



RESEARCH

Clinical and pathological features of breast cancer patients in the geriatric population

Geriatrik popülasyondaki meme kanserli hastaların klinik ve patolojik özellikleri

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Abstract

Purpose: A significant portion of patients diagnosed with breast cancer are over the age of 65. Elderly patients are often excluded from prospective clinical trials due to comorbidities. Clinicians have different treatment management options for elderly patients. Under-treatment or over-treatment may negatively affect treatment outcomes and prognosis. There are few data to guide treatment decisions. We present the clinical and pathological features of elderly breast cancer patients followed in our cancer center.

Materials and Methods: A retrospective review of files about surgically treated patients with breast cancer was conducted. The prognostic impact on overall survival and progression-free survival was assessed.

Results: The study encompassed a total of 101 patients. The median age was 67 (65-81) years. Approximately half of the patients were classified as TNM stage 2. The majority of them had undergone modified radical mastectomy. 15.8% received neoadjuvant chemotherapy. 84.2% had invasive ductal carcinoma histological subtype. progression-free survival was lower in patients receiving neoadjuvant chemotherapy with pathological N3 lymph nodes and in HER2-positive patients. The 5-year survival rate was 61.7% in patients with N3 pathological lymph nodes, 91% in those with N2 pathological lymph nodes, and 100% in patients with N1 or N0 pathological lymph nodes.

Conclusion: The pathological stage was associated with survival. The presence of pathological N3 lymph nodes resulted in lower progression-free survival and lower overall survival. Regardless of age, patients with good performance, who are not frail, and who have no comorbidities should be encouraged to receive current therapy.

Keywords: Geriatric breast cancer, overall survival, fragility

Öz

Amaç: Meme kanseri teşhisi konulan hastaların önemli bir kısmı 65 yaşın üzerindedir. Yaşlı hastalar genellikle eşlik eden hastalıklar nedeniyle prospektif klinik çalışmalardan hariç tutulur. Klinisyenlerin yaşlı hastalar için farklı tedavi yönetimi seçenekleri vardır. Yetersiz tedavi veya aşırı tedavi tedavi sonuçlarını ve prognozu olumsuz etkileyebilir. Tedavi kararlarına rehberlik edecek çok az veri vardır. Kanser merkezimizde takip edilen yaşlı meme kanseri hastalarının klinik ve patolojik özelliklerini sunuyoruz.

Gereç ve Yöntem: Cerrahi olarak tedavi edilen meme kanseri hastalarının dosyalarının retrospektif bir incelemesi yapıldı. Genel sağkalım ve progresyonsuz sağkalım üzerindeki prognostik etki değerlendirildi.

Bulgular: Çalışma toplam 101 hastayı kapsıyordu. Ortanca yaş 67'yd (65-81). Hastaların yaklaşık yarısı TNM evre 2 olarak sınıflandırıldı. Çoğunluğu modifiye radikal mastektomi geçirmişti. %15.8'i neoadjuvan kemoterapi aldı. %84.2'sinde invaziv duktal karsinom histolojik alt tipi vardı. Patolojik N3 lenf nodları olan ve neoadjuvan kemoterapi alan hastalarda ve HER2 pozitif hastalarda progresyonsuz sağkalım daha düşüktü. N3 patolojik lenf nodları olan hastalarda 5 yıllık sağkalım oranı %61,7, N2 patolojik lenf nodları olan hastalarda %91 ve N1 veya N0 patolojik lenf nodları olan hastalarda %100 idi.

Sonuç: Patolojik evre sağkalımla ilişkiliydi. Patolojik N3 lenf nodlarının varlığı daha düşük progresyonsuz sağkalım ve daha düşük genel sağkalımla sonuçlandı. Yaştan bağımsız olarak, iyi performans gösteren, güçsüz olmayan ve komorbiditesi olmayan hastalar güncel tedaviyi almaya teşvik edilmelidir.

