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Breast Cancer

Survival Outcome and Predictors of Survival in Elderly Breast Cancer Patients following Curative Treatment

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Abstract

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Objectives The lack of data on management of elderly breast cancer patients' population makes most oncologists reluctant to treat them with the standard treatment protocols as advised for the younger patients. This study was done to identify the survival outcome and predictors of survival in elderly breast cancer patients treated with curative intent.

Materials and Methods Newly diagnosed patients with breast cancer aged more than 65 years who received treatment with curative intent were included. Disease-free survival (DFS) and overall survival were estimated using the Kaplan–Meier method. Survival curves were compared using log-rank test. Cox regression analysis was done to find out the predictors of DFS.

Results This study included 112 elderly breast cancer patients. In our patient population, 79 (70.5%) were less than or equal to 70 years of age and 33 (29.5%) were more than or equal to 70 years. Median age was 68 years. Charlson comorbidity index score was six and above in 31 (28.1) patients. Median DFS in our study was 46 months. Median DFS was not reached in patients less than or equal to 70 years of age, whereas it was 50 months (47–53) among patients more than or equal to 70 years of age, *p*-value-0.009. In univariate analysis, age more than or equal to 70 years and locally advanced breast cancer were the predictors of DFS with hazard ratio (HR) of 2.8 (1.2–6.69), *p*-value 0.013 and 2.9 (1.12–7.6), and 0.027, respectively. In multivariate analysis, age more than or equal to 70 years was the only significant predictors of DFS with HR of 2.8 (1.2–6.5) and *p*-value of 0.015.

Conclusion Standard curative intent treatment was well tolerable among elderly patents. Elderly age more than 70 years was a unique predictor of DFS. We need to incorporate tools to assess life expectancy and functional status that will help us predict toxicity of treatment and survival advantage more precisely.

Keywords
- breast cancer
- elderly
- predictors
- outcome
- chemotherapy
- geriatric

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Introduction

Incidence of breast cancer (BC) in the elderly is high and recently there has been an increase in life expectancy, screening, and treatment methods, evolving for this population.[1] Median age at presentation of BC is 61 years and 45% of BC patients are diagnosed at 65 years and older and they are not always managed according to treatment guidelines.[2] In fact, there are less data to guide treatment decisions, particularly at the extremes of age due to underrepresentation of elderly breast cancer (EBC) on prospective clinical trials. Elderly patients are less likely to obtain chemotherapy due to several comorbidities and concern for chemotherapy-related toxicity.[3] Thus, older women are more likely to be treated with lower doses of chemotherapy than are younger women. We need more studies that focus solely on chemotherapy in older patients in the neoadjuvant, adjuvant, and palliative settings. This study aimed to identify the predictors and outcome in terms of disease-free survival (DFS) of EBC patients treated with curative intent.

Materials and Methods

Newly diagnosed patients with BC aged more than 65 years who received curative treatment during the period 01-01-2017 to 30-11-2019 were included in this retrospective study. The metastatic BC including oligometastatic disease was excluded in the study. Details of baseline patient characteristics including age, comorbidities, clinicopathological factors that included tumor histology, T stage, axillary lymph node status, clinical stage, hormone receptor status, human epidermal growth factor receptor-2 status, Ki-67 index and tumor grade, details of chemotherapy, surgery and radiation treatment protocol, toxicities, response, and follow-up were taken from case records. The follow-up was conducted every 3 months in the first 2 years after diagnosis, every 6 to 12 months thereafter. Clinical examination and mammogram were done as per standard guidelines. Lost to follow-up was defined as failure to contact with the patient on two consecutive occasions. Locoregional recurrence was defined as recurrence within the ipsilateral chest wall, supraclavicular and infraclavicular areas, axilla, and internal mammary region.

DFS was calculated from the date of registration to disease recurrence or death. Overall survival (OS) was defined as from the date of diagnosis to the date of death from any cause. This study has been approved by institute institutional review board/ethics committee.

Statistical Methods

Descriptive statistics were used to analyze the clinical and demographic characteristics of the population. DFS was estimated using the Kaplan–Meier method. Survival curves were compared using log-rank test. The predictors of DFS are identified by Cox regression analysis.

