Breast Cancer

Real-World Experience of Treating Young Adult Patients with Breast Cancer from a Single Center in Southern India

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South Asian J Cancer 2022;11(2):105–111.

Abstract

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Background Breast cancer in young adults is rare and accounts for 5 to 6% of all cancers in this age group. We conducted the present study to look at the demographic features, clinical presentation, and outcomes in this group of patients treated at our center.

Patients and Methods The study included breast cancer patients between the age of 15 and 30 years treated at our institute from January 2009 to December 2016. Data were analyzed retrospectively from case records. Event-free survival (EFS) and overall survival (OS) were calculated using the Kaplan–Meier method.

Results Young adult breast cancers were reported in 145 out of 6,000 patients (2.41%) diagnosed with breast cancer in the study period. The median age of the patients was 29 years (range: 21–30 years). Stage I, II, III, and IV was observed in 3.4, 33.7, 46.2, and 16.5% of patients, respectively. The median follow-up was 45 months (range: 1.7–128.1 months). The 5-year EFS and OS for stage I, II, III, and IV was 100, 74.5, 47.9, and 0% and 100, 90.8, 55.1, and 0%, respectively. On univariate analysis, stage of the disease and pregnancy-associated breast cancers were found to have a significant association with decreased EFS and OS ($p < 0.001$, $p = 0.008$ and $p < 0.001$, $p = 0.001$, respectively). On multivariate analysis, stage of disease and pregnancy-associated breast cancers remained significant predictors of EFS and OS.

Conclusion Breast cancers in young adults are rare but need to be diagnosed at an early stage to improve survival. Pregnancy-associated breast cancers need to be managed optimally without delay owing to their aggressive tumor biology.

Keywords

- breast cancer
- survival
- chemotherapy

Introduction

Breast cancer is the most common malignancy in women worldwide.[1] The incidence of breast cancer in India is increasing and accounts for 30% of all cancers in females.[2]

Breast cancer in adolescents and young adults (15–30 years) is rare and accounts for 5 to 6% of all cancers in this age group.[3–5] Breast cancer in the young is a challenge to treat due to posttreatment issues like prolonged amenorrhea, infertility, and tendency toward genetic predisposition.[3,6–8]

DOI https://doi.org/10.1055/s-0041-1735481 ISSN 2278-330X

How to cite this article: Iyer P, Radhakrishnan V, Krishnamurthy A, et al. Real-World Experience of Treating Young Adult Patients with Breast Cancer from a Single Center in Southern India South Asian J Cancer 2022;11(2):105–111.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

The most distressing complication in young breast cancer treatments is impairment of fertility which is a potential side effect of antineoplastic treatments.[9] The incidence of anticancer infertility depends on the age of the patient, type of chemotherapy administered, and use of tamoxifen.[9] It is very important to have a multidisciplinary team involving oncology and reproductive units to handle the fertility issues in cancer patients.[9] Moreover, they tend to present in advanced stages and exhibit aggressive tumor biology as compared with breast cancers in the older population.[3,6–8] There are very few studies from India evaluating the trend of breast cancer in the young adult subgroup and its outcome.[10,11] This study analyzes the demographic features, clinical features, and outcomes in this subgroup of patients at our center.

