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Original Article

Oncology Section

Synchronous Bilateral Breast Cancers

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ABSTRACT

Background: Bilateral breast cancer (BBC) is not an uncommon entity in contemporary breast clinics. Improved life expectancy after breast cancer treatment and routine use of contra-lateral breast mammography has led to increased incidence of BBC. Our study objective was to define the epidemiological and tumour characteristics of BBC in India.

Materials and Methods: A total of 1251 breast cancer patients were treated during the period January 2007 to March 2015 and 30 patients were found to have BBC who constituted the study population (60 tumour samples). Synchronous bilateral breast cancers (SBC) was defined as two tumours diagnosed within an interval of 6 months and a second cancer diagnosed after 6 months was labelled as metachronous breast cancer (MBC). Analyses of patient and tumour characteristics were done in this prospective data base of BBC patients.

Results: Median patient age was 66 years (range 39-85). Majority of the patients had SBC (n=28) and in 12 patients the second tumour was clinically occult and detected only by mammography of the contra-lateral breast. The second tumour was found at lower tumour size compared to the first in 73% of cases and was negative for axillary metastasis in 80% of cases (24/30). Infiltrating ductal carcinoma was the commonest histological type (n=51) and majority of the tumours were ER/PR positive (50/60). Her2 was overexpressed in 13 tumours (21%). Over 70% (22/30) of patients had similar histology in both breasts and amongst them grade concordance was present in about 69% (15/22) of patients. Concordance rates of ER, PR and Her2 statuses were 83%, 80% and 90% respectively. Bilateral mastectomy was the commonest surgery performed in 80% of the patients followed by bilateral breast conservation in 13%. At the end of study period, 26 patients were alive and disease free. Median survival was 29 months (range 3-86 months).

Conclusion: In most patients with BBC, the second tumour is identified at an early stage than index tumours supporting the importance of contralateral breast cancer screening at the time of primary diagnosis and during follow-up. BBC occurs more frequently in old age group and majority of these tumours are estrogen dependent. There is good pathological concordance between the index tumour and the contralateral breast cancer.

Keywords: Breast neoplasms, Estrogen receptor, Histology, Mammography

INTRODUCTION

Bilateral breast cancer (BBC) is not an uncommon entity in contemporary breast clinics. We have an increasing incidence of BBC as a result of improved life expectancy after breast cancer treatment and routine use of contra-lateral breast mammography in newly diagnosed breast cancers. Lobular cancer in the index breast, family history of breast cancer, young age at diagnosis of first cancer and BRCA mutations are important risk factors that are known to be at increased risk for BBC.

The second cancer can be synchronous or metachronous. Synchronous breast cancers have been variedly defined as two tumours diagnosed with in an interval of 1 month [1], 2 months [2], 3 months [3], 6 months [4] or 1 year [5]. Accordingly the incidence of SBC has been varying in different series. Controversies also exist about the origin of second cancer (metastatic spread or independent primary) and its prognostic significance. More often than not, women with BBC are treated with most radical surgeries based on the notion that these tumours are biologically aggressive. However, scientific evidence for this belief is divided. There is no population based or large sample size studies analysing the survival outcomes of BBC in Indian women. The objective of this study was to define the epidemiological and tumour characteristics of bilateral breast cancer in India. Here in this study we analysed the clinical and pathologic characteristics, treatment parameters and outcome of BBC in Indian women from a single institution cohort.

MATERIALS AND METHODS

We examined a consecutive cohort of breast cancer patients treated at our center between January 2007 to March 2015. A total of 1251 breast cancer patients were treated during this period. Clinical details were prospectively collected which include patient characteristics, tumour pathology, treatment variables, disease free survival and date of death. Patients were followed up with routine clinical examination, annual mammogram and other investigations if required.

In this period 30 patients were found to have BBC which constituted the study population. This study was approved by institutional ethical committee and informed consent was obtained from all the patients who were included in the study. Synchronous bilateral breast cancers (SBC) was defined as two tumours diagnosed within an interval of 6 months and a second cancer diagnosed after 6 months was labelled as metachronous breast cancer (MBC). A patient was considered to have positive family history when a first degree relative had a history of breast cancer. Analyses of various patient and tumour characteristics were done in this prospective data base of BBC patients.

RESULTS

Overall 30 patients had BBC during the study period and majority were synchronous tumours (93.3%; n=28). Most patients with synchronous tumours (n=25) had their second cancers diagnosed during the initial presentation. Three SBC patients had their contralateral cancers diagnosed during 3, 4 and 6 months after the first tumour. Two cases of MBC were diagnosed 16 and 54 months after the first tumour [Table/Fig-1]. Infiltrating ductal carcinoma was the commonest histological type (n =51) followed by DCIS, lobular and papillary types (n=7, 1, 1 respectively). DCIS was present as second tumour in 6 cases but one patient had DCIS in the index breast and metachronous invasive tumour in the contralateral breast after 16 months. The median tumour size was 2.1cms (range 0.2 to 7cms). The second tumour was detected at lower size than index tumour in 73% (n=22) of the cases.

