# ORIGINAL RESEARCH

# Breast Cancer in Women Aged 75 Years and Older

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## Abstract

**Objective:** Breast cancer is the most common cancer in women, with incidence and mortality increasing dramatically with age. Applying data of younger patients to the geriatric age group indicates "evidence biased medicine". Therefore, this study aimed to present the clinical and pathological features of breast cancer and treatment choices in older patients.

**Materials and Methods:** This study included 72 patients aged 75 years and older with breast cancer who were admitted to our medical oncology clinic between 2005 and 2013. Clinicopathological and demographic features, progression-free survival and overall survival and adjuvant and palliative treatments were recorded retrospectively. Categorical variables were presented as number (n) and percentage (%) and continuous variables as median and minimum-maximum. Survival curves were drawn using the Kaplan-Meier method. P<0.05 was considered as statistically significant.

**Results:** The study population consisted of 72 patients, with a median age of 78 (minimum-maximum: 75-88). The most common pathological type of breast cancer was invasive ductal carcinoma, followed by infiltrative lobular carcinoma. Steroid receptor positivity rates were high, and the cerbB2 status was mostly negative; older patients had favourable tumours. Endocrine therapy was the most preferred option in this geriatric patient group, and aromatase inhibitors were the most commonly chosen hormonotherapy. Endocrine therapy is the first choice in palliative treatment; however, chemotherapy was preferred in second- and third-line treatment in metastatic diseases.

**Conclusion:** According to available literature, geriatric patients show similarities in histologic and intrinsic subtypes with postmenopausal women, except for frailty and comorbidities. However, in geriatric patients, endocrine therapy is preferred as adjuvant and/or metastatic treatment because they are more susceptible to chemotherapeutic agents. Oncologists should consulate every older patient to geriatric medicine, and comprehensive geriatric assessment should be done to decide and continue treatment. Age should not be the only factor in decision-making.

**Keywords:** Geriatric patients, older women, breast cancer, aged women, decision-making, endocrine therapy, postmenopausal women

## Introduction

Breast cancer is the most common cancer in women, the incidence and mortality increase dramatically by ageing (1). The average age at diagnosis of breast cancer is 61 years, and the majority of women who die because of breast cancer are aged 65 years and older (2). Major improvements in public health like routine screening with mammography, and better treatment options like endocrine therapies or targeted therapies, better medical care after surgery have resulted in increased survival of patients with breast cancer. However, age-related disparity is seen in these improvements. In one study, the absolute risk

of breast cancer death decreased by 15.3% for women aged 50 to 64 years but only 7.5% for women 75 years and older (3). This may be related to that there are no screening guidelines in older women and routine mammography screening is ended after 74 years of age according to USPTF and American College of Physicians Guidelines. Older women were self-admitted to medical care with a palpable mass, however, they have more favorable tumors and early-stage disease (4).

The treatment of individuals who are aged 75 years and older is complicated and the goals of the treatment should be well-defined. It is important to guide the treatments by evaluating

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possible toxicities, functional loss, and quality of life. In data from clinical trials that enroll primarily younger patients, older patients with breast cancer are underrepresented (5,6). Therefore, evidence-based treatment guidelines are limited. Applying the data of younger patients to geriatric age group cause ''evidence biased medicine''. Lack of information needed to estimate the likelihood of toxicity can lead to life-changing results in older adults. It is essential to personalize management for geriatric patients. In the current study, it is aimed to present the clinical and pathological features of breast cancer and choices of the treatment in older patients.

## Materials and Methods

Our study was conducted by Declaration of Helsinki. This study was reviewed by the approval (date: 12.07.12, decision number: 12-6.1/7) of the local Ethics Committee of the Ege University (İzmir/Turkey). The participants provided informed consent.

### Study population

Patients who were admitted to the medical oncology clinic between 2005-2013 were evaluated, and 72 patients diagnosed with breast cancer aged 75 years and older were included. Clinicopathological features, demographic features, comorbidities, family history of malignancy, metastasis date and regions, progression status, progression-free survival and overall survival, adjuvant and palliative treatment regimens were recorded retrospectively.

Adjuvant treatment was given after surgery in order to reduce the chance of cancer coming back by destroying any remaining cancer cells. It usually refers to chemotherapy, radiation therapy, hormone therapy, and/or immunotherapy. Palliative treatment is the systemic treatment given to metastatic disease, which may include hormone therapy, chemotherapy, targeted therapy, or some combination of these.