Patients and Methods

We retrospectively analyzed 145 consecutive breast cancer patients between the age of 15 and 30 years treated at our institute between January 2009 and December 2016. Retrospective analysis of patient case records does not require formal ethics approval at our institute. The study was conducted according to the criteria set by the Declaration of Helsinki. Patient details were obtained from the case records. Histopathological confirmation of breast cancer was established with a core needle biopsy of the primary breast tumor. Prognostic markers like estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (Her2) were analyzed on the biopsy specimen using immunohistochemistry and reported according to standard guidelines. Patients with Her 2 2+ could not undergo fluorescence in situ hybridization (FISH) testing since it was not done at our center at that time. Staging workup done for all patients included chest X-ray, ultrasound of abdomen and pelvis, and bone scan. Additional imaging like computed tomography or magnetic resonance imaging was done if there was suspicion of distant metastasis. The staging was done as per the American Joint Committee of Cancer Staging 7th edition. Patients with stage I and II disease were classified as early breast cancer, stage III as locally advanced breast cancer (LABC), and stage IV as metastatic breast cancer. Treatment decisions for patients were taken by the hospital multidisciplinary breast cancer tumor board. Written informed consent was obtained from all patients before starting the planned treatment. Patients with early breast cancer underwent surgery followed by systemic treatments (chemotherapy and endocrine therapy) and adjuvant radiation therapy. Modified radical mastectomy (MRM) or breast conservation surgery (BCS) was the preferred surgical technique used. Patients with LABC received either neoadjuvant chemotherapy followed by surgery and sequential radiation or neoadjuvant chemoradiation followed by surgery.[12] Chemotherapy regimens used in the adjuvant and neoadjuvant setting included three cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by three cycles docetaxel or six cycles of paclitaxel and epirubicin or four cycles adriamycin and cyclophosphamide (AC) followed by four cycles of paclitaxel. Radiation therapy was delivered using megavoltage 6 (MV) X-rays to the chest wall, supraclavicular, and internal mammary nodal chains using either three-dimensional conformal therapy (3DCRT) or conventional techniques. The total radiation dose delivered was 46 to 50 Gy in 2 Gy per fraction for 5 to 6 weeks. Patients who received neoadjuvant radiation had a total dose of 40 Gy delivered to breast and nodal regions with either 3DCRT or conventional techniques. Patients with metastatic breast cancer were treated with palliative chemotherapy/endocrine therapy and radiation therapy as and when indicated. Endocrine therapy with tamoxifen 20 mg once a day for a total duration of 10 years was given if ER and PR were positive on the biopsy specimen. Access to trastuzumab for Her2 neu positive patients was limited at our center during the study period due to the high cost of drug and nonavailability of cheaper biosimilars. Patients with Her2 neu 2+ did not undergo FISH testing due to nonavailability of FISH testing at our institute at that time and lack of access to trastuzumab.

Pregnancy-associated breast cancers were defined as breast cancer diagnosed either during pregnancy or up to 1 year postpregnancy in the postpartum period.[13]

Event-free survival (EFS) was calculated from the date of diagnosis to date of relapse or progression or death. Overall survival (OS) was calculated from the date of diagnosis to date of death or last follow-up. All patients were censored for survival analysis at last follow-up or death whichever was earlier. EFS and OS were estimated using the Kaplan–Meier method and variables were compared using the log-rank test. Multivariate analysis was performed using Cox proportional hazard model. Statistical analysis was done using SPSS software (IBM SPSS Statistics Version 16.0).

Results

Breast cancer in young adults was diagnosed in 145 out of 6,000 (2.41%) patients diagnosed to have breast cancer during the study period. The median age of the patient was 29 years (range: 21–30 years). Stage I breast cancer was diagnosed in 5 out of 145 (3.4%) patients, stage II in 49 out of 145 (33.7%), stage III in 67 out of 145 (46.2%), and stage IV in 24 out of 145 (16.5%). Invasive ductal carcinoma was the most common pathology observed in 126/145 (86.8%) patients. Note that 54.4% (79/145) patients were ER-positive, 25.5% (37/145) patients were Her2 positive, 21.3% (31/145) patients were triple-negative, and 24.8% (36/145) patients had a report of Her2 status being inconclusive.

Pregnancy-associated breast cancers were observed in 32 out of 145 patients (22.06%). Among these patients, 2 out of 32 (6.25%) had stage I disease, 8 out of 32 (25%) stage II, 14 out of 32 (43.75%) stage III, and 8 out of 32 (25%) had stage IV disease. ER-positive tumors were observed in 13/32 (40.6%) patients, Her2 positive tumors in 5/32 (15.6%) patients, and triple-negative tumors in 5/32 (15.6%) patients. Remaining 9 out of 32 patients had Her2 2+ tumors for whom FISH was not done. Among this group of pregnancy-associated breast cancers, 20/145 (13.8%) were diagnosed with breast cancer in the postpartum period, 10/145 (6.9%) were in third

trimester, and 2/145 (1.3%) patients were diagnosed with breast cancer during the second trimester of pregnancy. There were no pregnancy losses in this group of patients. None of the patients with pregnancy-associated breast cancer received any investigations or treatment during pregnancy and reported only after delivery.