Sentinel lymph node biopsy (SLNB) using technetium-99 radio colloid and methylene blue dye was done in 27 tumours which were clinically node negative. Only two cases were SLNB positive and subsequent axillary clearance was done in them. The sentinel node identification rate was 100% and there was no false negative case in this group.

In the whole cohort, axillary nodal clearance was done for 31 tumours. The median number of nodes harvested during axillary clearance was 17 (range 8-35) and median number of metastatic nodes in axilla was 3 (range 0 -31). In the whole cohort, 37 tumours were negative for axillary nodal metastasis.

Variable	Synchronous(n=28)	Metachronous(n=2)
Interval between diagnosis of BBC		
0 (diag. at presentation)	25	0
0-6 months	3	0
> 6 months	0	2
Median age in years (range)	66 (39-85)	68
Menstrual Status		
Post-menopausal	22	2
Pre-menopausal	6	0
Mode of diagnosis of second tumour		
Clinical	17	1
Mammogram	11	1
Tumour histology (n=60)		
IDC	48	3
DCIS	6	1
Lobular	1	0
Papillary	1	0
SLNB (n=27)		
Total no. of procedures	24	3
Positive for metastasis	2	0
False negative	0	0
Axillary status (n=60)		
Node negative* (37) (61.6%)	34	3
Node positive (23) (39%)	22	1
N1 (1-3 nodes+)	12	0
N2 (4-9 nodes+)	4	0
N3(10 or more nodes+)	6	1
Extra-nodal Invasion	7	0
Lymphovascular invasion	11	1

[Table/Fig-1]: Patient and tumour characteristics of bilateral breast cancer
*includes both SLN negative and node negative in final histology after axillary clearance

Variable	Synchronous(n=28)	Metachronous(n=2)
ER + (n=50) (83%)	47	3
ER - (n=10)	1	9
PR+ (n=48) (80%)	45	3
PR- (n=12)	11	1
Her2 Overexpressed (n=13) (21%)	12	1
Normal (n=47)	44	3
Molecular type*		
Luminal A (n=38)	36	2
Luminal B (n=6)	6	0
Her2+ (n=7)	6	1
Basal Type (n= 2)	2	0
**Ki67 ** **		
Low (<15%) (n=7)	7	NA
Moderate (15-30%) (n=3)	3	NA
High (>30%)	0	NA

[Table/Fig-2]: Hormone receptor status and Ki 67 index of bilateral tumours
* -Luminal classification was possible for 53 invasive tumors with all known details
** - Ki-67 values were available for analysis in 10 tumour specimens of 5 SBC patients

Variable (n patients) (%)	Synchronous(n=28)	Metachronous(n=2)
Histology Type concordance (22) (73%)	21	1
Grade concordance (15/22) (69%)*	15	0
ER Concordance (25) (83%)		
Both (+)	23	1
Both (-)	2	0
ER discordance (5)(17%)		
One (+)/ other (-)	4	1
PR Concordance (24) (80%)		
Both (+)	20	1
Both (-)	3	0
PR discordance (24) (20%)		
One (+)/ other (-)	3	0
Her2 Concordance (27) (90%)		
Both (+)	5	0
Both (-)	21	1
Her-2 discordance (3)(10%)		
One (+)/ other (-)	2	1

[Table/Fig-3]: Rate of pathological similarity between two tumours in bilateral breast cancer
*Tumours graded by Elston-Ellis modification of Scarff-Bloom-Richardson grading system

Hormone receptor status of the tumours is detailed in [Table/Fig-2]. Majority of the tumours were ER positive (50/60; 83%) and PR positive (48/60; 80%). Most tumours were of luminal A category (n=38). Ki 67 values were available for 10 tumours in 5 SBC. Median Ki-67 index was 10 with range of 5-22. None of the tumours had high proliferative index as per Ki 67 values.

Comparison of pathological characteristics in bilateral breast tissue: Concordance rates of ER, PR and Her2 status were 83%, 80% and 90% respectively. Over 70% (22/30) of patients had similar histology in both breasts and amongst them grade concordance was present in about 69% (15/22) of patients [Table/Fig-3].

Treatment: Bilateral mastectomy was the commonest surgery performed in 80% of the patients (24/30) followed by bilateral breast conservation in 13% (4/30) [Table/Fig-4]. Neoadjuvant chemotherapy was given in 6 patients and two of these patients had breast conservation after NACT. Adjuvant chemotherapy was administered in 10 cases. Reasons for omitting chemotherapy in other patients included unfavorable risk benefit ratio, patient refusal or low risk features in tumour. Adjuvant radiation was given in 13 patients and regions irradiated are listed in the [Table/Fig-4].