Stage of the disease was established through the tumor, node and metastasis classification system. Early stage breast cancer includes ductal carcinoma *in situ*, stage 1 and stage 2a. Locally advanced breast cancer includes stage 2b, stage 3a, 3b and 3c. Vital status, date, and the cause of the death were determined through linkage with the Turkish national death registry.

Estrogen receptor (ER) and/or progesterone receptor (PR) positive, Cerb-2 negative, and proliferation rate of ki-67 lower than 14% were accepted as Luminal A subgroup. Luminal B subgroup was defined as either ER and/or PR positive, Cerb-2 positive; or ER and/or PR positive, C-erb2 negative, and proliferation rate of ki-67 status equal or higher than 14%. ER, PR and C-erb2 negative ones were described as a basaloid subtype. HER2 subtype defined as ER and PR negative and C-erb2 positive.

### Statistics

Categorical variables were given as number (n) and percentage (%). Continuous variables that followed a normal distribution was given as mean $\pm$ standard deviation values. Median and minimum-maximum values were presented for the variables where normal distribution was not observed.

Overall survival was defined as the time from diagnosis to death or the last follow-up examination. The effect of the subtype on survival of breast cancer patients was investigated using the log-rank test, and the Kaplan-Meier survival estimates were calculated. A value of $p < 0.05$ was accepted as statistically significant. The data obtained in the study were analyzed using IBM SPSS Statistics vn. 24.0 software (IBM Co., Armonk, NY, USA).

## Results

The study population was composed of 72 patients, with a median age of 78 (minimum-maximum: 75-88). The n of patients who had at least one comorbidity was 58 (80.6%), and the most common disease was hypertension followed by diabetes mellitus. The study sample was mostly overweight or obese. The demographic properties, general characteristics, and comorbidities are summarized in Table 1.

The most common pathological type of breast cancer was invasive ductal carcinoma (IDC), and the second one was infiltrative lobular carcinoma. ER and PR positivity rates were high and cerbB2 status was negative mostly, thus, older patients had favorable tumors. Hormone receptor status, subtypes of the diseases, and ki-67 status are given in Table 1. The most common subtype was luminal A disease. HER2 receptor positivity of immunohistochemistry and FISH method in the luminal b diseases are shown in Table 2.

The majority of the patients had a locally-advanced disease or early-stage disease at the time of diagnosis. The n of metastatic patients at diagnosis or during follow-up was 29 (40.3%). Most common metastasis regions were bone, lymph nodes, and lung.

The majority of the patients died within the follow-up time. When the registry of the Ministry of Health was controlled, it was revealed that cancer-related death occurred in 30 patients. Overall and progression-free survival according to subtypes and the whole group are shown in Table 3, Figures 1, 2.

Adjuvant and palliative therapies given to the patients were recorded. Endocrine therapy was the most preferred option in this geriatric patient group, that it is followed by radiotherapy and chemotherapy. Taxan-based chemotherapies were preferred as adjuvant chemotherapy in many patients, however, there are no major differences between chemotherapy regimens. Aromatase inhibitors were the most commonly chosen hormonotherapy. Only three patients received

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| Table 1. Demographic and clinicopathological features of the patients | |
|---|---|
| | Total sample (n=72) |
| **Age** | 78 (75-88) |
| **BMI** | 29.67 (17.78-39.80) |
| **Comorbidities*** Hypertension Diabetes mellitus Atherosclerotic heart disease Congestive heart failure Osteoporosis Dementia Depression Cerebrovascular disease COPD-asthma Hyperlipidemia Thyroid disease Malignancy Papillary thyroid cancer Endometrial cancer Colorectal cancer Hepatocellular cancer Rheumatological disease | 58 43 (39.1) 20 (18.2) 10 (9.1) 4 (3.6) 3 (2.7) 8 (7.3) 1 (0.9) 2 (1.8) 3 (2.7) 4 (3.6) 3 (2.7) 5 (4.5) 2 (1.8) 1 (0.9) 1 (0.9) 1 (0.9) 4 (3.6) |
| **Metastases status** **Absent** **Present** Bone Lymph nodes Lung Liver Skin Adrenal | 43 (59.7) 29 (40.3) 21 (45.7) 11 (23.9) 7 (15.2) 5 (10.9) 1 (2.2) 1 (2.2) |
| **ER** | |
| Negative | 18 (25) |
| 1+ | 4 (5.6) |
| 2+ | 9 (12.5) |
| 3+ | 41 (56.9) |
| **PR** | |
| Negative | 31 (43.1) |
| 1+ | 11 (15.3) |
| 2+ | 9 (12.5) |
| 3+ | 21 (29.2) |
| **CERB2** | |
| Negative | 50 (69.4) |
| 1+ | 1 (1.4) |
| 2+ | 9 (12.5) |
| 3+ | 12 (16.7) |
| **HER2-FISH** | |
| Negative | 49 (94.2) |
| Positive | 3 (5.8) |
| **Ki-67** | |
| <14% | 27 (67.5) |
| ≥14% | 13 (32.5) |