MRM was done in 61.3% (89/145) patients, BCS was done in 13.1% (19/145) patients, and 25.5% (37/145) patients were inoperable either due to locally advanced or metastatic disease. The most common chemotherapy regimen used was three cycles of FEC and three cycles of docetaxel and was given to 57.2% (83/145) patients, 26.2% (38/145) patients received a combination of paclitaxel and epirubicin chemotherapy, and 8.2% (12/145) patients received four cycles AC chemotherapy and four cycles of paclitaxel. Only 3 out of 37 patients with Her2 positive tumors received adjuvant weekly trastuzumab for 9 weeks. The patient demographic and clinical characteristics have been provided in ►Table 1.

The median follow-up was 45 months (range: 1.7–128.1 months). The 5-year OS and EFS were 60.5 and 52.1%, respectively. The 5-year EFS was 100, 74.5, 47.9, and 0%, and 5-year OS was 100, 90.8, 55.1, and 0% for stages I, II, III, and IV, respectively (►Fig. 1A and B). Patients with breast cancer diagnosed during pregnancy and the lactation period had a higher stage at presentation and inferior 5-year EFS and OS which was statistically significant as compared with patients with a diagnosis of breast cancer in the nonpregnancy period (EFS 33.3% vs. 57.6%, $p = 0.008$, OS 36.3% vs. 57.4%, $p = 0.001$) (►Fig. 2A and B).

On univariate analysis, there was no significance observed among patients with different socioeconomic status, literacy, parity, marital status, age at menarche, receptor status, ovarian suppression, or family history with regards to EFS or OS. Patients with advanced stages (stages III and IV) were further analyzed for survival based on Her2 neu status. The 5-year EFS and OS among 91 stage III and IV Her2 neu positive, Her2 neu negative, and Her2 neu 2+ groups were 0, 39.8, and 42%, respectively ($p = 0.56$), and 0, 51, and 45.4%, respectively ($p = 0.43$). Univariate analysis of factors impacting EFS and OS has been provided in ►Table 2.

On multivariate analysis, stage of disease and pregnancy-associated breast cancers were significantly associated with inferior EFS ($p < 0.001$ and $p = 0.004$, respectively) and OS ($p < 0.001$ and $p = 0.001$, respectively).

It was also observed that 11/145 (7.5%) patients had successful pregnancies after completion of breast cancer treatments.

Discussion

Breast cancer among young patients is rare and represents 5 to 6% of all cases in adolescents and young adults.[3–5] Our study reported a 2.41% incidence of breast cancer in young patients.

A family history of breast cancer is a significant risk factor for the development of breast cancer in young patients.[14] In our study, we elicited a 12% incidence of positive family history of breast and ovarian cancer in the first-degree

Table 1 Patient and tumor characteristics

Parameter	Number (%)
Median age	29 y (range: 21–30 y)
Age grouping	
15–20 y	0/145 (0)
21–25 y	23/145 (15.8)
26–30 y	122/145 (84.1)
Marital status	
Married	129/145 (88.9)
Unmarried	16/145 (11.3)
Parity	
Multiparous	83/145 (57.2)
Uniparous	30/145 (20.6)
Nulliparous	16/145 (11.03)
Unmarried	16/145 (11.0)
Family history	
Breast and gynecological cancers	18/145 (12.4)
Nil	127/145 (87.5)
Pregnancy-associated breast cancers	
Yes	32/145 (22.0)
No	113/145 (77.9)
Literacy	
Illiterate	10/145 (6.8)
Primary education	21/145 (14.4)
Secondary education	85/145 (58.6)
College	29/145 (20.0)
Monthly family income	
< 10,000 INR/month	119/145 (82.0)
≥ 10,000 INR/month	26/145 (17.9)
Stage	
I	5/145 (3.4)
II	49/145 (33.7)
III	67/145 (46.2)
IV	24/145 (16.5)
Receptor status	
ER+	79/145 (54.4)
Her2 3+	37/145 (25.5)
Triple-negative	31/145 (21.3)
Her2 neu 2+	36/145 (24.8)
Status at last follow-up	
Alive	84/145 (57.9)
Dead	61/145 (42.0)
Upfront sites of metastasis	
Bone	5/145 (3.4)

