

# Treatment results and patient characteristics for breast cancer patients older than 70 Years

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## ABSTRACT

**Objective:** The incidence of breast cancer (BC) subtypes varies according to age, and its treatment is more strenuous and requires much more attention in advanced ages. The aim of this study is to investigate patient characteristics and treatment results respectively for patients older than 70 years.

**Materials and Methods:** In this study, we examined 188 elderly BC patients treated in our hospital, at March 2008 - November 2019. Patient characteristics and demographics were investigated from patients' files retrospectively.

**Results:** Mean age of the patients was  $74.3 \pm 4$  years (All female). The presence of comorbid diseases was 76.1%. Major histology was invasive ductal carcinoma in 72.9% and mostly grade 2 differentiated, and the majority of patients were T2 size (58.5%). Oestrogen receptor (OR) positivity was seen in 83%, Progesterone receptor (PR) positivity in 72.3% of patients and *cerb2* positivity in 16.5%. Luminal B (47.9%) was the most common in molecular subgroup analysis. Patients with lymph node involvement (N1 33%; N2, 19.1%; N3, 6.9%) were higher than those without involvement (34%). Surgery type was modified radical mastectomy (MRM) for 51.6%, breast conserving surgery (BCS) for 39.4 % and lumpectomy for 7.4%. In a median follow-up time was 53.9 (9-101) months, local recurrence was seen in 5 (2.7%) patients and distant metastasis was developed in 16 (8.5%) patients. The median overall survival was worse in those with MRM than those with BSC ( $p=0.006$ ). In multivariate logistic regression analysis, only found that lymph node positivity was an independent risk factor for metastasis (HR; 4.15, 95% CI:1.019-16.933,  $P=0.047$ ).

**Conclusion:** While it was observed that the most important risk factor for metastasis risk in elderly patients was lymph node positivity; The hormonal status and *her2* conditions were not affected in terms of metastasis. It was thought that tumor clinical course and relapse may differ in the elderly population compared to general BC patients.

**Key words:** Breast cancer, elderly, treatment, comorbidity, survival

## INTRODUCTION

Elderly women with breast cancer (BC) are increasing rapidly because of the rising average life expectancy of the population. Nearly 50 % women diagnosed BC are > 65 years old (1). Treatment options of BC are generally substandard in older patients. There are some studies showing that tumor subtype and patient age are important prognostic factors to determine optimal treatment (2,3). Although the primary surgical approach is generally conservative in advanced age patients (4), standard surgery methods are increasing rapidly like younger patients, especially with little or no comorbidities (5-11). Although axillary dissection is controversial due to treatment morbidity in clinically negative patients (12-16), in a group of more high-risk patients who are healthy, lymph node evaluation may supply important information about adjuvant treatment options such as chemotherapy (17). Adjuvant treatment decisions such as chemotherapy, hormonotherapy, radiotherapy can change some factors including patient life expectancy, comorbidities and patient choice. In patients with breast-conserving surgery, ipsilateral tumor recurrence is reduced by postoperative adjuvant radiotherapy (18-20). On the other hand, hormone receptor-positive, axillary negative low-risk patients hormonotherapy option without radiotherapy was investigated (21).

## Research Article

Received 29-01-2022

Accepted 25-02-2022

Available Online: 01-03-2022

Published 30-03-2022

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Since, patients with cardiovascular disease and diabetes have a high risk of Trastuzumab treatment, it is more appropriate to treat healthy, fit patients with pre-cardiac tests and cardiac monitorization (22-25).

While bone fracture and musculoskeletal disorders are more prominent in the use of aromatase inhibitors, thromboembolic events and the risk of endometrial cancer are at the forefront of the use of tamoxifen in the treatment-related side effect. Therefore, pre-treatment bone mineral density measurements and calcium/vitamin D supplements are important especially in patients receiving aromatase inhibitors (26-28).

Due to the presence of comorbid diseases in these patients, treatment toxicity due to adjuvant poly-chemotherapy is also high (29). However, factors such as life expectancy, stage of disease and expected chemotherapy benefit are also highlighted in the decision of adjuvant chemotherapy (30-32).

## MATERIAL and METHODS

In this study, we examined 188 elderly BC patients respectively treated in our hospital, at March 2008-November 2019. Table 1 shows the treatment modalities of the patients. Surgery type was mastectomy for 51.6%, breast conserving surgery for 39.4% and only lumpectomy for 7.4%. Axillary dissection was performed at 67%.

Sentinel lymph node biopsy was applied for 42%. Postoperative adjuvant RT was given for 97.9%. While radiotherapy doses were 46-50 Gy in 23-25 fractions generally, hypofractionated radiotherapy was applied for 6 patients as 2.30-2.66 Gy in 16-18 fractions. Only breast or chest wall irradiation was applied for 31.9%. In addition to breast or chest wall irradiation, nodal irradiation (supraclavicular + level 3 axillary) was performed at 55.3%. Intraoperative radiotherapy was applied in two patients as 20 Gy.

