

Clinical features and prognostic factors of early breast cancer at a major cancer center in North India

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Abstract

BACKGROUND: Data on the clinical profile of early breast cancer (EBC) from India is scant. Due to differences in genetics, environment, lifestyle, socio-demographic structure and ethnicity, the presentation and behavior of breast cancer in India may be different. **AIMS:** To analyze the clinical presentation and outcome of EBC patients. **SETTINGS AND DESIGN:** A single center retrospective study. **MATERIALS AND METHODS:** Data from 487 EBC patients registered and treated at our institute from 1993 through 1999 were analyzed. Cox's multivariate regression test was used to determine prognostic factors for overall and disease-free survival (OS & DFS). **RESULTS:** The median age was 47 years and 49.7% patients were pre-menopausal. Ninety-six per cent patients presented with a lump. Stages I, IIa, and IIb comprised 7.8%, 38.8%, and 47.6% respectively. Only 11.3% patients opted for breast-conserving surgery (BCS) while the remaining 88.7% underwent modified radical mastectomy (MRM). Adjuvant chemotherapy was administered to 275 (56.5%), and radiotherapy to 146 (29.9%). Estrogen receptor status was known in 173, of whom 93 (53.7%) were positive. Most patients were prescribed Tamoxifen for 5 years. At a median follow-up of 48 months, 126 (25.9%) patients had relapsed (systemic 107, loco-regional 19) and 94 (19.3%) had died. Five-year DFS and OS were 73% and 78%, respectively. On multivariate analysis, \geq four positive nodes adversely influenced survival ($P < 0.01$). **CONCLUSIONS:** The median age at presentation was 47 years, significantly lower than most Western figures. The majority (86.4%) had a lump size $>$ two cm. BCS was done in only 11% and the rest underwent MRM. Nodal involvement was the significant prognostic factor.

Key Words: Breast cancer, India, epidemiology, prognosis

Introduction

The age-standardized rates of breast cancer in India are significantly lower, almost one quarter to one-third of those in North America and Europe respectively.^[1] The postulated reasons for the lower incidence of this disease are believed to be lower socioeconomic status, delayed menarche (14 years *vs.* 12.6 years in white women), relatively early age at birth of first child, high parity and nearly universal and prolonged breast-feeding. However,

the mortality rates are proportionally higher, with an incidence/mortality ratio of 0.48 compared with 0.25 in North America.^[2] Late diagnosis is a major factor for increased mortality as the majority of the patients present in advanced or metastatic stage. This is primarily attributed to lack of access to medical facilities, virtually non-existent breast cancer screening programs, lack of awareness and social-cultural attitudes. Accordingly, five-year survival rates have been poorer, reported as 42% and 48% in two population-based

studies.^[3,4] Early breast cancer (EBC) constitutes about 30% of the breast cancer load in our country.^[5] There is no published case series on EBC from India. We undertook this study to analyze the presentation and outcome of EBC in a major cancer center in North India.

Materials and Methods

Case records of all the female patients registered at the Breast Cancer Clinic at our institute over a seven-year period from January 1993 to December 1999 were retrieved. EBC was defined as tumors of less than five centimeters (T1, T2), with either impalpable (N0) or palpable (N1) but not fixed lymph nodes with no evidence of distant metastases (M0), corresponding to Stages I and IIa by AJCC/UICC TNM classification.^[6] Patients with tumors more than five cm (T3) were included if they had N0 M0 disease, Stage IIb. All EBC cases with pathological confirmation either by fine needle aspiration cytology or core biopsy and who had been treated by at least one mode of treatment (surgery, chemotherapy or radiotherapy) were included in the analysis. Data from 487 patients were thus analyzed. A proforma was completed for each patient that included social, demographic, clinical, and treatment profile. All patients were followed up every three months after completion of initial treatment and those who failed to attend were contacted by phone or by personal visits. Data available as of May 2001 were used for the analysis of end-points and survival. So the last year of follow-up was 2001.

Statistical methods

The association between the characteristics of the patients and survival was evaluated with a Cox-model in univariate and multivariate analysis. Disease-free survival (DFS) was defined as the interval from the date of surgery to relapse, the appearance of a second primary cancer (including a contralateral breast cancer) or death, whichever occurred first. Overall survival (OS) was defined as the interval from the date of diagnosis to death or last contact with the patient. Cumulative survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Two-tailed probability (*P*) values of ≤ 0.05 were regarded as significant. Exact *P* values were reported only when *P* ≥ 0.01 .

