

# Clinicopathological Profile and Treatment Outcomes of Bilateral Breast Cancer: A Study from Tertiary Cancer Center in South India

## Abstract

**Background:** Bilateral breast cancer (BBC) is a rare clinical entity with limited data regarding clinicopathological aspects and treatment guidelines. **Materials and Methods:** This was an observational study of patients diagnosed with BBC from August 2012 to July 2014. Synchronous breast cancers (SBCs) was defined as two tumors diagnosed within an interval of 6 months and metachronous breast cancer (MBC) as second cancer diagnosed after 6 months. **Results:** Out of 750 breast cancer patients seen during a 2-year period, 35 had BBC. Ten patients were diagnosed as SBC whereas 25 patients as MBC. Among patients with MBC, the average time for development of contralateral breast cancer was 5 years. In 8 patients, the contralateral breast cancer was detected mammography whereas rest 27 patients were detected by clinical breast examination. At a median follow-up of 24 months, 23 (66%) patients were disease free, 9 (26%) patients had disease relapse, and 3 (8%) patients succumbed to the progressive disease. **Conclusions:** Every patient with breast cancer should be regularly followed up with clinical breast examination at a more frequent interval. The role of frequent clinical breast examination appears more than mammography especially beyond 5 years for early detection of contralateral breast cancer.

**Keywords:** Bilateral breast cancer, metachronous breast cancer is, synchronous breast cancer

## Introduction

Bilateral breast cancer (BBC) is a rare clinical diagnosis. There are relatively less data pertaining to the clinicopathological profile, treatment recommendations, and outcome of patients with BBC. Overall the incidence of BBC is 1.4%–12% of all breast cancer reported in various studies.<sup>[1-4]</sup> The incidence of synchronous breast cancer (SBC) is 0.7%–3% whereas that of metachronous breast cancer is (MBC) 5%–10%.<sup>[2,3,5]</sup> This wide variation in the incidence may be attributable to varying time span used to define BBC. Different groups have defined SBC as two tumors occurring within an interval of 1 month,<sup>[6]</sup> 2 months,<sup>[7]</sup> 3 months,<sup>[8]</sup> 6 months,<sup>[9]</sup> or 1 year.<sup>[10]</sup> Controversies also exist about the origin of second cancer (metastatic spread or independent primary) and its prognostic significance. There is a two to six fold increased risk of developing contralateral breast cancer in women with first primary as compared to the general population.<sup>[11]</sup> There is an increasing incidence of BBC due to improved diagnostic techniques, longer survival, and patient education.<sup>[1,12]</sup>

The prognosis of BBC has been reported to be worse than that of unilateral breast cancer (UBC)<sup>[13-16]</sup> and the biological aspects, as well as the optimum therapy, are still remains controversial.<sup>[17,18]</sup> The present study was done to analyze the clinicopathological characteristics and treatment outcome at a tertiary cancer center in South India.

## Materials and Methods

This was an observational study carried out at a tertiary cancer center in South India. Patients diagnosed with BBC in the department of medical oncology were taken into the study. The case files of all patients diagnosed with breast cancer were reviewed from August 2012 to July 2014. Patients diagnosed with BBC were taken up for the study and treatment outcomes as well as the follow-up data were recorded. Two tumors diagnosed within an interval of 6 months was defined as SBCs whereas MBC as second cancer diagnosed after 6 months. The analysis of patient's characteristic including age, pre-/post-menopausal status, family history of breast/ovarian/other

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cancer, mode of detection, and histological features among the two breasts was done. Patients were followed up for treatment outcomes and disease recurrence. Those not on regular follow-up were contacted telephonically.

