Patients alive or lost to follow up were censored. All patients were treated and followed up every three months for one year, 6 monthly for the next two years and then annually. They also have annual mammographic review.

Statistical analysis

SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA) was used for statistical analysis and t and Z tests for comparison of different variables. A P value less than 0.05 considered to be significant. Kaplan Meier analysis was used to compare survival among unilateral and bilateral breast cancer patients including synchronous and metachronous breast cancers.

RESULTS

437 patients were registered in the period between Jan 2005 and Dec 2012. Their median age was 46 years. Median age at menarche were 13 years, 14.8% had a positive family history in unilateral breast cancer while 15.1% of BBC had a positive family history ($P>0.05$) which was not significant. Among these patients, 25 (5.7%) had bilateral breast cancer 11(2.5%) of them were synchronous BBC and 14 (3.2%) were metachronous BBC.

Table 1 shows patient's characteristics of bilateral breast cancer compared to unilateral disease.

The mean interval for development of metachronous BBC was 33.4 months, while the median interval was 22.3 months. The median age of BBC patients was 41 years. They were younger

Table 1. shows characteristics of bilateral breast cancer group (2) compared to unilateral disease group (1)

Variable	Unilateral BC (412) Group (1)	Bilateral BC (25) Group (2)	P value
Median age	46 years	41 years	0.02
Tumor size			
T1	21 (5.8%)	0	< 0.05
T2	161 (44.8%)	5 (27.8%)	
T3	112 (31.2%)	3 (16.7%)	
T4	65 (18.1%)	10 (55.6%)	
Lymph nodes			
Positive	225 (66.2%)	9 (50%)	NS
Negative	115 (33.8%)	9 (50%)	
Stage			
I	15 (4%)		0.038
II	199 (53.8%)	9 (39.1%)	
III	111 (30%)	9 (39.1%)	
IV	45 (12.2%)	5 (21.8%)	
Hormone receptor			
Positive	208 (62.1%)	7 (38.9%)	0.007
Negative	127 (37.9%)	11 (61.1%)	
Her+2			
negative	127 (66.8%)	(81.8%)	
positive	63 (33.2%)	2 (18.2%)	
Surgery			
Mastectomy	294 (72%)	18 (72%)	
BCS	76 (18.7%)	5 (20%)	
Biopsy	38 (9.3%)	2 (8%)	
Adjuvant Chemotherapy			
Yes	313 (75.9%)	19 (76%)	
Radiotherapy	92 (22.3%)	9 (36%)	
Hormonal therapy	208 (62.1%)	7 (38.9%)	

than unilateral BC ($p=0.02$). 19/25 (76%) were premenopause. Histopathologically, all patients who had BBC had invasive ductal carcinoma in the first tumor. At the occurrence of the second tumor 16/17 (94%) patients of them had a histopathological diagnosis of invasive ductal carcinoma and 1(6%) had invasive lobular carcinoma. 13/18 (72%) of BBC patients had a tumor size of T3+T4, While a tumor size of T3+T4 presented in 177/359 (49%) of unilateral BC patients.

Regarding the tumor stage, BBC had advanced Breast cancer (stage III and IV) in 14/17(61%), while in unilateral BC 156/370 (42%) had stage III and IV. $P=0.038$.

Comparing patients with synchronous and metachronous breast cancer, metachronous breast cancer patients had similar stage to first breast cancer patients. They had negative hormone receptor status ($P=0.007$). There was no significant difference in overall survival of patients with unilateral BC and synchronous BBC $p=0.355$. However, patients with unilateral breast cancer had better overall survival in comparison to metachronous BBC $p=0.003$, and there was no significant difference in overall survival between synchronous and metachronous BBC $p=0.554$.