Results

The median age was 47 years (range 23-82 years), 242 (49.7%) women were pre-menopausal and 236 (48.5%)

postmenopausal and for nine the menopausal status was unknown. Median ages at menarche and menopause were 14 years (range 12-17 years) and 46 years (36-56 years), respectively. Thirty-four patients (7%) had a first-degree relative with history of breast cancer. Four hundred and seventy women (96.5%) presented with breast lump, 77 (15.8%) had pain and 24 (4.9%) had nipple discharge in addition. Details of clinical and pathological staging are shown in Table 1.

All patients underwent surgery; 258 (52.9%) were operated on in other hospitals and then referred to our center for further management. Eighty-four (17.2%) out of these required an additional surgical procedure due to inadequate or close margins or inadequate axillary clearance. Modified radical mastectomy (Patey's) was the commonest procedure performed in 432 (88.7%) patients, and breast-conserving surgery (BCS) was carried out in 55 (11.3%) patients. Invasive ductal carcinoma was the commonest histology in 452 (92.8%) patients followed by invasive lobular carcinoma in 14 (2.9%), and medullary carcinoma in seven (1.4%).

Adjuvant radiotherapy was given to 146 (29.9%) patients; indications included T3 tumor size, ≥ 4 positive axillary nodes, positive margins, and BCS. Chemotherapy was administered to 275 (56.5%) women. Most of the patients (*n*=250) were given CMF regimen (cyclophosphamide, methotrexate and 5-fluorouracil) and 25 (9.1%) received anthracycline-based chemotherapy. Estrogen receptor (ER) status was known for only 173 women of whom 93 (53.7%)

Table 1: Clinical and pathological staging of 487 early breast cancer cases

Staging	Clinical		Pathological	
Tumor size	No.	Patients (%)	No.	Patients (%)
T1	55	(11.3)	134	(27.5)
T2	361	(74.1)	298	(61.2)
T3	60	(12.3)	29	(6.0)
Tx	11	(2.3)	26	(5.3)
Nodal status				
N0	254	(52.2)	246	(50.5)
N1	225	(46.2)	217	(44.6)
Nx	8	(1.6)	24	(4.9)
Stage				
I	38	(7.8)	79	(16.2)
II a	189	(38.8)	180	(37.0)
II b	232	(47.6)	183	(37.6)
III	21	(4.3)	None	
Unknown	7	(1.4)	45	(9.2)

were positive. Most patients therefore had unknown ER status and, as was the practice at that time, were also prescribed Tamoxifen. The median duration of Tamoxifen use was 43 months. Ovarian ablation was performed in 62 (26%) premenopausal patients by open laparotomy or laparoscopic surgery in 34 patients and by radiotherapy in the remaining. All patients received some form of adjuvant systemic therapy except for seven patients registered during 1993.

At a median follow-up of 48 months, 126 (25.9%) patients had relapsed. Thirteen (2.7%) had local recurrence; six (1.2%) had recurrence in regional lymph nodes and 107 (22%) in distant organs. Bone was the commonest site of first metastatic recurrence in 32 patients followed by lung—30, liver—20, brain—13, nodes—seven, contralateral breast—two, skin—one, choroid—one and pericardium—one. At last follow-up, 354 (72.7%) patients were alive and disease-free, 39 (8%) were alive with disease and 94 (19.3%) had died; 85 (90.4%) had died due to disease progression, one due to chemotherapy toxicity and eight deaths were unrelated to breast cancer.

DFS and OS at five years were 73% and 78% respectively (Figures 1, 2). In univariate analysis age, tumor size, nodal status, stage and number of positive lymph nodes emerged as significant factors (Table 2). When multivariate analysis of all significant factors was performed, lymph node status emerged as the only significant prognostic factor ($P < 0.01$), Figures 3 and 4.

Discussion

Breast cancer accounts for 19-34% of all cancer cases among women nationally.^[7-9] As per the data from

national and regional cancer registries, it is the commonest cancer amongst women in Delhi, Mumbai, Ahmedabad, Kolkata and Trivandrum.^[7-11] In all other Indian registries, it is listed as the second leading site among women. The age-standardized incidence rates vary from 9-28.6 per 100,000 women, the lowest being from the rural area-based registry Barshi.^[8] The majority of the patients seek medical advice when the disease is fairly advanced. EBC constitutes only 30% of the breast cancer cases seen at regional cancer centers in India^[3] whereas it constitutes 60-70% of cases in the developed world. There is no prospective or retrospective published case series on EBC from India.