Chemotherapy was given for 66.1 %. Neoadjuvant chemotherapy was given for 6 patients. Chemotherapy protocols were Adriamycin + Cyclophosphamide (AC) plus Taxane, Cyclophosphamide + Adriamycin+ 5 \_fluorouracil (CAF), AC and Cyclophosphamide + Epirubicin + 5-Fluorouracil (CEF) plus Dosectaxel. AC plus Taxane was the most preferred chemotherapy protocol (60.4%). Adjuvant hormone therapy were given for 81.9%. Hormonotherapy protocols were aromatase inhibitors for 70.2%, tamoxifen for 2.1% and both of them for 2.1%.

Comorbidity was seen in 143 (76.1%) of patients due to advanced age. Comorbid diseases were detected as hypertension (62.2%), diabetes mellitus (28.7%), coronary artery disease (12.2%), chronic obstructive pulmonary disease and asthma (6.9%), thyroid dysfunction (5.9%). Apart from these diseases, hyperlipidaemia, congestive heart failure, cerebrovascular event, dysrhythmia, Alzheimer's, depression, pulmonary hypertension, hyperparathyroidism, Parkinson's and heart valve diseases were less than 5%.

The age, features of histopathology, hormone and nodal status, tumor size, types of treatment, date of progression and last outpatient control or the date of exitus were retrieved from the patients' hospital records.

## RESULTS

### Patient characteristics

Table 2 shows the characteristic features of the 188 patients. All female, the mean age of the patients were 74.3 years ( std. deviation 4.025). The family history was present in 30 (16%) patients. Histopathology was compatible with invasive ductal carcinoma in 72.9%, mucinous carcinoma in 8%, ductal carcinoma in situ in 5.9%, papillary carcinoma in 5.3%, invasive lobular carcinoma in 4.8% patients. Tumor localization was right for 48.9%, left for 43.6%. Tumor size were T1 for 25.5%, T2 for 58.5%, T3 for 8.5% and T4 for 4.3%. The majority of patients were T2 size (58.5%). Patients with lymph node involvement (N1,33%; N2,19.1%; N3,6.9%) was higher than those without involvement (34%). Nodal status was unknown for 4.8%. Tumor stage were stage 1 for 14.9%, stage 2 for 50%, stage 3 for 29.8% and stage 4 for 1.1 %. Half of the patients were stage 2A and 2B. Histopathological grades were as following; grade 1 for 7.4%, grade 2 for 46.8 and grade 3 for 38.8%.

The surgical margin was negative in 79.8% of patients. Surgical margin positivity was present in 6.9% and less than 1 mm of surgical proximity in 6.9% of patients. Lymph node positivity was shown in 37.9% of the 79 patients with sentinel lymph node biopsy. ER positivity was present in 83%, PR positivity in 72.3% of patients and *cerb2* positivity in 16.5% patients. Luminal B (47.9%) was the most common in molecular subgroup analysis. The 27.7% of patients have Luminal A, 9% of patients have basal-like, 4.8 of patients were *her2* overexpressed molecular subtype.

### Survival data and prognostic factors

In a median 53.9 (9-101) months follow-up, 22 patients had exitus. Graphic 1 shows the general survival of the 188 patients. Local relapse was seen in 5 (2.7%) patient, 16 (8.5%) patients also developed distant metastasis and the median life expectancy was not reached. In graphic 2, survival curves are seen according to metastasis status. Although median values were not obtained in hypertensive patients, the median OS was worse (84 vs. 95 months,  $P=0.08$ ). However, the median survival in diabetic patients was similar (87 vs. 88 months,  $P=0.611$ ). In the group with coronary artery disease, median overall survival (OS) was worse numerically and the difference was close to statistical signification ([79.7 (69.6-89.7) vs. not reached,  $P=0.078$ ). According to hyperlipidemia, chronic obstructive pulmonary disease, asthma, histologic subtypes, nuclear grade, surgical boundary proximity or positivity, oestrogen and progesterone receptor, *Her-2* status, *Ki* 67% ( $>10$  vs  $<10\%$ ), luminal subtypes, tumor laterality (left vs right) and adjuvant chemotherapy survival was similar ( $P\geq 0.05$  all). The median survival time was worse in those with MRM than those with BSC ( $82 \pm 3.6$  vs.  $94 \pm 2.7$ ),  $p=0.006$  .T1 stage was again associated with good overall survival ( $P=0.02$ ). OS was similar according to whether there was nodal involvement or not. Median survival in patients receiving nodal radiotherapy was worse than those without (Enel 85.3 vs. 94.1,  $p=0.031$ ).

