

Original Article:**Breast cancer in young: experience at a tertiary care centre in Tirupati, Andhra Pradesh**

B. Manilal,¹ D. Bhargavi,² Rashmi Patnayak,³ Amitabh Jena,¹ K. Sudheer Reddy,² V. Venkat Sampath,² A. Vindhya Vasini,² Manickavasagam,² S. Raja Sundaram¹

*Departments of ¹Surgical Oncology, ²Medical Oncology, ³Pathology,
Sri Venkateswara Institute of Medical Sciences, Tirupati*

ABSTRACT

Background: Breast cancer occurring at an young age (≤ 40 years) is associated with aggressive behavior and worse prognosis compared to the older patients.

Methods: We retrospectively studied the case records of young patients (≤ 40 years) with histopathologically confirmed breast cancer seen during the period June 2009 to December 2012 at our tertiary care teaching hospital. Clinical, histopathological features were analyzed and survival out comes were evaluated.

Results: Out of the 520 patients with histopathological diagnosis of carcinoma breast, 100 patients were aged 40 years or below. Clinical stage III (54.8%) was the most common stage. Majority of tumours were grade 3 (43%) and triple negative (47.3%). Median follow up period was 42.8 months. Five-year median disease free survival was 30 months and overall survival was 40 months. On univariate analysis for overall survival (OS), tumour grade ($p=0.004$), stage ($p=0.003$), distant metastasis ($p<0.001$), perineural invasion ($p=0.04$) were significant. For disease free survival, tumour grade ($p<0.001$), lymphovascular invasion ($p=0.04$), perineural invasion ($p=0.04$) and recurrence ($p<0.001$) were significant.

Conclusions: Breast cancer in the young is associated with higher stage and grade. Higher stage, grade, metastatic recurrence are associated with unfavourable outcome.

Key words: *Breast cancer; Young females; Survival outcome*

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INTRODUCTION

Age is considered as an important risk factor for breast cancer.^{1,2} Breast cancer is primarily a disease of older or postmenopausal women, and is rare in young women. Breast cancer patients aged younger than 40 years are considered to be young.³ The incidence of breast cancer in young women is low (< 17 cases per 100,000).⁴ It has been suggested that age of the patient at diagnosis is related to breast cancer survival. Young age is associated with more aggressive behaviour and unfavourable

prognosis compared to the older patients.⁵ In India, the age of developing a breast cancer has shown a changing trend and an increasing number of patients are being diagnosed below the age of 40 years.⁶ The poor prognosis associated with young breast cancer patients could be due to delayed presentation, advanced disease stage, and unfavorable tumor characteristics like nodal status, and presence of distant metastasis at diagnosis.⁷⁻¹⁰ Further, young age at diagnosis remains an independent prognostic factor for recurrence and breast cancer related death even after correction for

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Corresponding author: Dr B Manilal, Assistant professor, Department of Surgical oncology, Sri venkateswara Institute of Medical sciences, Tirupati, India.
e-mail: bmanilal@ymail.com

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age and tumour characteristics.⁷⁻¹⁰ The aim of the present study was to evaluate clinical and pathological characteristics and survival outcomes in young women with breast cancer in our institute.

MATERIAL AND METHODS

The study was carried out in the Surgical Oncology department at our tertiary care teaching hospital in Tirupati, Andhra Pradesh, during the period June 2009 to December 2012. The study was approved by Institutional Ethics Committee. All young patients (age $\leq$ 40 years) with histologically confirmed breast cancer were included. Patients with recurrent tumours, in situ carcinoma, male breast cancer, patients who were lost to follow-up during treatment period were excluded. Data collection included various parameters like age and stage at the time of diagnosis, tumour histology, neo-adjuvant chemotherapy, surgical treatment, adjuvant chemotherapy and radiotherapy, hormonal therapy received, lymph node status, tumour grade, presence of lymphovascular invasion (LVI), perivascular invasion (PVI), perineural invasion (PNI), oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status. Data regarding patients with metastasis were not included in statistical analysis. Disease was staged according to American Joint Committee of Cancer (AJCC) system.¹¹ Pathological grade was assessed by modified Bloom Richardson classification.¹² Hormonal receptors were determined by immunohistochemistry. The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline recommendations¹³ were used to evaluate the HER2neu status.¹³ Patients who did not turn up for follow-up, were communicated through telephone and enquired about their current health status.