## Results

A total of 750 breast cancer patients were seen during 2 years, out of which 35 (4.6%) had BBC. Ten patients (28.6%) were diagnosed as SBC whereas 25 patients (71.4%) were diagnosed as MBC. The median age at presentation for BBC was 42 years (range: 24–60 years). All the patients diagnosed with BBC in this study were women. The median age of menarche and first child birth was 13 and 23 years, respectively. Average number of children was 2.3, with the maximum number of children being 5. Thirty-two patients gave a history of breast feeding their child, and 3 were nulliparous. A positive family history of breast cancer was seen in 3 patients only. Median BMI was 24. At the time of diagnosis, 23 were premenopausal and 12 were postmenopausal. Among patients with MBC, the average time for development of contralateral breast cancer was 5 years (range 8 months– 98 months). In 8 patients, the contralateral breast cancer was detected by mammography whereas the rest 27 were detected clinically. Pathologically, out of 70 tumors, 66 were invasive ductal carcinomas (IDC), 2 medullary carcinoma, and 2 poorly differentiated carcinoma. Fifty-seven tumors were of grade 3 and 13 were grade 2. Out of 70 tumors, 26 were triple negative, 38 estrogen receptor (ER)/progesterone (PR) positive, and 16 HER2 positive. The discordance of ER, PR, and HER 2 between right and left breast tumor were seen in 9 (25%), 12 (34%), and 11 (31%) patients, respectively. The clinical and pathological characteristics have been shown in Tables 1 and 2, respectively.

Of the 70 tumors, 56 were treated with modified radical mastectomy and 8 with breast conserving surgery. Six tumors could not be operated on as they were locally advanced, inoperable, and progressed in spite of neoadjuvant chemotherapy (NACT). Six patients with SBC and nine patients with MBC received NACT for contralateral breast cancer. All patients received chemotherapy, radiation therapy, and hormonal treatment as indicated during management. At a median follow-up of 30 months, 23 (66%) patients were disease free, 12 (34%) patients had disease relapse (8 locoregional and 4 systemic recurrences). Among these 12 patients, 3 patients succumbed to disease progression after recurrence.

## Discussion

BBC is a rare clinical entity. The incidence of BBC in our study was 4.6% which was similar to the other published data.<sup>[1-4]</sup> The incidence of SBC and MBC varies considerably because of conflicting cutoff time to define this entity. According to these criteria, range is

**Table 1: Clinical characteristics of bilateral breast cancer**

Variable	Synchronous		Metachronous	
	First tumor	Second tumor	First tumor	Second tumor
Median age at diagnosis in years (range)	39.5 (24-57)		45 (24-60)	
Time interval between two tumor in months	0		60 (8-98)	
Stage				
I	0	1	1	2
II	3	2	6	9
III	6	5	18	10
IV	1	1	0	4

**Table 2: Pathological characteristics of bilateral breast cancer**

Variable	Synchronous		Metachronous	
	First tumor	Second tumor	First tumor	Second tumor
Histological type				
IDC	10	10	25	21
Medullary				2
Poorly differentiated				2
Grade				
I	0	0	0	0
II	3	1	5	4
III	7	9	20	21

IDC – Invasive ductal carcinomas

from 1 month to 1 year which makes a comparison of studies difficult. The incidence of SBC and MBC was 3% and 7% respectively as reported by Chaudary *et al.*<sup>[1]</sup> In 1993 Robinson *et al.* reported the incidence of SBC as 1.7% and of MBC as 2.4%.<sup>[19]</sup> In this study, those having second primary in the contralateral breast within 6 months were defined as SBC and those beyond 6 months as MBC. The incidence of synchronous and MBC in our study was 1.3% and 3.3%, respectively. There is a three times increased risk of developing a second breast cancer in women who developed first breast cancer before the age of 40 years, compared to those who develop first breast cancer after the age of 40 years.<sup>[1]</sup>

Younger age, family history and lobular histology are the risk factors for BBC as reported in literature.<sup>[20-23]</sup> The median age of presentation for BBC in our study was 42 years (24–60 years) which was younger than UBC.<sup>[24]</sup> At the time of diagnosis, 23 patients were premenopausal and 12 patients were postmenopausal in our study. This was an obvious finding due to younger age at presentation for BBC. A positive family history was defined as breast cancer in any first or second degree relative and was seen in only 3 patients (8.5%). The association of positive family history and occurrence of BBC has been reported by Bernstein *et al.*<sup>[21]</sup>

Few studies have shown a possible association between the stages of first breast cancer to the occurrence of second breast cancer.<sup>[25-27]</sup> In the present study, 55% of synchronous and 72% of metachronous first breast cancer were stage III. Among the 70 tumors, 57 (81%) were grade 3 and rest being grade 2. Robbins and Berg first reported lobular carcinoma as the most common histology for BBC.<sup>[28]</sup> The most common histology reported by Bernstein *et al.*<sup>[21]</sup> was medullary carcinoma and according to Li *et al.*,<sup>[22]</sup> IDC was the common histology in BBC. In the present study, the most common histology was an invasive ductal carcinoma, present in 66 patients (94%). Medullary carcinoma was seen in 2 tumors (3%) and poorly differentiated carcinoma in another 2 tumors (3%).