Outcomes: In our study population, four patients (13%) developed lymphedema. Three of this four patients had radiation to regional nodal basin in addition to chest wall due to extensive axillary nodal metastasis (> 4 nodes +) or extra-capsular spread. Median follow-up was 16 months (range 1 to 84 months). Median survival estimated by Kaplan-Meir method was 29 months (range 3-86 months) with 95% confidence interval of 23-42 months. In this period breast cancer related events were noted in 4 cases (13%). Two patients developed systemic recurrence and succumbed to the disease after overall survival of 14 and 32 months respectively. Two other patients developed local as well as systemic recurrence after 27 and 60 months respectively, which was treated with hormone therapy in one and palliative chemotherapy in other. The other 26 patients (87%) are alive and without evidence of recurrence.

DISCUSSION

Synchronous breast cancers constitute about 0.2-3% incidence of all newly diagnosed breast cancers [6]. MBC has a cumulative

Variable	Synchronous(n=28)	Metachronous(n=2)
SURGERY PERFORMED		
Bil. Mastectomy (n=24)	22	2
Bil. MRM	12	0
U/L MRM and C/L Mast.+SLNB	5	1
Bil. Mast +SLNB	3	1
Bilateral BCS (n=4)	4	0
U/L BCS+ C/ L Mastectomy (n=2)	1	1
NACT	6	0
Adj.Chemo	9	1
Adj.RT	13	0
(i)Bilateral Radiation (n=11)	11	0
Bilateral CW alone	1	0
Bilateral CW+ RN*	4	0
CW+ Breast	2	0
Bil. Whole Breast	4	0
(ii)Unilateral CW radiation (n=2)	2	0
Adj. Hormone Therapy	21	2
Adj. Trastuzumab	2	0
Complications		
Lymphedema	4	0
Outcomes		
Death Due to disease	1	1
Systemic and local recurrence	2	0
Alive and disease Free	25	1

[Table/Fig-4]: Treatment parameters and outcome of bilateral breast cancer
*- RN-Regional nodal irradiation included radiation to axilla and supraclavicular areas

incidence of 12% after 10 years of index cancer [6]. In most studies of BBC, majority are metachronous tumours [3-7]. In our study, the incidence of SBC and MBC was 2.4% and 0.16% respectively. The reason for low incidence of MBC is because our group is a relatively recent cohort (8 years) compared to the other studies where patients were derived from a 30 year cancer data base (36 years in Carmichael et al., [7] and 30 years in Hartmann et al., [3]). As follow-up increases, corresponding increase in MBC is expected.

As much as 36% of second tumours (11/30) were diagnosed by mammography of the contra-lateral breast. Knowledge of mammographic pattern of index tumour (as mass/calcification) is advisable as the second tumour is expected to have a similar pattern [8]. MRI of the breast is reported to have better sensitivity than mammogram in young age patients. However, high false positive rates and limited availability of MRI guided biopsy facilities restricts its routine use in newly diagnosed cases. We recommend the use of MRI when breast conservation is planned, to rule out multi-focality or multi-centricity which is more common in bilateral cancers.

Median age of 66 years rules out hereditary cause of SBC in our patients. It is reported that up to 39% of patients have positive family history in SBC [9,10] compared to 5% positive family history in unilateral cases. In our group, family history was present in 30% of BBC patients which is similar to the above reports. Lobular histology, a recognized risk factor for bilateral cancers was found in only one of 60 tumour specimens. Similar to us, two other groups [11,12] evaluating BBC in India found no lobular carcinomas in their patients.

One challenge in management of BBC is identifying whether second tumour is an independent event or metastasis from the index tumour. Differing tumour types, different degree of differentiation and presence of in-situ component are histological features suggesting a second primary rather than intra-breast metastasis [13]. However this criterion is not infallible. RS Saad et al., and Imyanitov et al., demonstrated that bilateral tumours, despite having similar pathological characteristics and hormonal statuses can be clonally independent events [14,15]. Common background of environmental and host factors can lead to bilateral cancers developing along similar molecular pathways and accordingly there might be concordance of tumour morphology.

In our cohort, histological and grade concordance was present in over 70% of tumours. Concordance rates of ER, PR and Her2 status between two tumours in BBC, were 83%, 80% and 90% respectively. These findings are similar to those obtained in other studies: Renz et al., in his study of BBC demonstrated 54% histological similarity and 86% and 79% concordance of ER and PR status between two tumours [16]. Baker et al., reported concordance rates in histological type, ER, PR and Her2 statuses to be 53%, 73%, 64% and 88% respectively [17]. Cordani et al., found similar ER and PR values in index and contralateral breast tumours [18]. They also found higher similarity in ER levels than PR levels in SBC. These findings suggest that PR expression is primarily regulated by estrogen and ER [19].