(*Continued*)

Table 1 (*Continued*)

Parameter	Number (%)
Lung	8/145 (5.5)
Liver	4/145 (2.7)
Brain	0/145 (0)
Multiple	7/145 (4.8)
No metastasis	121/145 (83.4)
Sites of relapse	
Local	24/145 (16.5)
Bone	12/145 (8.2)
Lung	9/145 (6.2)
Liver	11/145 (7.5)
Brain	7/145 (4.8)
Lung and liver	6/145 (4.1)
Contralateral breast and axilla	1/145 (0.6)
No metastasis	75/145 (51.7)
Surgery	
MRM	89/145 (61.3)
BCS	19/145 (13.1)
Not done	37/145 (25.5)
Chemotherapy	
Adjuvant	50/145 (34.4)
Neoadjuvant chemotherapy alone	30/145 (20.6)
Neoadjuvant chemoradiation	40/145 (27.5)
Palliative	20/145 (13.7)
Not given	5/145 (3.4)
Ovarian suppression	
BSO	35/145 (24.1)
Radiocastration	1/145 (0.7)
Medical suppression	12/145 (8.2)
No suppression	97/145 (66.8)
Radiation	
Given	107/145 (73.7)
Not given	38/145 (26.2)

Abbreviations: BCS, breast conservation surgery; BSO, bilateral salpingo-oophorectomy; ER, estrogen receptor; MRM, modified radical mastectomy.

relative. Studies on young breast cancers from India are few and have reported a family history of 6 to 8%.[10,11] However, none of the patients in our study underwent testing for germline BRCA mutation due to the high cost of testing.

It is known that breast cancers at a young age tend to present in advanced stages, have a higher tumor grade, and are hormone receptor-negative.[3,6,7] In our study, we observed a higher rate of ER-positive tumors as compared with triple-negative and Her2 positive subtypes. Yao et al observed higher rates of ER-negative tumors in patients < 30 years of age as compared with patients in the 31 to 50 years age group.[15] He also observed that ER-positive tumors in young patients were more aggressive than older patients and associated with higher recurrence rates and poorer survival.[15] In our study, we did not observe any differences in outcome among patients with different receptor status. However, comparisons with the older population were not made.

In our study, only 3 out of 37 patients with Her2 neu positive tumors received trastuzumab and remaining patients could not afford it. During the study cheaper biosimilar trastuzumab was not available in India. It has been reported in the literature that 19.1 to 59.9% of patients in resource-limited settings did not receive trastuzumab due to various reasons out of which the most common being the high cost of treatments and difficulties with drug funding.[16] The majority of patients at our center are currently receiving adjuvant trastuzumab due to the availability of less expensive biosimilars.

Pregnancy-associated breast cancer present in advanced stages due to delay in diagnosis and treatment.[13,17–19] However, no differences have been observed in OS between pregnancy and nonpregnancy-associated breast cancer in literature.[13,18,19] Genin et al reported an incidence if 14.5% pregnancy-associated breast cancers in their study.[19] In our study, we observed 22.06% of the cancers were pregnancy-associated. We also observed that these tumors were advanced in the presentation as reported in the literature.[13,18,19] However, the 5-year EFS and OS in this group of patients was inferior as compared with nonpregnancy-associated patients (33.3% vs. 57.6%, $p = 0.008$ and 36.3% vs. 57.4%, $p = 0.001$, respectively) and this is contrary to what has been reported in the literature.

Radecka and Litwiniuk observed that young women with breast cancers below the age of 40 years were at increased risk of local and systemic recurrence as compared with their older counterparts.[3] They also observed higher rates of local recurrence following BCS as compared with older women.[3] Freedman and Partridge observed that young patients who had negative tumor margins and a nonextensive intraductal component had similar recurrence rates as compared with older patients after BCS.[20]

In our study, we observed only one recurrence post-BCS and five recurrences post-MRM. This suggests that negative margins and the extent of intraductal components determine the risk of local recurrence in young patients.[20]

There are two studies reported from North India on young breast cancers.[10,11] Both studies have evaluated the impact of age on the prognosis of breast cancers. They conclude that majority of young breast cancers are advanced in presentation, have aggressive tumor biology, and poor outcomes as compared with older women.