The median age at presentation was 47 years. The incidence rates in India begin to rise in the early thirties and peak at ages 50-64 years.^[8] In the US, rates peak at the age group of 75+ years. Age-specific incidence rates in India remain relatively stable compared with the US where rates rise dramatically after 65 years of age. The lower age at diagnosis is also seen for other cancers in India, the reasons are not entirely clear but a major factor could be under-diagnosis and under-reporting amongst the elderly population.^[12] There was equal distribution of pre- and post-menopausal women, 49% vs. 48% respectively. It is reported that whereas 73% of white female patients are postmenopausal at diagnosis, only 35%, 49%, and 52% of Asian, black, and mixed-race patients, respectively, are postmenopausal.^[13]

In our series, 16% patients had Stage I and 74% had Stage II disease. This is in contrast to that reported in studies from developed countries. In a study by Kemperman et al,^[14] 58% of the patients with EBC had Stage I and 33% had Stage II disease. Mansfield et al^[15] and Jacobson et al^[16] with 60% and 52% patients

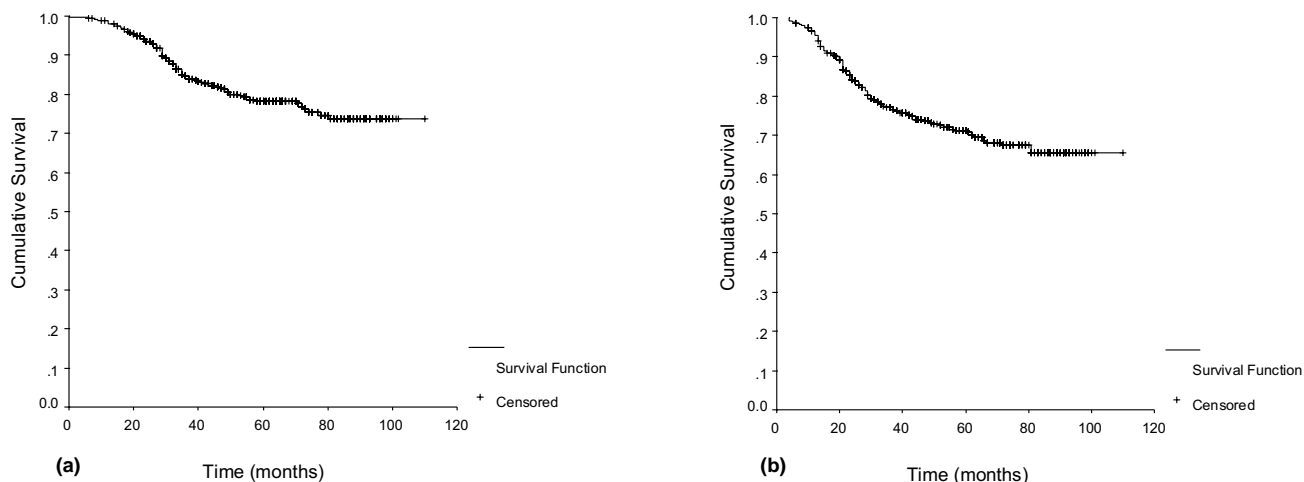


Figure 1: Kaplan-Meier curves of overall survival (a), and disease-free survival (b) for 487 early breast cancer cases

Table 2: Factors affecting outcome on univariate analysis in 487 early breast cancer cases