Estrogen receptor positivity is reported to be in higher in SBC than MBC [20]. RS Saad et al., and Beckmann et al., reported 76% and 87% ER positivity in BBC [14,21]. Our study the ER positivity rate was 83% similar to the above studies. In one study, Her2 overe xpression was found in 71% of BBC tumour specimens as compared to 35% in unilateral cancers [22]. They postulated that Her2 over-expression could be the reason for increased mortality in BBC. However most other groups report Her2 incidence around 20-25% which is similar to values (21%) observed in our study [6,23]. About three-fourth (73%) of tumours were luminal A sub-type whereas the incidence of triple negative tumours was extremely low (3.3%). The second tumour was found at lower tumour size compared to the first in 73% of cases and was negative for axillary metastasis in 80% of cases (24/30). The above findings suggest that not all BBC present with an aggressive phenotype and most second tumours are diagnosed at an indolent stage. BBC presenting in older age group as in our group seems to be estrogen dependent.

Bilateral mastectomy is the most common surgery performed in women with BBC. Even though second tumours are diagnosed at an earlier stage than the index tumour, breast conservation is not commonly opted due to stress related to diagnosis of two cancers. Cost concerns accompanying the need for bilateral RT in cases of BCS could also be a prohibitive factor. Heaton KM and his colleagues from MD Anderson cancer center reported that breast conservation appears feasible in BBC with similar local recurrence rates as in unilateral cases [24]. Bilateral tangential irradiation required after BCS can lead to overlapping radiation fields in the medial aspects of both breasts conferring an increased risk of skin and soft tissue damage. CT simulation is advocated in bilateral irradiation as the medial margins of radiation portals can be delineated accurately, thereby preventing skin damage due to overlapping fields [25].

Data about the performance of SLNB in BBC is sparse. ASCO guidelines based on expert consensus state that SLNB is appropriate for patients with multi-centric disease [26]. Our results indicate that SLNB can be performed in BBC without increased risk of false negative rates. Lymphedema is extremely troublesome complication which is best prevented than managed. To decrease the incidence of lymphedema we recommend performing SLNB in clinically node negative patients. Also, meticulous RT planning techniques can prevent radiation induced damage to lymphatics in axilla and decrease lymphedema.

The choice of adjuvant therapy is based on higher risk tumour. Adjuvant hormone therapy is administered when either of the cancers are ER positive. For patients who have undergone bilateral axillary clearance and require chemotherapy, we place chemoport in subclavian vein at a separate session. Implantable port placement at the same session with breast surgery is not recommended as it can lead to greater catheter related complications. Postoperative complications like seroma and wound gaping can cause tube

malposition, blockage and exposure of catheter. Besides after the completion of wound healing, chemoport can be easily placed under local anaesthesia as an outpatient procedure.

International evidence on prognosis of BBCs is divided. Most authors indicate that SBC and MBC diagnosed within 5 years of index cancer are associated with poorer prognosis. Hartmann and colleagues analysed the mortality rates of over 100,000 breast cancer patients from Swedish cancer data base [3]. They found that women with SBC and MBC occurring within 10 years are more likely die of breast cancer compared to unilateral patients. In contrast population based studies from Australia, Switzerland and Geneva demonstrated that BBC was not associated with impaired survival [27-29]. Nichol et al., matched 207 SBC cases with 621 unilateral cancers using 11 high risk variables and found that breast cancer specific survival was not different between two cohorts after adjusting for the high risk features [30]. Similarly Irvine et al., matched 68 SBC patients with 132 unilateral breast cancer patients using 8 variables and observed no significant difference in survival outcomes of two groups [31]. Based on the above findings we can safely conclude that survival in BBC is equivalent or moderately lower than unilateral breast cancer patients.

LIMITATION OF THE STUDY

Our study is limited by sample size and single institution data. Strengths include prospectively collected data base, availability of pathological details in all tumours, accurate follow-up and protocol based treatment to all patients. Important deductions from our study are that majority of second tumours can be picked up at an earlier stage and most of these are estrogen dependent tumours. Treatment decisions should be guided by individual patient and tumour features rather than offering radical treatment uniformly in all BBC cases.

CONCLUSION

Synchronous BBC constitutes about 2% of newly diagnosed breast cancers. In most patients with BBC, the second tumour is identified at an early stage than index tumours supporting the importance of contralateral breast cancer screening at the time of primary diagnosis and during follow-up. BBC occurs more frequently in old age group and majority of these tumours are estrogen dependent. There is good concordance between the index tumour and the contralateral breast cancer with reference to histological type, grade, ER, PR and Her2. Bilateral breast conservation is feasible as in unilateral breast cancer.

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