

Contralateral Breast Primary in Breast Cancer Survivors-An Experience from a Tertiary Care Centre in Thiruvananthapuram, Kerala, India

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ABSTRACT

Introduction: Improved life expectancy after breast cancer treatment has led to increased incidence of contralateral breast cancers. There are no well established guidelines for the management of these cancers. There is a paucity of Indian data regarding contralateral breast cancers.

Aim: To describe the clinicopathological profile and prognostic outlook of patients with contralateral breast cancers.

Materials and Methods: This was a retrospective cross-sectional study in which all patients who underwent surgery for non metastatic breast cancer between January 2006-December 2010 at Regional Cancer Centre, Thiruvananthapuram, Kerala, India, were identified. The follow-up data of these patients (6240 patients) were retrieved from medical records division in January 2020. The medical records of all these patients who developed contralateral breast cancer were analysed.

Results: A total of 98 patients (1.57%) developed contralateral breast cancer. Most of the second breast cancers were presented at a lower stage than index cancer. Twenty five patients (25.51%) contralateral breast cancers were detected after five years. A

total of 58 patients (59.18%) had interval cancer. Among them, 32 (55.17%) were detected by the treating doctor and 26 patients (44.83%) were symptomatic. The median duration of follow-up was 98 months (range 24-150 months). The five year Overall Survival (OS) was 80.5% and five year Disease Free Survival (DFS) was 62.8%. The patients who developed contralateral breast cancer within three years had lower five year OS when compared to those who developed after three years (75.5% vs 86.7% $p=0.85$). Five year OS was 74.8%, 81% and 85% for patient reported interval cancer, physician detected interval cancers and mammogram detected cancers respectively ($p=0.9$).

Conclusion: Most contralateral breast cancers presented in a lower stage than index cancer. Contralateral breast cancer has got a reasonably good five year OS. There is no significant OS difference between mammogram detected second cancer and interval cancer. There was a need for more frequent clinical breast examination even after five years to detect contralateral primary in an early stage. Cost effectiveness of frequent follow-up mammogram examinations compared to clinical examination should be evaluated in future prospective studies.

Keywords: Clinical breast examination, Follow-up mammogram, Interval cancers

INTRODUCTION

Contralateral breast primary cancer is not uncommon. It is known that adjuvant hormonal therapy decreases the incidence of contralateral breast cancers [1,2]. The improvement of breast cancer treatment over the past decades has increased the number of cancer survivors and hence more patients are prone to the development of contralateral breast cancers in their later life. A breast cancer survivor has a two to six-fold increased risk for a second primary in the contralateral breast [3]. The cumulative absolute risk of contralateral second primary at 10 years is 4.1% in patients with the family history and 8.1% in patients with breast cancer in first degree relative [4].

Diagnosis of contralateral breast primary cancer is a real challenge as there are no universally accepted standard protocols to differentiate between a second primary and a metastasis. The various criteria available are Haagensen CD and Stout AP clinical criteria, Robbins GF and Berg JW pathological criteria and Chaudary MA et al., pathological criteria among which the latter is the most commonly quoted one [5-7]. Chaudary MA et al., criteria is based on clinical and pathological findings. The criteria favouring contralateral primary include: (i) the presence of carcinoma in situ in the contralateral tumour; (ii) the second primary should be histologically different from the first tumour; (iii) the degree of the second primary histological differentiation should be higher than the first tumour; (iv) if there is no histological difference, then there should not be evidence of local, regional or distant metastasis from the first tumour. The risk factors for contralateral breast primary cancer include young age at diagnosis, genetic mutations, family history, lobular histology and advanced stage of primary cancer [8-10].

There are no well established guidelines for the management of these cancers. There is a paucity of Indian data pertaining to the clinicopathological profile and prognostic outlook of patients with contralateral breast cancers. The available Indian studies are on a small number of patients [9,11-14]. The objective of this study was to describe the clinicopathological profile and survival outcome of patients with contralateral breast primary cancer.

MATERIALS AND METHODS

The present study was a retrospective cross-sectional study conducted after obtaining approval from the Institutional Review Board (Approval number: 01/2018/06). All patients who underwent surgery for breast cancer between January 2006 to December 2010 at Division of Surgical Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India, were identified. Patients who had oligometastatic disease or who underwent surgery for palliation were excluded. During the above period, 6240 patients with non metastatic carcinoma breast underwent surgery were included.