Statistical analysis

For discrete variables proportions were calculated. Continuous variables are depicted as mean $\pm$ standard deviation; or median (range). Disease free survival (DFS), overall survival (OS) was estimated using Kaplan-Meier curves. DFS was calculated from the date of diagnosis to the date of recurrence. Overall survival was calculated from the date of diagnosis to 1st May 2014. The influence of various clinical parameters and pathological factors on DFS and OS were compared using log rank test. A p-value less than or equal to 0.05 was taken as significant. Data were analyzed using Statistical Packages for Social Sciences (SPSS), version 17 software (SPSS Inc; Chicago).

RESULTS

During the study period, of the 520 patients that were diagnosed with carcinoma breast, 100 were aged 40 years and below. Seven patients had metastatic disease at the time of presentation. Mean age at presentation was 35.1 years; most of the patients were between 31 to 40 years (Table 1). Tumour was lateralized to right side in 47 patients and to left side in 44 patients. Two patients had bilateral disease. None of the patients had family history of breast cancer. Majority of patients (n=88) had undergone modified radical mastectomy (MRM). Five patients undergone breast conservation therapy (BCT). Duct cell carcinoma (not otherwise specified) was the most common histopathological type (Table 2). Stage distribution of the tumor was as follows; stage I (1.1%); stage II (44.1%); and stage III (54.8%). Clinical stage III (54.8%) was the most

Table 1: Age distribution

Age (years)	No.
21-25	05
26-30	11
31-35	24
>35	53

Table 2: Histopathological types

Histopathological type	No.
Infiltrating duct cell carcinoma (NOS)	87
Lobular carcinoma	2
Paget's with malignant transformation	2
Medullary carcinoma	1
Tubular carcinoma	1

NOS = not otherwise specified

common stage at presentation followed by stage II. Twenty two patients received neoadjuvant chemotherapy [4 cycles of adriamycin (60mg/m²) and cyclophosphamide (600mg/m²)]. All the patients received adjuvant chemotherapy with Adriamycin (60mg/m²), cyclophosphamide (600mg/m²) and paclitaxel (175mg/m²). Radiotherapy was administered to patients with node positive disease, tumour size more than 5 cm, and those who had undergone BCT. Two patients achieved pathological complete response (PCR) following neoadjuvant chemotherapy. All hormone receptor positive patients had received tamoxifen. Majority of tumours were grade 3 (43%). Axillary lymph nodes showed metastatic tumor deposits in 47 patients (50.5%). Most of the tumours exhibited lymphovascular invasion (LVI) (n=41; 80.6%), perineural invasion (PNI) (n=25; 66.7%), and perivascular invasion (PVI) (n=20; 64.5). Triple-negative tumours were evident in 72(47.3%) patients. Among the hormone receptor positive cases, ER, PR expression was noted in 33 (35.5%) and 37 (39.8%) patients respectively. HER2 receptor was positive in 18 (19.4%) patients, negative in 60 (64.5%) patients, and equivocal in 15 (16.1%) patients (Table 3).

The mean DFS was 35.2±16.5 months. OS was 40.6 months (13.8). Local recurrence was noted in 23.7%, distant metastases was seen in 28% as detected by contrast enhanced computed tomography (CECT). Among distant metastases, pulmonary metastasis and bone metastasis were found in 12 (11.8%) patients each and hepatic metastasis were found in 6

(6.5%) patients. On univariate analysis, tumour grade (p=.004), stage (p=.003), distant metastases (p<0.001), PNI (p<0.001) had significant impact on overall survival. Tumour grade (p<0.001), LVI (p=0.04), PNI (p=0.04) and distant metastases (p<0.001) had significant impact on disease free survival (Figures 1 and 2).