Results

A total 112 newly diagnosed elderly BC patients aged more than 65 years who received treatment with curative intent were included in the study. Baseline characteristics of the study is given in ►**Supplementary Table S1** (available in the online version). In the study population, 79 (70.5%) were less than or equal to 70 years of age and 33 (29.5%) were more than or equal to 70 years. Median age was 68 years. Right-side BCs were seen in 51.8% (58) and left-side BCs in 48.2% (54) of patients. About 1.8% (2) had second primary. The median age of menarche was 14.5 years and median age of menopause was 48 years. About 8.9% (10) patients were nulliparous and 91.1% (102) were multiparous. Family history of BC was seen in 4.6% (5). Major comorbidities were hypertension in 56.3% (63), diabetes 44.6% (50), coronary artery disease 5.4% (6), hypothyroidism 5.4% (6), chronic liver disease 1.8% (2), dyslipidemia 1.8% (2), and bronchial asthma in 3.6% (4). Screen-detected cancer was seen in 5.4% (6) patients in age less than or equal to 70 years and none in age more than or equal to 70 years. Charlson comorbidity index score was 6 and above in 31 (28%) patients. In this study, 43.8% (49) patients were EBC and 63 (56.3%) patients were locally advanced breast cancers (LABC). Eighty-four patients (75%) had luminal type, 6 patients had her2neu enriched (5.4%), and triple negative in 22 patients (19.6%). Most common histology was invasive ductal carcinoma in 94.6% (106). A total of 93 patients (83%) received curative intent of chemotherapy. Among them, neoadjuvant chemotherapy was received by 33 patients (35%) and 60 patients (65%) received adjuvant chemotherapy. FEC (5-flurouracil, epirubicin, cyclophosphamide) followed by docetaxel was the most common chemotherapy regimen received in 49 patients (43%). Only six patients (5.3%) received dose dense chemotherapy. During chemotherapy, there were 42 toxicity events of various grade2 and above toxicities. Three patients (2.6%) expired due to chemotherapy-related toxicities. All three patients who expired were belonged to age more than 70 years. Eleven patients (12%) defaulted chemotherapy due to intolerance to chemotherapy-related toxicities. About eight patients (7.1%) underwent dose reduction of chemotherapy due to toxicities. About 22 patients (19.6%) received anti-Her2 neu therapy, of which 16 patients (72%) received Finland Herceptin (FinHer) trial (FINHER) regimen. This regimen included nine trastuzumab infusions administered at a weekly interval along with 3 weekly injections of docetaxel. It was followed by 3 weekly injections of FEC at a 21-day cycle. Breast conservative surgery (BCS) was done only in 11 patients (10%) and modified radical mastectomy was done in 101 patients (90%). About 69 patients (61.6%) underwent adjuvant radiation. Eleven BCS patients (10%) underwent adjuvant radiation. About nine patients (8.2%) had grade 2 dermatitis following radiation. None of our patients received neoadjuvant hormonal treatment. About 82 patients (73%) received adjuvant endocrine therapy. Aromatase inhibitors in adjuvant settings were given in 80 patients (71.4%) of which 75 patients (67%) received letrozole and 5 patients (4.4%) received anastrozole. Two patients (1.7%) received Tamoxifen as adjuvant hormonal therapy in elderly population. About 52 patients (46.4%) underwent bisphosphonate therapy. One patient (1.8%) had prolonged surgical site infection and another patient (1.8%) had worsening of underlying cirrhosis as perioperative morbidity. ►**Table 1** shows comparison of two age categories

Table 1 Comparison of two age categories of elderly breast cancer patients

Characteristics	Age ≤ 70 ($n = 79$)	Age ≥ 70 years ($n = 33$)	*p*-Value
Side of the lesion			
Left Right	43 36	11 22	0.042
Duration of symptoms			
Less than 3 months More than or equal to 3	39 40	11 22	0.10
CCI			
Less than 6 More than OR equal to 6	58 21	23 10	0.68
Performance status			
0 1 2 3	5 73 1 0	2 22 7 2	**0.01***
Tumor stage			
1 2 3 4	10 43 7 19	4 10 3 16	0.06
N stage			
0 1 2 3	31 28 17 3	11 11 8 3	0.678
Stage			
EBC LABC	35 44	14 19	0.85
Grade1	0	2	
2 3	39 40	21 10	**0.02***
Molecular type			
Luminal Her 2 Neu TNBC	59 5 15	25 1 7	0.76
Hormone status			
Positive Negative	57 22	25 8	0.7
Her2 Neu status			0.15
Positive Negative	60 19	29 4	
NACT			0.6
Yes No	22 57	11 22	
Response to NACT			
CR PR SD	5 16 1	1 10 0	0.4
Type of surgery			
BCS MRM	7 70	4 29	0.40
Bisphosphonate use			0.35
Yes No	36 40	13 20	
Recurrence and death			
Yes No	11 68	11 22	**0.01***
Recurrence			
Yes No	8 71	7 26	0.1
Death events			
Yes No	7 72	8 25	**0.02***