A meta-analysis of 16 studies on pregnancy outcomes in breast cancer survivors who received systemic treatment and surgery reported an overall pooled estimate of 14% of becoming pregnant, and among those who became

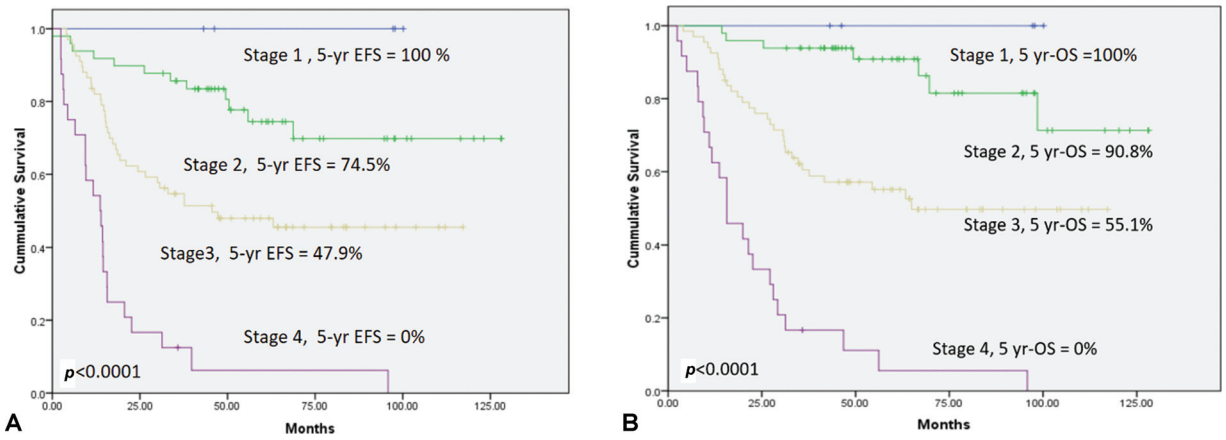

Fig. 1 Kaplan–Meier survival curves for all stages for (**A**) event-free survival and (**B**) overall survival.

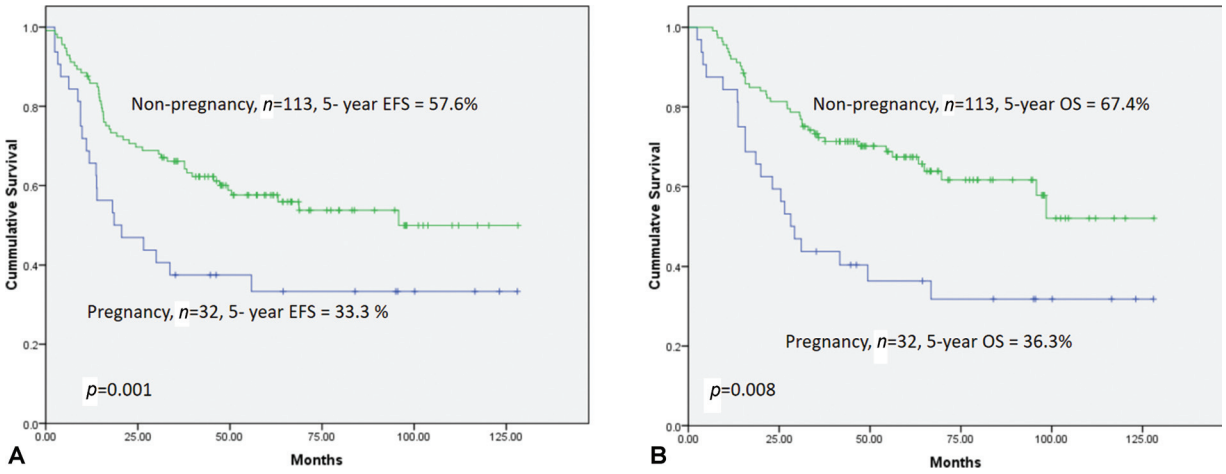

Fig. 2 Kaplan–Meier survival curves for pregnancy and nonpregnancy-associated breast cancers for (**A**) event-free survival and (**B**) overall survival.