DISCUSSION

In India breast cancer is the most common cancer in urban females, and the second most common in the rural women.¹⁴ More than 100,000 new breast cancer patients are diagnosed annually in India.¹⁵ Due to lack of awareness majority of Indian breast cancer patients present late. At the time of presentation they either have palpable lumps or are at an advanced stage.¹⁶ Young age has been associated with larger tumour size, higher number of metastatic lymph nodes, poorly differentiated tumours, low rates of hormonal receptor positive status and early loco regional recurrences.^{17,18} Breast cancer diagnosed at young age is considered to be different from that observed in older individuals. Young women commonly have different concerns and issues regarding fertility, contraception and pregnancy. The absence of screening programs in breast cancer until the age of 40 years predisposes these patients to present at advanced stages.

Table 3: Hormone receptor status

Hormone receptor status	No. (%)
Oestrogen receptor	
Positive	33 (35.5)
Negative	60 (64.5)
Progesterone receptor	
Positive	37 (39.8)
Negative	56 (60.2)
Human epidermal growth factor receptor 2	
Positive	18 (19.4)
Negative	60 (64.5)
Equivocal	15 (16.1)
Triple negative	44 (47.3)

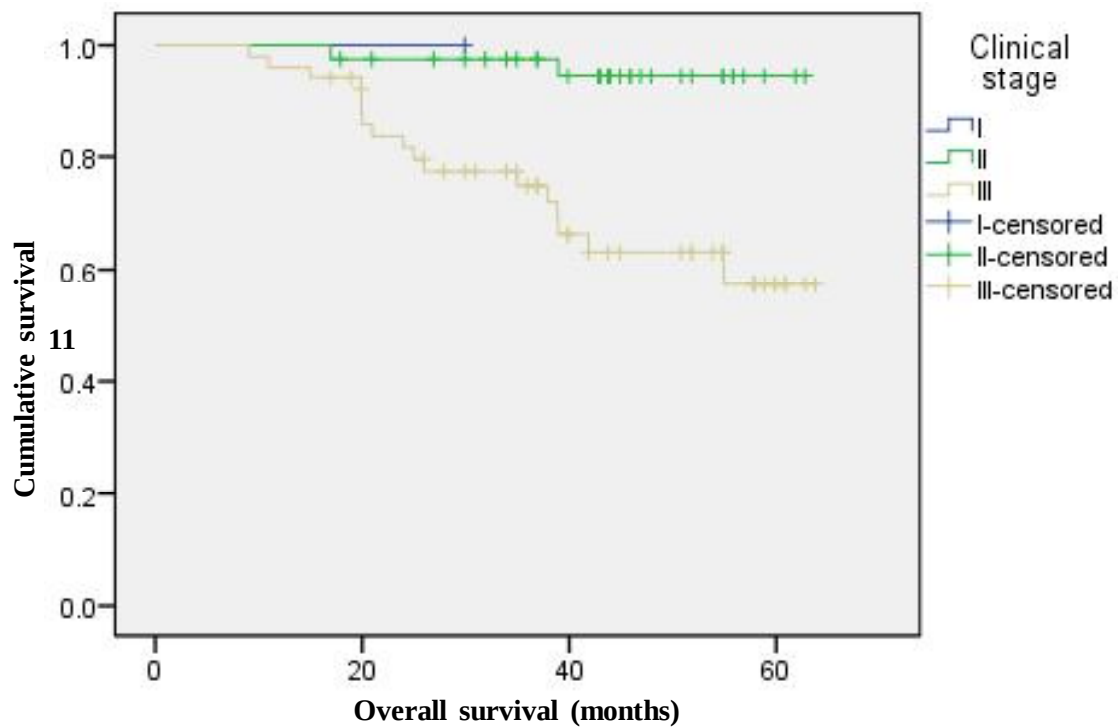


Figure1: Kaplan-Meier analysis: effect of clinical stage on overall survival ($p=0.003$)