Abbreviations: BCS, breast conservation surgery; CCI, CCI, Charlson comorbidity index; CR, complete remission; EBC, early breast cancer; LABC, locally advanced breast cancer; MRM, modified radical mastectomy; ; NACT, neoadjuvant chemotherapy; PR, partial remission; SD, stable disease; TNBC, triple negative breast cancer.
*Shows significant *p*-values.

of EBC patients. Among different variables between patients above or below 70 years of age, only performance status and recurrence and death showed a significant *p*-value 0.01*.

Survival Outcome and Predictors of Survival

Univariate analysis of 3-year DFS shows that only age (≤ 70 vs. ≥ 70 years) and LABC versus EBC had any statistical significance. Univariate analysis reveals that LABC (hazard ratio [HR]: 2.9 (1.12–7.6), *p*-value: 0.027) and age more than or equal to 70 years (hazard ratio (HR) of 2.8 (1.2–6.69), *p*-value: 0.013) were the predictors of DFS (►**Supplementary Table S2**, available in the online version>). Univariate analysis of 3-year OS shows that only age more than or equal to 70 years and nonluminal type had statistical significance (HR: 3.17, confidence interval [CI]: 1.15–8.7, *p*-value: 0.026* and HR: 2.77, CI: 0.92–7.4; *p*-value 0.05*, respectively) (►**Supplementary Table S3**, available in the online version>).

In multivariate analysis age more than or equal to 70 years was the only significant predictors of DFS with HR of 2.8 (1.2–6.5) and *p*-value of 0.015 (►**Table 2**). Both nonluminal type and age more than or equal to 70 years were not seen as the predictors of OS at 3 years. Kaplan–Meier survival curve showed DFS and OS in EBC patients as given in ►**Figs. 1** and **2**.

Table 2 Multivariate analysis of DFS and OS

	Sig.	Hazard ratio	95.0% CI for HR	
			Lower	Upper
Multivariate analysis of DFS				
• LABC	0.075	2.379	0.915	6.184
• More than 70 years	0.015	2.843	1.225	6.596
Multivariate analysis of OS				
• Nonluminal	0.049	2.777	1.006	7.666
• More than 70 years	0.023	3.245	1.173	8.978

Abbreviations: CI, confidence interval; DFS, diffusion-free survival; HR, hazard ratio; LABC, locally advanced breast cancer.

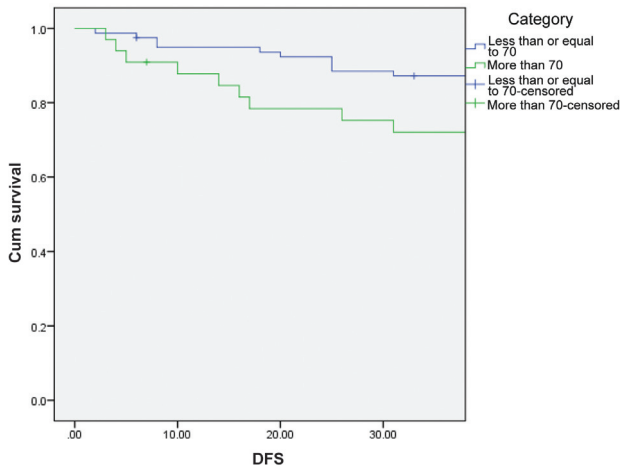

Fig. 1 Kaplan–Meier survival curve showing disease-free survival (DFS) in elderly breast cancer patients.

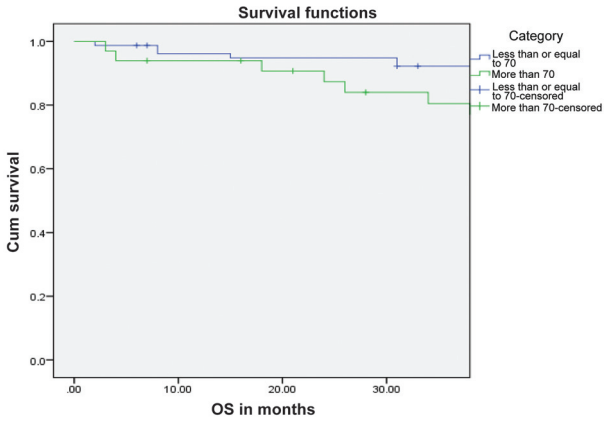

Fig. 2 Kaplan–Meier survival curve showing overall survival (OS) in elderly breast cancer patients.