The follow-up data of these patients were retrieved from medical records division in January 2020. It was found that among these 6240 patients, 98 (1.57%) developed a second primary in contralateral breast cancer. The medical records of all these patients were retrieved and information was collected using a structured proforma. Study variables collected included demographic details, clinicopathological factors like time gap between two cancers, mode of detection of contralateral breast cancer, Tumour (T) stage, Node (N) stage, hormone receptor status of both cancers. All patients

were contacted over phone to know the status at last follow-up (whether they were alive disease free, alive with disease or died).

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 11.0.1, Lead Technologies, Inc., US. Continuous variables were expressed as mean and Standard Deviation (SD) and categorical variables as counts and percentages. DFS and OS were computed using the Kaplan-Meier method. Survival curves were obtained by using the Kaplan-Meier method and clinicopathologic factors were compared with the log-rank test.

RESULTS

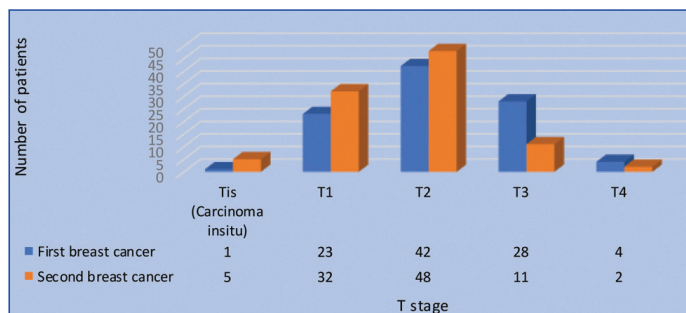
A total of 98 patients (1.57%) developed contralateral breast cancer during the study period. Among them, 52 patients (53.06%) were premenopausal at the time of diagnosis of first breast cancer. The mean age at diagnosis of first breast cancer was 51.2 years. A significant family history of breast cancer in the first or second degree relatives was present only in 11 patients (11.22%). The mean age at menarche was 12.9 years. The mean age of first full term pregnancy was 22.8 years. The mean duration of breastfeeding was 42.1 months. The median number of children was two.

Fifty five (56.12%) patients developed second cancer within three years and 18 patients (18.37%) developed second cancer between three and five years of diagnosis of first breast cancer. One important finding was that in around 25 patients (25.51%), a contralateral second breast cancer was detected after five years. At the time of diagnosis of second cancer, 28 patients (28.57%) were on hormonal treatment. A total of 40 cases (40.82%) were detected during the follow-up mammogram examination and 58 patients (59.18%) had interval cancer i.e., between two follow-up mammogram examinations. Among the interval cancers, 32 (55.17%) of them were detected by the treating doctor during clinical examination and 26 patients (44.83%) were symptomatic [Table/Fig-1].

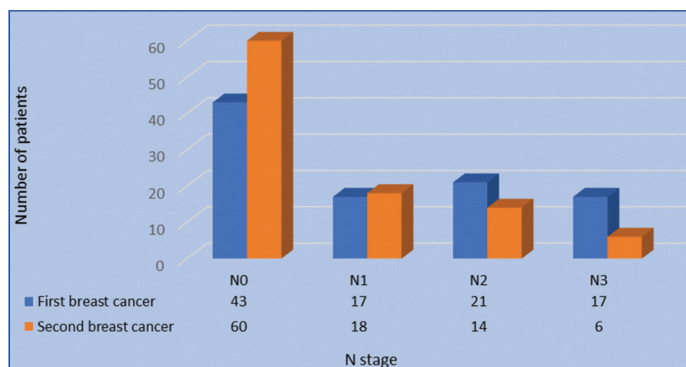
Parameters		Total=98 patients
Interval cancers (n=58)	Patient reported cancers	26 (44.83%)
	Detected by treating physician	32 (55.17%)
Mammogram detected cancers		40 (41%)

[Table/Fig-1]: Contralateral breast cancers: Mode of detection.