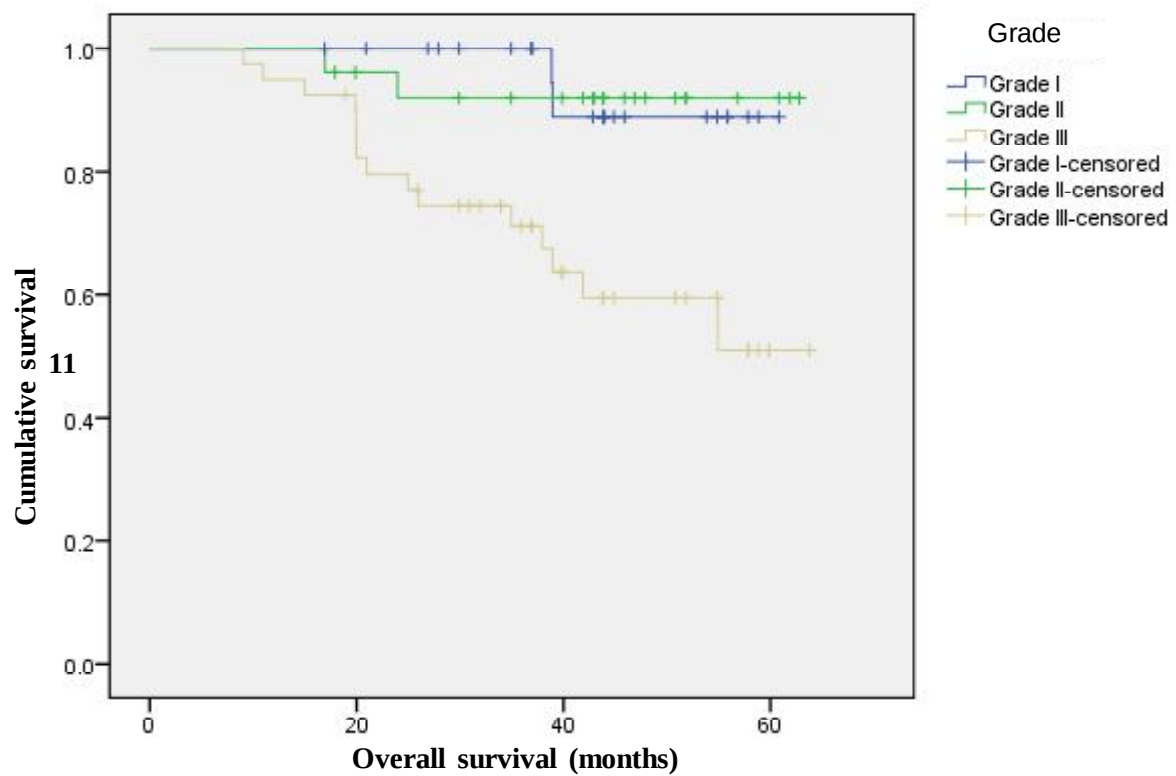


Figure 2: Kaplan-Meier survival analysis: grade and the effect on overall survival ($p=0.004$)

Majority of breast cancer presenting in younger women are invasive and most commonly are infiltrative duct cell carcinoma. Duct cell carcinoma (not otherwise specified) was the major histological type in our patients. In another study also this entity was commonly described.³ Stage III was the most common stage noted in another study.³ In our study, most (54.8%) patients had stage III disease at the time of presentation.

In a study¹⁹ from Nepal, it was reported that younger patients had more LVI, PVI and low expression of ER, PR receptors and a high proportion of triple negative tumours.¹⁹ Another study²⁰ from China had concluded that Chinese women present with breast cancer at an earlier age. Younger women present with more advanced disease and more aggressive tumour characteristics like higher pathological grade, poorly differentiated tumours, more nodal involvement, and LVI.²⁰ Another study²¹ also reported high grade tumours, hormone receptor negativity in young women with breast cancer. Tumours in young age were associated with higher stage and grade; poor histological grade has been shown to have a worse prognosis in younger women.²² Young age is an independent adverse prognostic indicator of survival in breast cancer patients.²³ Our observations were similar.

In our previous study we had found that in our patients (young and old) ER status was low, and proportion with p53 positivity was high.²⁴ According to published literature, most of the breast cancers in young women are ER and PR negative indicating a poorer prognosis.^{5,25} Moreover, the aggressive triple negative (ER, PR, HER-2 neu) breast tumours were reported to be higher in young patients.²⁶ Triple negative patients are aggressive in nature as they are less likely to be responsive to the conventional hormonal and targeted antibody treatment. The prevalence of triple negative status in young women was reported to be high in a study from

south India.²⁷ We have observed a higher proportion of triple negative tumours (47.3%) in our study. In other studies^{19,22} triple negative breast cancers were observed in 22.4% and 25.5% cases respectively.