Due to the lack of median survival in the subgroups, no analysis could be done on the independent factors affecting OS and disease-free survival due to the short follow-up time and the very small number of patients who relapsed.

When the factors affecting metastasis are examined, logistic regression analysis only found that lymph node positivity was an independent risk factor for metastasis (HR:4.15, 95%CI:1.019-16.933,  $p=0.047$ ), ER, PR, Her2 condition, surgical type, tumor size, adjuvant chemotherapy, hormone therapy, grade, comorbid diseases and age were not an independent risk factor for metastasis risk ( $p>0.05$  all).

**Table 1.** Demographical and clinical characteristics of the patients

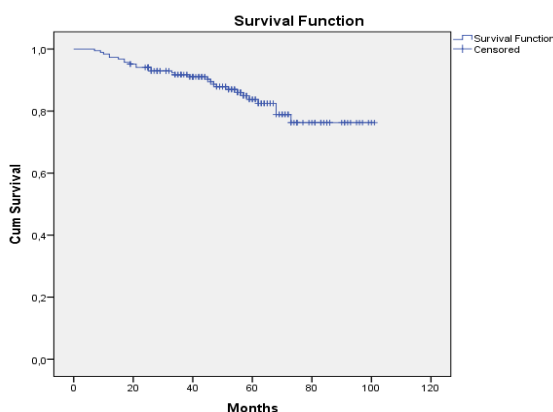
Variables	%
Age (years), mean $\pm$ SD	74.3 $\pm$ 4
<b>Histological subtype</b>	72.9
Invasive ductal carcinoma	4.8
Invasive lobular carcinoma	8
Mucinous carcinoma DCIS	5.9
Papillary carcinoma	5.3
<b>Histopathological grade</b>	
Grade1	7.4
Grade2	46.8
Grade3	38.8
<b>Molecular subtypes</b>	
Luminal A subtype	27.7
Luminal B subtype	47.9
Triple negative	9
Her2 type	4.8
<b>Pathological stage</b>	
Stage 1	14.9
Stage 2	50
Stage 3	29.8
Stage 4 (clinical or pathological)	1.1
<b>Receptor Status</b>	
ER positive	83
PR positive	72.3

SD, standard deviation, ER, oestrogen receptor; PR, progesterone receptor

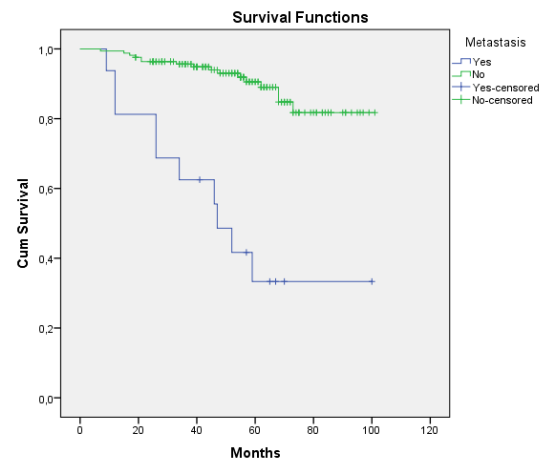
**Table 2.** Treatment modalities of the 188 patients

Treatment Modality	%
Mastectomy	51.6
BCS	39.4
Lumpectomy	7.4
Radiotherapy	97.9
Chemotherapy	66.1
Hormonotherapy	81.9

BCS, Breast conserving surgery



**Graphic 1.** Overall survival of 188 patients



**Graphic 2.** Overall survival according to metastasis status

## DISCUSSION

Some studies showed that surgery is safe method for elderly patients, especially if they are fit and have little or no comorbidities (5-8). The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) have recommended that patients 70 years or older should be offered the same surgery as their younger counterparts (9). Patients who had surgery had a significantly better outcome and primary hormonotherapy without surgery should be used for elderly patients with short life expectancy (10,11).

In our study, surgery type was mastectomy for 51.6%, breast conserving surgery for 39.4% and lumpectomy for 7.4%. Despite, the presence of 76.1 comorbid disease, standard surgical treatments was applied to the patients. On the other hand, the average survival time was worse in those with MRM than in those with BSC ( $p=0.006$ ). This can be explained by the fact that patients with MRM are more advanced stage than those with BSC.

In the elderly patients, the role of axillary dissection is controversial because of the morbidity of the procedure, especially in clinically node-negative patients (12-16). NSABP -32 showed that omission of the axillary lymph node dissection in patients with clinically node-negative disease had no impact on OS and disease-free survival and regional control (16).

On the other hand, the role of sentinel lymph node biopsy has been searched with some reports. Because, in a group of more high-risk patients who are healthy, lymph node evaluation may supply important information about adjuvant treatment options such as chemotherapy (17).