	Total	Relapse n (%)	Deaths n (%)	DFS Months	P	OS Months	P
Menopausal status							
Pre	242	72 (29.7)	48 (19.9)	68	NS	79	NS
Post	236	53 (22.4)	44 (18.5)	76		76	
Age*							
<30	21	10 (47.6)	8 (38.1)	42	0.01	57	0.04
30-50	285	80 (28.0)	54 (19.1)	71		79	
>50	181	36 (20.0)	31 (17.1)	79		80	
Tumor size*							
T1	134	23 (17.1)	14 (10.4)	82	0.03	87	<0.01
T2	298	91 (30.5)	73 (24.5)	67		74	
T3	29	6 (20.6)	5 (17.2)	82		84	
Tx	26	6 (23.8)	2 (7.6)	76		90	
Nodal status*							
N0	246	42 (17.0)	35 (14.2)	83	<0.01	85	0.01
N1	217	74 (34.1)	54 (25.0)	62		72	
Nx	24	10 (41.6)	4 (16.0)	63		81	
Stage*							
I	79	9 (11.3)	6 (7.5)	88	<0.01	91	<0.01
Ila	180	38 (21.1)	32 (17.7)	78		82	
Ilb	183	64 (34.9)	49 (26.90)	64		72	
Unknown	45	15 (33.3)	6 (13.0)	67		84	
No. Lymph-nodes*							
0	246	42 (17.0)	35 (14.2)	84		86	
1-3	151	43 (28.5)	29 (19.3)	70	<0.01	79	<0.01
≥4	66	31(51.5)	26 (41.0)	46		58	
ER status							
Positive	93	19 (20.4)	11 (11.8)	79	NS	87	NS
Negative	80	24 (30)	12 (15.19)	63		81	
Unknown	314	83 (26.4)	70 (22.2)	73		76	
Surgery							
MRM	432	116 (26.8)	89 (20.6)	79	NS	77	NS
BCS	55	10 (18.1)	4 (7.2)	72		92	

Table 2: Continued

	Total	Relapse n (%)	Deaths n (%)	DFS Months	P	OS Months	P
Adjuvant chemo							
Yes	275	80 (29.0)	58 (21.1)	68	NS	76	NS
No	212	46 (21.7)	35 (16.4)	78		82	
CMF	249	69 (27.7)	50 (20.1)	70		77	
FEC	25	11 (44)	8 (32)	55		65	
Ov. S							
No	180	57 (32.3)	38 (20.8)	67	NS	76	NS
Yes	62	15 (25.5)	11 (18.4)	74		82	
Treatment groups (all)							
Tam + CT	221	65 (29.4)	49 (22.1)	68		74	
Tam	190	42 (22.1)	31 (16.2)	77	NS	83	NS
Tam + CT+ Ov. S	46	12 (26.0)	7 (15.5)	73		87	
Tam + Ov. S	16	3 (18.7)	3 (18.7)	81		80	
CT	7	3 (42.8)	2 (28.5)	53		68	
No Adjuvant	7	1 (14.2)	1 (14.2)	83		83	
Treatment groups (Premenopausal)							
Tam + CT	127	44 (34.6)	27 (21.2)	63		76	
Tam	43	9 (20.9)	8 (18.6)	78	NS	81	NS
Tam + CT+ Ov. S	45	12 (26.6)	8 (17.8)	73		85	
Tam + Ov. S	15	3 (20.0)	3 (20.0)	79		80	
Treatment groups (Postmenopausal)							
Tam + CT	93	21 (22.5)	22 (23.6)	75		69	
Tam	142	32 (22.5)	22 (15.4)	77	NS	82	NS

Abbreviations: DFS: disease-free survival, OS: overall survival, NS: not significant, ER: estrogen receptor, BCS: breast conserving surgery, MRM: modified radical mastectomy, Tam: Tamoxifen, CT: chemotherapy, Ov. S: ovarian suppression, CMF: Cyclophosphamide, Methotrexate, 5-fluorouracil, FEC: 5-fluorouracil, Epirubicin, Cyclophosphamide.
*The favorable clinical prognostic factors in the univariate analysis were: age, tumor size, nodal status, stage, and number of positive lymph nodes. Multivariate analysis, however, retained the number of positive lymph nodes as the only prognostic factor that affected DFS and OS ($P < 0.01$).