The median survival has not reached in less than or equal to 70 years where as it was 50 months (47–53) in more than 70 years that was statistically significant with *p*-value of 0.009. Median OS was not reached in both.

Discussion

Decision making in management of EBC should not be driven by age alone but should involve geriatric assessments, consideration of life expectancy, risks of mortality, and patient preferences.[4] Globally, especially in developed countries, life expectancy has increased over the past two decades. Life expectancy can be considered as a main reason for increased incidence of BC in elderly. BC-specific mortality from BC increases with age. Women over the upper age limit for screening programs should not be discouraged to undergo individual screening that is common among community practice, thinking that cancer in the elderly does not kill, mistakenly interpreted as a zero-risk situation and it may lead to late diagnosis with more advanced cases.[4] In elderly women also, early diagnosis carries a better prognosis. Our study also clearly identifies that elderly woman especially aged above 70 years had poor survival in terms of DFS confirming that age is a better predictor of survival in EBC. None of the factors like tumor size, nodal status, stage of BC, histological subtype, grade, molecular subtypes, hormonal receptor positivity, and Charlson comorbidity index showed any significance in our study. In a study from India by Reddy et al,[5] receptor positivity was observed in 79% of elderly patients and 9% had triple-negative disease that was similar to our study showing 75% of hormone receptor positivity and triple negativity in 19.6%. Our patients received chemotherapy in 83% including neoadjuvant and adjuvant chemotherapy and 7.1% had dose reduction in chemotherapy due to toxicities. In a 10-year update of the CALGB 49907 trial, regarding the adjuvant treatment in EBC with women aged 65 years and older patients, standard chemotherapy remains superior to capecitabine alone among hormone receptor–negative patients (HR: 0.66; $p = 0.02$), but not among hormone receptor–positive patients (HR: 0.89; $p = 0.43$).[6] However, recent study of 2004 elderly patients aged above 70 years demonstrated that adjuvant chemotherapy was not associated with OS (HR: 0.96, 95% CI: 0.77–1.20, $p = 0.71$) and advised cautious recommendation or the omission of chemotherapy may be considered in select elderly patients.[7] Study by Rocque et al[8] revealed that resistance to de-escalation clinical trial participation from BC survivors and patient advocates were mainly due to anxiety and fear of recurrence. However, avoidance of physical and financial chemotherapy toxicities and lessened impact on daily life were attractive aspects of reduced-intensity treatment among patients vulnerable to treatment-related financial toxicity. In clinical practice, the benefit/risk ratio in elderly patients is difficult to estimate because chemotherapy-induced toxicity is worse than in younger individuals. So, the choice of adjuvant treatment for elderly must also be based both on chronological and biological age.[9] One of such kind with clinical implication on prognostic and predictive biological factors is oncotype Dx and Mama print. Biological factors such as telomerase or DNA methylation have reported a potential diagnostic value for early cancer detection and for cancer risk susceptibility evaluation.

In patients with multiple comorbidities, aggressive treatment may not result in a survival benefit compared to younger women. Omission of chemotherapy in patients over age 75 will not affect BC specific or OS as evidenced by a study from Yamada et al.[10]

In contrast, another study found that physicians carefully selected patients likely to derive treatment benefit with improved OS from adjuvant chemotherapy especially in node-positive, estrogen receptor–positive elderly patients with BC with multiple comorbidities.[11]

Conclusion

Standard curative intent treatment was well tolerable among elderly patents. Elderly aged more than 70 years was a unique predictor of DFS. We need to incorporating tools to assess life expectancy and functional status that will help us predict toxicity of treatment and survival advantage more precisely.

Note

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Authors' Contributions

TM Anoop designed the study, drafted the manuscript, supervised the study, and treatment; Rona Joseph P participated in the design, supervision of the study, and treatment; Rajeev KR participated in the design, supervision of the study, and treatment; Steffi Chacko participated in the design of the study; Saikumar involved statistical analysis; Mintu Mathew participated in data collection; all authors read and approved the final manuscript. Bhavya S kumar involved data collection and statistical analysis.

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Conflict of Interest

None declared.

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