Table 2 Univariate analysis of factors predicting EFS and OS

Parameter	Number (*n*) Total of 145	5-year EFS	*p*-Value	5-year OS	*p*-Value
Marital status			0.262		0.149
Married	129	50.2		57.9	
Unmarried	16	66.7		81.3	
Parity			0.434		0.471
Multiparous	83	59.1		59.1	
Uniparous	30	41.8		54.7	
Nulliparous	16	37.5		61.4	
Unmarried	16	66.7		81.3	
Pregnancy-associated			0.001		0.008
Yes	32	33.3		36.3	
No	113	57.6		67.4	
Literacy			0.277		0.125
Illiterate	10	30		40	
Primary education	21	61		57.1	
Secondary education	85	52		57.9	
College	29	54.5		76.3	

(*Continued*)

Table 2 (*Continued*)

Parameter	Number (*n*) Total of 145	5-year EFS	*p*-Value	5-year OS	*p*-Value
Monthly income			0.201		0.317
< 10,000 INR	119	50		59.2	
≥ 10,000 INR	26	61		67.2	
Family history			0.354		0.580
Breast cancer	14	63.5		68.2	
Ovarian cancer	4	75		75	
Nil	127	50.1		59.2	
Surgery			< 0.001		< 0.001
MRM	89	63.3		75	
BCS	19	80.5		94.7	
Inoperable	37	0.08		0.08	
Ovarian suppression			0.106		0.022
Yes	48	60.8		73.0	
No	97	48.0		54.5	
ER status			0.477		0.414
Positive	79	53.5		62.6	
Negative	66	50.4		57.8	
Her2 neu status(all stages)			0.644		0.258
Positive	37	45.1		43.4	
Negative	66	52.6		69.7	
2 +	42	56.4		62.7	
Her2 neu (stage III, IV)			0.566		0.434
Positive	25	0		0	
Negative	41	39.8		51	
2+	25	42		45.4	
Stage			< 0.001		< 0.001
I	5	100		100	
II	49	74.5		90.8	
III	67	47.9		55.1	
IV	24	0		0.05	

Abbreviations: BCS, breast conservation surgery; EFS, event-free survival; ER, estrogen receptor; MRM, modified radical mastectomy; OS, overall survival.

pregnant, 12% experienced a miscarriage.[21] Pregnancy rate after treatment for breast cancer survivors was on an average 40% lower than the general population pregnancy rate.[21] We observed a pregnancy rate of 7.5% in our cohort of patients. Details regarding miscarriages in our study could not be captured due to the retrospective nature of the study.

The 5-year EFS and OS in our study are low as compared with studies reported in literature especially in stage III and stage IV tumors. This suggests that stage is the single most important prognostic factor in young breast cancer patients. Moreover, tumors in advanced stages in young patients tend to behave very aggressively and hence need to be managed with optimum systemic and local therapies.

Our study is the first study from the southern part of India on young adult breast cancer and confirms the findings reported in the literature. Pregnancy-associated breast cancers were more in our study as compared with literature and their outcomes are significantly poor as compared with nonpregnancy-associated cancers. However, our study has limitations as it is retrospective in nature, majority of Her2 neu positive patients did not receive anti-Her2 targeted therapy and a subset of Her2 2+ patients did not undergo FISH testing. Currently, at our center, we are doing FISH testing for all Her2 2+ tumors and the majority of the Her2 positive patients receive trastuzumab.

Conclusion

Young adult breast cancers are limited in number but need to be diagnosed early to improve survival in this subset of patients. Pregnancy-associated breast cancers need a high index of suspicion to be detected early and need multimodality management due to aggressive tumor biology.

Study Design and Ethics

Retrospective analysis of patient case records do not require formal ethics approval at our institute. The study was conducted according to the criteria set by the Declaration of Helsinki. Written informed consent was obtained from all patients before starting the planned treatment.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

None.

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