| Table 1. Continued | |
|---|---|
| | Total sample (n=72) |
| **Subtype** | |
| Basaloid | 10 (13.9) |
| Luminal A | 30 (41.7) |
| Luminal B | 20 (27.8) |
| HER2 | 12 (16.7) |
| **Stage** | |
| Unknown | 5 (6.9) |
| Early-stage | 26 (36.1) |
| Local-advanced | 30 (41.7) |
| Metastatic | 11 (15.3) |
| **Histology** IDC ILC Others Basaloid Unspecified | 47 (66.2) 8 (11.3) 15 (21.1) 1 (1.4) 1 (1.4) |
| **Outcome** Exitus Cancer-death Other causes Follow-up | 52 (72.2) 40 (76.9) 12 (23.1) 20 (27.8) |
| *Because of the retrospective design of the study, comorbidty data of some patients were missing ILC: Infiltrative lobular carcinoma, BMI: Body mass index, IDC: Invasive ductal carcinoma | |

tamoxifen. Eight patients were treated with trastuzumab for adjuvant therapy.

Endocrine therapy is the first choice in palliative treatment, however, chemotherapy was preferred as second and third-line treatment in metastatic diseases. Detailed treatment options are shown in Table 4. In luminal A disease, the majority of the patients received endocrine therapy. Only two of the patients did not receive anti-estrogen therapy. All of the patients except one with luminal B disease received anti-estrogen treatment for adjuvant therapy. Treatment regimens are given in Table 4.

## Discussion

In our study, breast tumors in patients aged 75 years and older showed high rates of ER/PR content, low ki-67 proliferation, and low cerbB2 positivity. Geriatric patients had less aggressive tumors like postmenopausal women, and steroid receptor positivity rates increase with age (7,8). The hormone-negative disease is relatively uncommon in older women according to several studies in the literature (9,10). In our study, it is found that hormone-negative disease is also rare. The subtypes in older women resemble postmenopausal women defined many studies in literature.

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The most common histologic type was IDC in compliance with the literature (11,12). However, other rare histopathologies like mucinous or medullary carcinoma were also seen. It was found that older patients with breast cancer are more likely to present with earlier stages. In a study which was performed in women 70 years of age and older, it was found that older patients with breast cancer presented at early stages (13). Obesity is one of the risk factors of breast cancer (14). In our study the population was overweight or obese.

In the early stage of the disease, the main treatment choice is surgery. Older patients with breast cancer have not undergone surgery according to many studies (15-17), because of comorbidities (11,18,19). On the other hand, a study has shown that there is no difference regarding comorbidities in older women with and without breast cancer. A review from the Cochrane database has found that there is no survival benefit between undergoing surgery and not (20). In our study, most of the patients had at least one comorbid disease, but the primary surgery rate was not recorded. So,
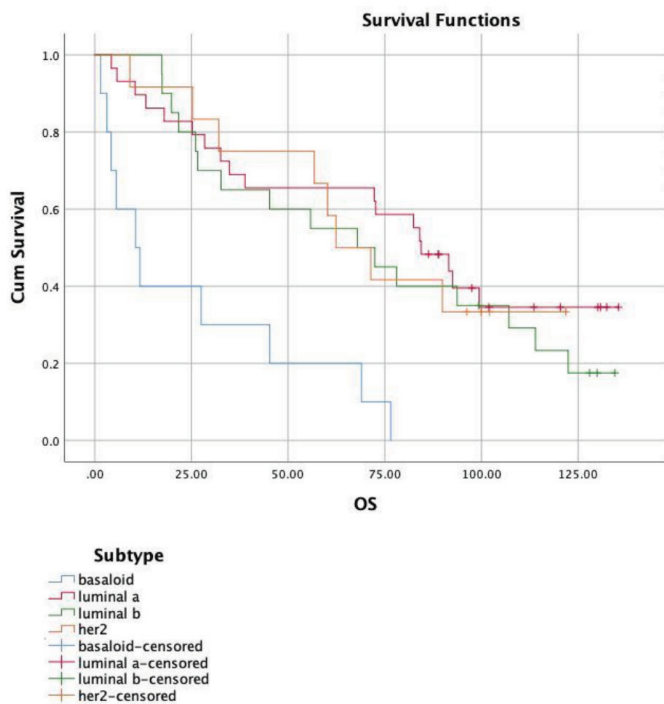