Younger breast cancer patients have been reported to have mutation in germ line BRCA-1 or BRCA-2 in 15%-20% of the cases.²⁸ A large-scale genomic analysis concluded that breast cancer arising in young women is a unique biologic entity driven by unifying oncogenic signaling pathways. It is characterized by less hormone sensitivity and higher HER-2/EGFR expression.²⁸ However, none of our patients gave history of familial breast cancer.

Results from various clinical trials suggest that based on age alone, young women with breast cancer should be regarded as high-risk patients and be given adjuvant chemotherapy.²⁹⁻³¹ A meta-analysis³² of randomized trials that evaluated the efficacy of incorporating taxanes into anthracycline-based regimens showed that the addition of taxanes was associated with superior results in all age groups. All our patients had received adjuvant chemotherapy.

A recent report from the Adjuvant Tamoxifen: Longer Against Shorter trial³³ demonstrated that continuing tamoxifen treatment for 10 years provides further protection against recurrence and breast cancer mortality. Young patients with ER-positive tumours may be the true beneficiaries of longer tamoxifen treatment because their time to natural menopause is longer than that of older patients. No prospective study to date, however, has evaluated the effectiveness of adjuvant tamoxifen in patients aged less than 35 years.³¹ There are few ongoing trials,^{34,35} the result of which might throw light on these issues. All our hormone receptor positive patients had received tamoxifen.

Few studies have reported ipsilateral breast tumour recurrence (IBTR) after BCT to be significantly higher in younger patients than in older patients.^{36,37} Survival in younger women has been worse for all stages of breast cancer as compared to older women.³⁸ The relative risk of locoregional recurrence was found to increase 7% for every 1-year decrease in age.³⁹ Young age (<35 years) was observed to be an important predictor of mortality after adjusting for confounding variables, with a relative risk of 1.50.⁴⁰ Another study⁴¹ found that the risk of breast cancer recurrence for women diagnosed below the age of 40 was 1.53 [(95% confidence intervals (CI), 1.37 to 1.74) times higher than in those diagnosed above 40 years. In our study, we found that 5 year median overall survival was 40 months and disease free survival was 30 months. Local recurrence and distant metastases were noted in 23.7% and 28% patients respectively. Among 93 patients, 19 patients succumbed to death. In a recent article from India, the authors noted that young age (< 35 years) is strongly associated with locoregional recurrence and metastases at the time of follow-up.⁴² Pulmonary metastases were most common in our patients followed by bone and liver metastasis.

Although its incidence is low, breast cancer in young is unique in several clinical and biological aspects that need therapeutic consideration. Usually the diagnosis is delayed in young patients, resulting in an advanced stage at presentation. This may be due to a lack of proper screening programs for young women, lack of awareness or to the aggressiveness of the disease itself. IBTR after BCT is significantly more frequent in young patients. Although total mastectomy is not mandatory, a sufficiently wide resection margin is required for lumpectomy, and boost radiotherapy should be considered in local treatment in young age patients.³¹

Systemic recurrence and mortality after treatment is more frequent in younger patients than in older women, especially in those with hormone receptor positive breast cancer. This may be caused by the lower incidence of menopause after chemotherapy, poor compliance with appropriate hormone therapy, and/or intrinsic tumour resistance to tamoxifen.³¹ Chemotherapy has greater benefits in younger women, suggesting that aggressive chemotherapy should be considered. In addition to all these, younger women require greater psychological as well as social support before and after treatment. Appropriate counseling also is required regarding fertility preservation and possible pregnancy. BRCA1/2 mutation tests should be done in these females to determine if they have hereditary breast cancer.³¹

Breast cancers in young women have more aggressive features and diagnosed at a later stage and have been associated with poorer outcomes. Differences in gene expression profile suggest that breast cancer in young women may be a distinct entity. Advanced clinical stage, grade, distant metastasis, perineural invasion and lymphovascular invasion had a significant negative impact on survival. Younger women tend to present with advanced stage, high grade, and triple negative tumors. They had higher prevalence of lymphovascular, perineural and perivascular invasion. Breast cancer awareness programs, screening programs, easy access to health care systems may help to increase the awareness and early detection of breast cancer in young females.

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