Gong *et al.* emphasized that the synchronous cancer were more likely to have same TNM stages among the first and second tumor as compared to metachronous cancer. According to them, the concordance of stage between two tumor was 64% in synchronous and 32% in the metachronous breast tumor.<sup>[29]</sup> In the present study, the concordance of TNM stage between right and left breast tumor was found in 6 patients of synchronous whereas 9 patients (36%) with MBC had same TNM staging of right and left breast tumor.

There are only few studies that have reported the association of ER/PR and HER2 status with risk of developing second breast cancer. Women with ER positive breast cancer are associated with lower risk of recurrence and better prognosis.<sup>[30]</sup> The reduced risk of BBC in premenopausal women with ER positive first tumor was also reported by Mariani *et al.*<sup>[31]</sup> No association of BBC with hormonal status has been reported by Li *et al.*<sup>[22]</sup> Saad *et al.*, and Beckmann *et al.*, reported 76% and 87% ER positivity in BBC.<sup>[32,33]</sup> In our study, 32 tumors (45%) were ER positive, 17 tumors (24%) were PR positive. The incidence HER2 overexpression as reported by Gong *et al.* in BBC was 44%.<sup>[29]</sup> The higher incidence of HER2 expression in BBC has been attributed to the poor prognosis. In our study, HER2 positivity was seen in 16 tumors (23%). Twenty-six tumors (37%), in our study, were triple negative. On the classification of the tumor based on surrogate IHC markers,<sup>[34]</sup> 13 tumors were luminal A; 24 tumors were luminal B; 6 tumors were HER2 enriched; and 26 tumors were basal type. The incidence of ER/PR positive tumors was less and that of TNBC subtype was higher. Baker *et al.* reported concordance rates in ER, PR, and Her2 statuses to be 73%, 64%, and 88% respectively.<sup>[35]</sup> In our study, the concordance rate of ER, PR, and HER2 between right and left tumor were seen in 75%, 66%, and 69% patients, respectively.

Most of the surveillance guidelines suggest yearly examination and mammography for patients with breast cancer after 5 years.<sup>[36,37]</sup> Fifty percent of the contralateral breast cancer were detected after 5 years of follow-up. In

the present study, the contralateral breast cancer was more commonly detected through clinical examination rather than mammography. This may suggest a role for more frequent clinical examination beyond 5 years for the early detection of contralateral breast cancer.

There is no clear consensus regarding the prognosis of BBC. Most of the studies have shown that BBC diagnosed within 5 years of index cancer is associated with poorer prognosis. The mortality rates of more than 100,000 breast cancer patients were analysed by Hartmann and colleagues from Swedish cancer data base.<sup>[8]</sup> They found higher likelihood of death in BBC occurring within 10 years when compared to unilateral patients. In contrast, there was no difference in survival was found in population based studies from Australia, Switzerland, and Geneva.<sup>[14,38,39]</sup> In the present study, after a median follow-up of 30 months, 23 (66%) patients were disease free and 12 (34%) patients had disease relapse. Those with disease relapse 8 had locoregional whereas 4 had systemic recurrences. Among these 12 patients with disease recurrence, 3 patients succumbed to disease progression.

### Limitation of study

An important limitation of our study was that most patients with HER2 positive tumors did not receive anti-HER2-based therapy due to financial constraint. Only 4 out of 16 HER2 positive tumors got HER2 directed therapy making the survival data for this subgroup difficult to interpret.

### Conclusions

BBC represents a small subset of breast cancer. The incidence of BBC is higher in younger premenopausal women as compared with older women. The contralateral breast cancer can be detected in the early stage with a clinical examination at regular intervals. There may be a role for more frequent clinical examination beyond 5 years for detection of MBC. These tumors have with poor outcome with standard treatment as compared to UBC and treatment should be individualized based on tumor characteristics.

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### Conflicts of interest

There are no conflicts of interest.

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