In our study, approximately 50% of patients in this age group usually refer to the hospital later stage of the disease, especially stage 2A and 2B. Since the majority of patients are in advanced stages, the proportion of patients with axillary dissection is also high (67%). SLNB was administered to 79 patients who were clinically negative with axillary at the beginning of the disease, and the lymph node positivity rate was 37.9% for these groups of the patients.

In patients with breast-conserving surgery, ipsilateral tumor recurrence is reduced by post-operative adjuvant radiotherapy (18-20). Unless there is an advanced comorbid disease, adjuvant radiotherapy can be well tolerated with minimal morbidity in these patients. On the other hand, 1326 patients over 65 years of age, low risk, hormone-positive, axilla negative and hormonotherapy were retrospectively evaluated in the work of PRIME 2 (Post-operative Radiotherapy In Minimum -risk Elderly) (21). In this study, the recurrence rates in the ipsilateral breast were 1.3% in RT areas and 4.1% were not found in those who did not, while OS was not different.

In our study, BCS and lumpectomy were applied for 46.8 %; mastectomy was applied for 51.6% patients. Postoperative adjuvant radiotherapy was not given only in 4 mastectomy patients with early stage. While treatment is well tolerated in all patients, local recurrence was seen only in 5 patients (2.7%). On the other hand, survival was found to be worse in patients receiving nodal radiotherapy than those who did not, and this can be explained by the fact that patients receiving nodal radiotherapy are at a more advanced stage.

Adjuvant Trastuzumab treatment is effective in patients with Her2 over precipitation. However, patients with cardiovascular disease and diabetes have a high risk of cardiac toxicity (22-24). Therefore, it is more appropriate to treat healthy fit patients with precardiac tests and cardiac follow-up (25).

In our study, her-2 over expression was detected for 4.8% of patients and cerb-b2 was positive for 16.5 % of the patients. Adjuvant Trastuzumab treatment was applied to 21 patients. Echo, VS cardiac tests were performed to all patients before treatment. Pericarditis due to treatment were developed in 2 of patients, and cardiac tamponade was developed in one patient.

Endocrine treatment options are applied in hormone receptor-positive advanced age patients as well as in young patients. While thromboembolic events and the risk of endometrial cancer are at the forefront of the use of tamoxifen, bone fracture and musculoskeletal disorders are more prominent for aromatase inhibitors as treatment-related side effects. Therefore, pre-treatment bone mineral density measurements and calcium/vitamin D supplements are important, especially in patients receiving aromatase inhibitors (26-28).

In our study, hormonotherapy was given to most patients since receptor positivity rate is also high. Bone mineral density measurements and calcium/vitamin D supplements were done to all the patients before treatment.

Due to the presence of comorbid diseases in elderly patients, treatment toxicity due to adjuvant poly-chemotherapy is also high (29). However, factors such as life expectancy, stage of disease and expected chemotherapy benefit are also highlighted in the decision of adjuvant chemotherapy. (30,31,32). As in younger patients, poly-chemotherapy regimens are more effective (33). In the CALGB TRIAL, standard adjuvant chemotherapy with CMF or doxorubicin plus cyclophosphamide was more effective than Capecitabine alone in fit patients over 65 years (29).

In this study, chemotherapy was applied 66.1% of patients. AC plus Taxol was the most preferred protocol (60.4%) since patients applied to the hospital generally at advanced stages of the disease. Although, treatment was well tolerated in most of the patients, hepatotoxicity was seen in one patient during Taxol treatment.

In our study, 22 patients were ex during the follow-up. Distant metastasis was detected in 16 (8.5%) patients. Bone was the most common site of metastasis (4.8%). When the factors affecting metastasis were examined, it was observed that only lymph node positivity was an independent risk factor for metastasis in logistic regression analysis ( $p=0.047$ ).

During the follow-up period, secondary cancers were seen in 2 patients, including melanoma in one patient and endometrial cancer in one patient after four years of the treatment.

## CONCLUSION

In the present study, the disease was frequently detected at an advanced stage due to patients were applied to the hospital lately in these age groups. However, standard treatment approaches have been applied to the majority of patients and treatment was well tolerated in most of the patients. While it was observed that the most important risk factor for metastasis risk in elderly patients was lymph node positivity; hormonal status and her2 conditions were not affected in terms of metastasis. It was thought that tumor clinical course and relapse might differ in the elderly population compared to general BC patients.

**Author Contributions:** GE, FK, ARÜ, GSK, MBA: Concept, Data collection and/or processing, Analysis and/or interpretation, Literature review, FK: Writing, Revision

**Acknowledgments:** None

**Conflict of interest:** The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Ethical approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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