Majority of the first breast cancers were T2 (42 patients, 42.86%) or T3 (28 patients, 28.57%). Most tumours in second breast cancers were T1 (32 patients, 32.65%) or T2 (48 patients, 48.98%). Ductal Carcinoma In Situ (DCIS) was seen in one patient and five patients among the first breast cancer group and the second breast cancer group respectively. A total of 43 patients (43.88%) were node negative at diagnosis of first breast cancer whereas it was 60 patients (61.22%) in second breast cancer [Table/Fig-2,3]. Most of the patients had stage 2 (47 patients, 47.96%) or stage 3 (40 patients, 40.82%) disease at the time of diagnosis of first cancer, whereas the incidence of stage 1 tumour (24 patients, 24.49%) was higher in second breast cancer. Hormonal receptor positivity was seen in 41 patients (41.84%) in first breast cancer, but only in 21 patients (21.42%) in second breast cancer. In first breast cancer HER2/neu receptor status was positive in 20 patients (20.41%) and it was unknown in 54 patients (55.1%) whereas in second breast cancer 31 patients (31.63%) were HER2/neu positive. On analysis to identify the extent of concordance with regard to clinical stage [Table/Fig-4] it was found that there was 31.63% concordance (31 patients) in TNM stage between two cancers [15]. Out of 41 hormone receptor positive patients only 6 patients (14.63% concordance) developed a hormone receptor positive second breast cancer and among 57 hormone receptor negative patients 42 developed (73.68% concordance) hormone negative contralateral breast cancer [Table/Fig-5].



[Table/Fig-2]: T stage distribution of first and second breast cancers. Tis (Carcinoma in situ)



[Table/Fig-3]: N stage distribution of first and second breast cancers.

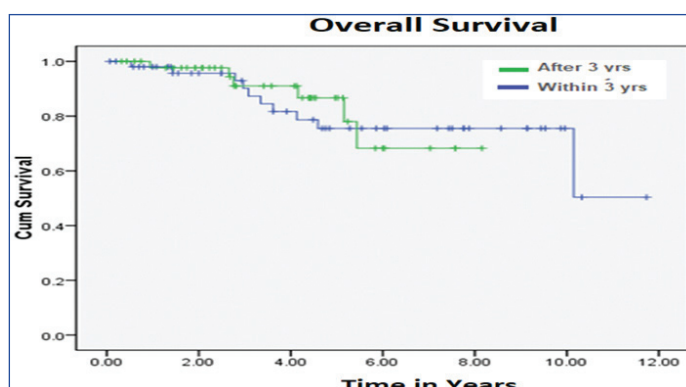
First breast cancer	Second breast cancer				Total
	Stage 0	Stage 1	Stage 2	Stage 3	
Stage 0	0	1	0	0	1
Stage 1	3	3	2	2	10
Stage 2	2	13	21	11	47
Stage 3	0	7	26	7	40
Total	5	24	49	20	98

[Table/Fig-4]: AJCC 7th stage concordance between first and second cancer [15].

First breast cancer	Second breast cancer		Total
	Hormone receptor positive	Hormone receptor negative	
Hormone receptor positive	6	35	41
Hormone receptor negative	15	42	57
Total	21	77	98

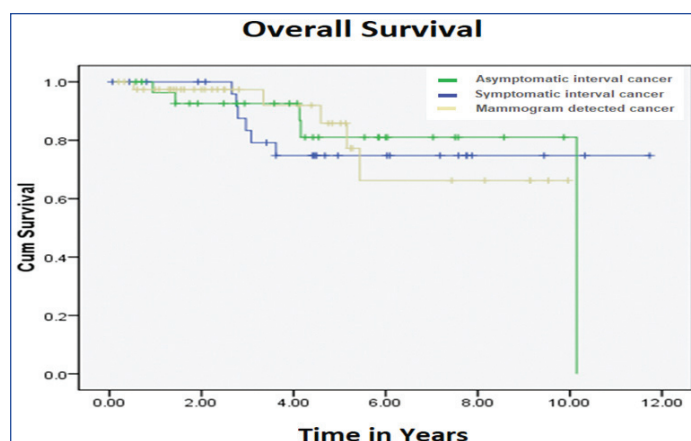
[Table/Fig-5]: Comparison of hormonal receptor status between first and second breast cancers.

The median duration of follow-up was 98 months (range 24-150 months). The five year OS was 80.5% and five year DFS was 62.8%. The patients who developed contralateral breast cancer within three years had lower five year OS when compared to those who developed after three years (75.5% vs 86.7% p=0.85). This difference was not statistically significant [Table/Fig-6]. Five year OS was 74.8%, 81%



[Table/Fig-6]: Kaplan Meier curve comparing five year OS between contralateral breast cancers detected within three years and after three years.

and 85% for symptomatic interval cancer, asymptomatic interval cancer detected by physician and asymptomatic cancer detected by follow-up mammogram respectively. But this difference was not statistically significant ($p=0.9$) [Table/Fig-7].



[Table/Fig-7]: Kaplan Meier curve comparing three year OS between asymptomatic interval cancer, symptomatic interval cancer and follow-up mammogram detected cancer.