**Figure 1.** Overall survival (OS) (in months) curves according to subtypes
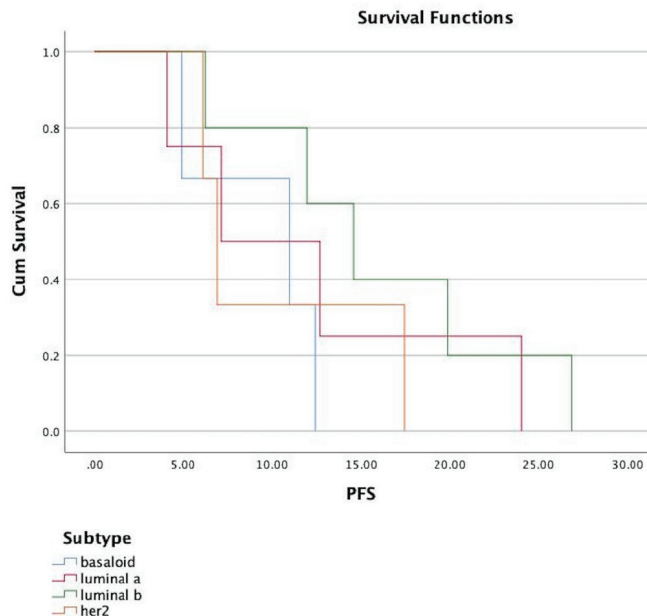


**Figure 2.** Progression-free survival (in months) curves according to tumor subtypes

**Table 2. Immunohistochemistry and FISH positivity of HER2 receptor in luminal B disease**

| Luminal B | Immunohistochemistry | | | FISH | |
|---|---|---|---|---|---|
| | HER2 0/1+ | HER2 2+ | HER2 3+ | HER-2 positive | HER-2 negative |
| N | 15 | 5 | 0 | 1 | 15 |
| % | 75 | 25 | 0 | 6.3 | 93.8 |

**Table 3. Medians for overall and progression-free survival time in months according to molecular subtypes**

| Overall survival | | | | | p | Progression-free survival | | | | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | | | 95% CI | | |
| | Est | Std. error | Lower bound | Upper bound | | | Est | Std. error | Lower bound | Upper bound | |
| Basaloid | 10.586 | 4.860 | 1.060 | 20.113 | <0.001 | | 10.981 | 4.966 | 1.247 | 20.714 | 0.435 |
| Luminal A | 84.460 | 7.515 | 69.731 | 99.190 | | | 7.134 | 4.307 | .000 | 15.576 | |
| Luminal B | 67.923 | 18.599 | 31.469 | 104.378 | | | 14.597 | 2.881 | 8.950 | 20.244 | |
| HER2 | 62.400 | 9.681 | 43.426 | 81.374 | | | 6.904 | 0.644 | 5.641 | 8.167 | |
| Total | 71.375 | 9.264 | 53.218 | 89.533 | | | 11.967 | 3.409 | 5.385 | 18.649 | |
| CI: Confidence interval | | | | | | | | | | | |

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the authors could not report a relationship with surgery and comorbidities among patients.

Endocrine therapy is the main treatment option in older patients, and aromatase inhibitors are preferred to tamoxifen (21). In BIG 1-98 study by Crivellari et al. (22) has stated that letrozole is superior to tamoxifen regardless of the age of the patient. Aromatase inhibitors are well-tolerated in geriatric patients with less adverse reactions like thromboembolic events, endometrial cancers, and impaired cognition than tamoxifen which is essential for this age group (21).

Pooled clinical trial data within the Alliance for Clinical Trials in Oncology and studies using surveillance, epidemiology, and end results data suggest that older patients benefit from chemotherapy as much as younger patients (23,24) but, they may experience higher rates of treatment-related toxicity, including cardiotoxicity and bone marrow disorders (24). Albeit that chemotherapy benefit, some other studies determined a decline in the choice of chemotherapy when the patients