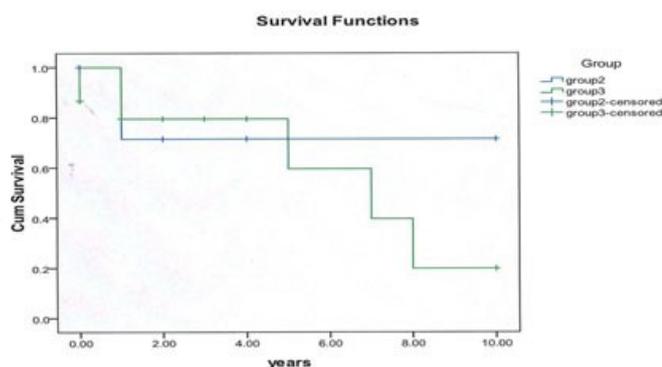


Fig. 1. Survival of Synchronous group (2) & Metachronous BBC group (3) $P=0.554$
Group (2) Synchronous Bilateral Breast Cancer
Group (3) Metachronous Bilateral Breast Cancer

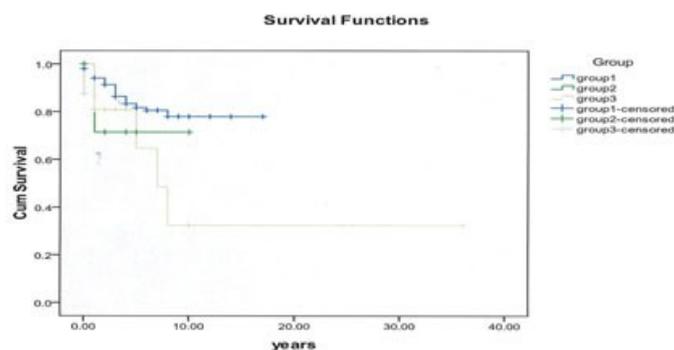


Fig. 2. Survival comparisons between group (1) & group (2). ($P=0.003$). Group (1) & group (3) ($P=0.355$)
Group (1) Unilateral BC. Group (2) synchronous BBC.
Group (3) metachronous BBC

DISCUSSION

The incidence of bilateral breast cancer is variable and may reach up to 20% in patients in whom a breast cancer diagnosis was made by contralateral biopsy and mastectomy in clinically negative breasts (2,9).

The risk of a primary breast cancer in the contralateral breast is approximately 1% per year (10).

Patient age younger than 55 years at the time of diagnosis or lobular tumor histology appear to increase this risk to 1.5%. (11). The development of a contralateral breast cancer is associated with an increased risk of distant recurrence (12,13). BBC in our patients presented in 5.7%, 2.5% were synchronous and 3.2% were metachronous breast cancer. Our patients were of younger age at the time of their initial breast cancer diagnosis. Beckmann KR et al found no age difference between women with unilateral and bilateral breast cancer. (4)

In the previous studies, age was considered to be predictive for contralateral breast cancer (14,15,16).

In our study patients had a larger tumor size and more advanced stage of the first tumor in BBC patients in comparison to unilateral breast cancer patients. Our patients were not strict in their follow up and sometimes missed their appointments. This could explain why the second breast cancer was diagnosed late and at an advanced stage. Kheirelseid E et al showed smaller contralateral tumor size and earlier stage when compared to unilateral tumors and the initial tumors BBC.(2)

In Beckmann K. et al showed no statistically significant difference in demographic or clinical characteristics between index tumor for synchronous and metachronous cases.(4) In our study, there was no difference in ER status between the initial and contralateral tumors. In addition, patients with BBC were more likely to be ER negative than those unilateral BC. However, the study by Coradini et al, shows no difference in ER and PR status positivity between initial and contralateral tumors.(17)

In the study by Kheirelseid E et al, there was a low rate of PR positivity in patients with bilateral tumors compared to those with unilateral disease (2). A Non-significant difference suggests that the first tumors in synchronous cases was more likely to be symptomatic and self detected rather than screen detected compared with metachronous index cancers.

The reported survival rate for women with BBC as compared with unilateral BC has varied considerably. Both a similar prognosis and a poorer prognosis in bilateral BC have been found. (18,19,20,21,22)

The study by Beckmann K. et al, women with BBC had significantly worse survival compared with women with unilateral BC. $P=0.001$ (4). Kheirelseid et al showed no significant difference in overall survival between bilateral and unilateral BC ($P=0.073$), however comparison of patients with synchronous disease to those with metachronous disease yielded a significant difference with P value of (0.01) with reduced overall survival in synchronous tumors.(2). Verkooijen et al found no increased mortality for bilateral breast cancer.(21)

CONCLUSION

Patients with BBC were younger, presented with more advanced tumor size and more likely to have ER and PR negative receptor status. Patients with BBC had shorter overall survival.

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