DISCUSSION

The incidence of contralateral breast primary has increased with increase in number of breast cancer survivors. The management of these tumours is a clinical challenge as there are no standard management protocols. The aim of this study was to describe the clinicopathological profile and survival outcome of these patients. This study was one of the largest studies on contralateral breast primary among Indian patients.

This was a retrospective analysis of 98 patients who developed contralateral breast cancer. Most of them were above the age of 40 years. Bernstein JL et al., first reported the association of positive family history and occurrence of contralateral breast cancer [16]. But in this study significant family history of breast cancer in first or second degree relatives were seen only in 11.22% of patients. When clinicopathological factors were analysed, it was seen that most of the tumours in second breast cancer were in a lower T stage. The T2, T3 tumours were more common in the first breast cancer whereas T1, T2 tumours were more common in the second breast cancer. Similarly, the proportion of N0 patients was more in second breast cancer. As a result, it was seen that second breast cancer presented in an equal or lower stage than index cancer.

The proportion of patients with hormone positivity was relatively low in this study. This may be due to the fact that the risk for contralateral breast cancer is low for patients on endocrine treatment [17]. On the contrary, some other authors reported higher proportion of hormone receptor positivity in patients with bilateral breast cancers (Saad RS et al., and Beckmann KR et al., 76% and 87%, respectively) [18,19]. Studies have reported an incidence of HER2/neu overexpression to up to 44% [20]. During the study period, HER2/neu receptor was not commonly tested in our institute hence it was difficult to arrive at a meaningful conclusion regarding HER2/neu status.

In the present study, there was only 31.63% concordance for TNM stage in the first and second breast cancer. A study by Gong SJ et al., showed similar rates with 32% concordance for stage in patients with metachronous breast tumours [20]. Similarly, another Indian study showed 36% concordance for stage [21]. In this study, concordance for hormone positivity was 14.63% and for hormone negativity was 73.68% between the first and second breast cancer. Studies have shown a concordance rate for hormone receptor status to range from 61-75% [21,22].

Most of the guidelines recommend clinical examination and mammogram studies as methods for follow-up. The National Comprehensive Cancer Network (NCCN) recommends quarterly clinical examination for up to 5 years followed by annual examination

and annual mammogram examination [23]. The European Society for Medical Oncology (ESMO) guidelines suggest regular follow-up visits every 3-4 months in the first two years, every 6-8 months from 3-5 year and annually thereafter along with an annual mammogram [24]. There is no randomised data to support any type of follow-up methods or protocol. But the benefit cost of follow-up and burden to the health system were to be considered before adopting any follow-up protocol. In this study, 43.9% contralateral cancers were detected after three years and 25.5% were detected after five years. This may suggest a role for more frequent follow-up even beyond five years for the early detection of contralateral breast cancer. Similarly, 60% contralateral cancers were interval cancers and half of them were detected by clinical examination rather than mammography. This suggests the importance of clinical examination during each follow-up visit rather than excessively depending on mammogram reports.

In this study, the patients who developed second primary within three years had a lower survival than those who developed after three years. This may be due to the aggressive biology of the disease. In this study, 58 patients (59.18%) developed interval cancer. Various authors have reported that interval breast cancer is associated with an advanced stage at presentation but there is no strong evidence on the survival of these cancers. In one study, it was seen that interval breast cancer presented with larger tumours than the screen detected breast cancers but there was no survival difference [25]. On the contrary, another study which involved 2245 patients showed that interval cancers had more advanced tumours with a lower five year OS when compared to screen detected breast cancer [26]. In this study, there was no difference in five year OS between interval and mammogram detected cancers. This implies that early detection of a non palpable breast cancer by annual mammogram examination may not translate into a survival advantage for the patient.

Limitation(s)

First limitation was the retrospective nature of the study. Another important limitation of this study was that HER2/neu receptor status of most of the patients were not known and lack of HER2/neu directed therapy in these patients might have influenced the survival outcome.

CONCLUSION(S)

Second cancer which develops in the contralateral breast is a matter of concern for patients with breast cancer. Most of them present in a lower stage than index cancer. The contralateral breast cancer has got a reasonably good five year OS. There is no significant OS difference between mammogram detected second cancer and interval cancer. There is a need for more frequent clinical breast examination even after five years to detect contralateral primary in an early stage. The cost-effectiveness of frequent follow-up mammogram examinations compared to clinical examination should be evaluated in future prospective studies.

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