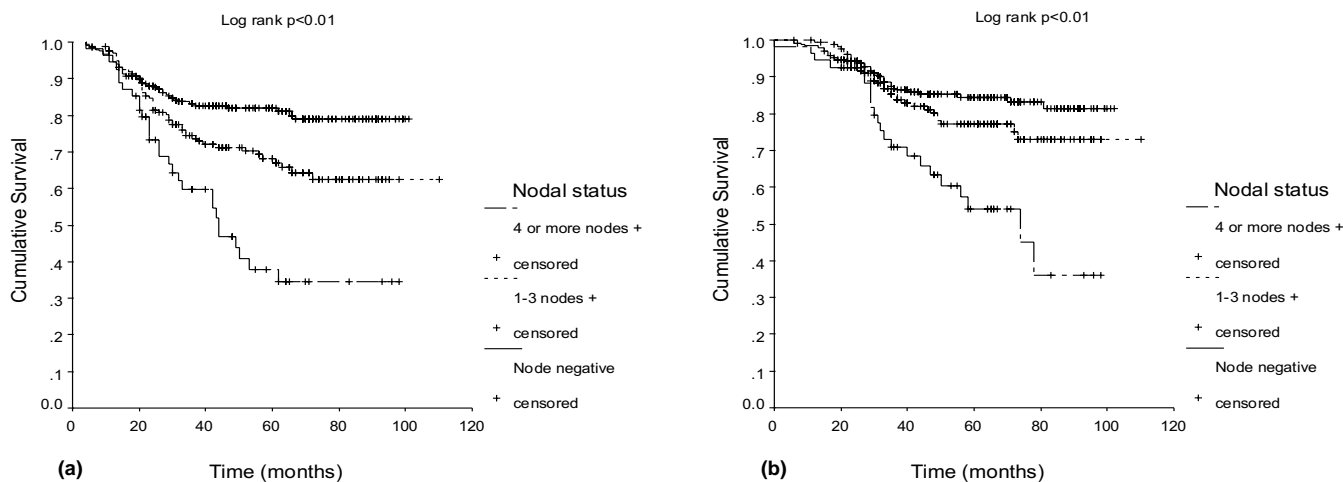


Figure 2: Kaplan-Meier curves of disease-free (a) and overall survival (b) for 487 patients with early breast cancer, depending upon the number of lymph nodes involved

with Stage I respectively also reported similar results. In almost all developed countries, the use of routine screening mammography has led to the detection of very early lesions. As mammographic facilities are not widely available here and there is no nation-wide breast-screening program, the commonest mode of presentation remains a lump in the breast, 96% of the patients in the present series presented with a breast lump. Besides this, other determinants like genetic, socioeconomic, cultural factors and accessibility to medical centers with cancer facilities and the dominance of traditional medicine practitioners in many areas has a major impact on incidence and survival.

Surgery was performed initially on all the patients. BCS was done in only 11% patients. The acceptance of BCS in India is different from that in the developed world. Data from the American College of Surgeons show that in 1995, 58% of Stage I and 36% of Stage II cancers were treated by breast-sparing techniques.^[17] In an annual review of the United Kingdom National Screening Programme, the breast conservation rate in about 6000 screen-detected cancers was 75%.^[18] In a study from our center, BCS was offered to 200 suitable breast cancer patients between June 1993 and June 1998; 25% opted for breast conservation and the remaining preferred mastectomy.^[19] Over the past five to six years, however, the trend is changing especially in the urban areas, as more women are opting for breast conservation. ER status was not routinely tested in our patients during the earlier part of the study period, hence this information is available in only 35% of patients, 53% of these being positive. In previous two studies from India by Raina et al^[20] and Redkar et al,^[21] ER positivity was shown to be 50.5% and 43.9%, respectively. At least 60-80% of the patients are found

to be ER-positive in the studies reported from Europe and America.^[22,23] These differences in receptor distribution between Indian and Caucasian patients might be attributed to either lower average age at diagnosis of Indian patients or real racial differences. CMF was the preferred chemotherapy because it was more cost-effective, however, of late this trend has changed and anthracycline-based chemotherapy has become the standard.

We observed first recurrences at loco-regional sites in 4% of the patients as compared with 22% in metastatic sites. In an EORTC trial, the actuarial recurrence at eight years was nine per cent in Stage I and Stage II patients treated with surgery followed by RT.^[24] In the Milan trial, loco-regional recurrence following postoperative RT and CT was 11%.^[25] Our lower rate of loco-regional recurrences may be due to more frequent practice of mastectomy. For the whole cohort of patients, DFS and OS in our study were 73% and 78% respectively. Patients with Stage I had DFS and OS of 88% and 91% respectively while the corresponding figures for Stage II A were 78% and 82% and that for II B 64% and 72%. These figures are consistent with the five-year relative survival rates of 98%, 88%, and 76% for Stages I, II A and II B, respectively as per American Cancer Society statistics.

In conclusion, breast cancer is a major public health problem in India. Late presentation is a major concern, as large numbers of EBC patients are still diagnosed in clinical Stage II. Patient preference for mastectomy is an important reason for the under-utilization of breast conservation therapy. Education/awareness campaigns, improvement of socioeconomic conditions, better access to diagnostic resources, availability of higher standards

of health care, use of breast self-examination, and screening mammography if implemented nationally would go a long way towards increasing early diagnosis and improved survival with a consequent possible rise in incidence of early cases as is happening in the West.

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