| Table 4. Adjuvant and palliative treatments of the patients | |
|---|---|
| **Adjuvant therapy** | 65 (100) |
| Chemotherapy | 15 (23.1) |
| Radiotherapy | 16 (24.6) |
| Hormonotherapy | 34 (52.3) |
| **Adjuvant chemotherapy regimen** | 15 (100) |
| Anthracycline-based | 3 (20) |
| Taxan-based | 5 (33.3) |
| Other | 1 (6.7) |
| Unknown | 6 (40) |
| **Adjuvant hormonotherapy** | 34 (100) |
| AIs | 22 (64.7) |
| TMX | 3 (8.8) |
| Unknown | 9 (26.4) |
| **First-line therapy\*** | 27 (100) |
| Chemotherapy | 7 (25.9) |
| AIs | 15 (55.6) |
| TMX | 2 (7.4) |
| Trastuzumab | 3 (11.1) |
| **Second-line therapy** | 14 (100) |
| AIs | 4 (28.6) |
| GnRH agonists | 2 (14.3) |
| Chemotherapy | 6 (42.9) |
| Trastuzumab | 2 (14.3) |
| **Third-line therapy** | 11 (100) |
| AIs | 1 (9.1) |
| GnRH analogs | 2 (18.2) |
| Chemotherapy | 6 (54.5) |
| Tamoxifen | 2 (18.2) |
| *First-line therapy regimens of two metastatic patients were missing* | |

become older (11,22). In the present study, it was found that chemotherapy is the least chosen treatment pattern in the advanced-geriatric patient group.

Adjuvant radiotherapy in geriatric patients is a well-discussed topic and plays an important role in early-stage breast cancer for local recurrence. There are at least four large randomized clinical trials that were researching the beneficial effect of radiotherapy. Despite the fact that radiotherapy is beneficial for local recurrence, no benefit is observed in disease-free survival and overall survival (25-28). In the current study, the quarter of the patients was treated with radiation, however, radiotherapy decision should be personalized.

Independent from age, metastatic disease remains incurable and the main goal of the treatment is the control of the disease and gain the highest function (29). Even though they have metastatic disease, in one study it was shown that one-fifth of the patients died from non-breast cancer causes (30). In our study this ratio was 23%. For hormone-receptor positive and HER2 negative metastatic disease endocrine therapy is the mainstay of the treatment. For triple-negative disease, which is resistant to hormonotherapy, chemotherapy should be given in older patients. In HER2 disease, trastuzumab plus chemotherapy improved survival compared with chemotherapy alone at first-line treatment (31). Even though older women can tolerate anti- HER2 regimens, there is an increased risk of cardiotoxicity (32).

The triple-negative disease has the worst overall survival among the molecular subtypes (33) as in the current study. The longest survival is seen in luminal A subtype in compatible with the literature (34). In a study done in postmenopausal women, it was found that age is the most determinant factor of decreased survival in early-stage disease. However, comorbidity rather than age has a bigger impact on survival in stage 3 disease and metastatic disease (35).

### Study Limitations

There are some limitations in this study. This study had retrospective design and data was collected from single center. Another limitation of the study was some of the patients had missing data like ECOG and Karnofsky scores, comorbidities, and treatment choices. The study group included 75 years and older women; therefore, the results of the study population were compared with the literature, control group was not formed. Nevertheless, the aim of the study was not performing comprehensive geriatric assessment, so that the frailty scores, nutritional and cognitive status of the patients were missing. Further studies examining the association of frailty with management decisions and outcomes will clarify this point.

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## Conclusion

Treatment patterns should be planned by calculating the expected life-time other than cancer in older women. The geriatric patient group shows similarities in histologic and intrinsic subtypes with postmenopausal women according to the literature except for their frailty and comorbidities, however in geriatric patients endocrine therapy is preferred as adjuvant and/or metastatic treatment due to their susceptibility to chemotherapeutic agents. Patient preferences should be evaluated during the oncologist's decision- making process of adjuvant therapy. Chemotherapy should be tailored according to benefits and toxicities in the aged group.

This study shows geriatric women have similar tumors like postmenapausal women, however they are treated differently. It is known that geriatric patients is more fragile to anti-cancer treatments, and oncologist are afraid of their ages beside from their clinical, physical and psychological status. Oncologists should consulate every older patient to geriatric medicine and comprehensive geriatric assessment should be done to decide and continue treatment. Moreover, this study shows ageism should not be interfered in anti-cancer therapy and geriatrician should be included to decision-making process. Age should not be the only factor for decision-making.

### Ethics

**Ethics Committee Approval:** This study was reviewed by the approval (date: 12.07.12, decision number: 12-6.1/7) of the Local Ethics Committee of the Ege University (İzmir/Turkey).

**Informed Consent:** The participants provided informed consent.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: G.B., E.A., B.K., Concept: G.B., E.A., B.K., Design: G.B., M.G.O., E.A., B.K., Data Collection or Processing: G.B., E.A., Analysis or Interpretation: G.B., M.G.O., B.B.D., Literature Search: G.B., M.G.O., B.B.D., B.K., Writing: G.B., M.G.O., B.B.D., B.K.

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