Anahtar kelimeler: Geriatrik meme kanseri, genel sağ kalım, kırılmalılık

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INTRODUCTION

Breast cancer is the most common malignant tumor in women, and its frequency increases with age. Epidemiological studies show that mortality rates due to breast cancer increase with age¹⁻². There has been an increase in screening and treatment methods for breast cancer in the last ten years³. Approximately half of patients diagnosed with breast cancer are 65 years of age or older. In the future, the number and percentage of breast cancer diagnosed in older patients are predicted to rise⁴. Clinical, pathological, and biological features of breast cancer in elderly patients are different than in younger. Breast cancer in the elderly, compared to the younger population, presents with larger tumor size but lower grade, and they tend to be more hormone-positive and human epidermal growth factor receptor 2 negative (HER2-negative)⁵. Routine mammography screening is not recommended in healthy women over 70. Compared to younger patients, older women are more likely to be diagnosed on physical examination rather than imaging and are often seen with larger tumors⁶. Despite more favorable biological tumor characteristics, the disease is diagnosed at a more advanced stage. There are differences in treatment methods in older patients compared to younger patients⁷.

Physiological age, associated comorbidities, life expectancy, and age-related frailty contribute to treatment decisions. Typically, breast cancer in the elderly are more indolent tumors and respond very well to endocrine therapy. These differences in tumor characteristics and the patient's comorbidities are considered when planning treatment. Elderly patients are at higher risk for morbidity and mortality, especially from chemotherapy, radiotherapy, and surgery⁸. Clinicians often administer reduced doses of chemotherapy and radiotherapy to older patients to minimize toxicity. Elderly patients are usually excluded from prospective clinical studies due to their fragility and comorbid diseases⁹. Management of breast cancer in this population is challenging due to the heterogeneous nature of the disease and the exclusion of elderly patients from clinical trials. Breast cancer research primarily focuses on younger populations, creating a significant gap in data and treatment options for older patients. This neglect results in a substantial lack of effective strategies for older people. A comprehensive geriatric assessment should be performed for each patient before starting

treatment. Under-treatment or over-treatment may negatively affect treatment outcomes and prognosis. Performing axillary lymph node dissection in the elderly may significantly affect quality of life as it increases the risk of lymphedema. As a result, many older patients do not receive care consistent with established treatment guidelines, highlighting the urgent need for more inclusive research and recommendations focused on these patients¹⁰. This study aims to fill this knowledge gap in elderly patients and provide valuable insights to improve the care of geriatric breast cancer patients. We conducted a comprehensive examination of the clinical and pathological features, as well as the progression-free survival (PFS) and overall survival (OS), of female patients aged 65 and older who were diagnosed with invasive breast cancer and admitted to our center. This research aims to enhance our understanding and improve treatment outcomes for this population.

MATERIALS AND METHODS

Sample

This study was approved by the ethics committee of Manisa Celal Bayar University (29/05/2024 and No. 2439). The patients did not obtain consent since this was a retrospective file review. Patients diagnosed with breast cancer who applied as outpatients to Manisa Celal Bayar University Hafsa Sultan Hospital medical oncology clinic between 2020 and 2023 were included in the study. Approximately 800 breast cancer patients over the age of 18 applied to the outpatient chemotherapy unit between 2020 and 2023. Patients aged 65 and over at the time of diagnosis were included in the study. Exactly 101 patients were eligible for the study. Attention was paid to file reliability, and patients with no clinical follow-up were excluded from the study. The inclusion criteria were being over 65 years of age and having a surgery plan. The exclusion criteria were being under 65 years of age, having metastatic disease at the beginning, and discontinuing treatment and follow-up for any reason. The files of these patients were reviewed retrospectively.

Procedure

Various clinical and pathological characteristics, including age, comorbidity, tumor marker, type of surgery, site of tumor involvement, histological subtype, estrogen receptor (ER), progesterone receptor (PR), HER2, ki-67 status, molecular

subtype, treatment received (neoadjuvant/adjuvant chemotherapy, adjuvant radiotherapy), TNM stage, pathological T and N stage were recorded. The hospital's electronic record system and patient files in the archive were used to access patients' demographic data.

Treatment

Anthracycline and taxane chemotherapy were given for HER2-negative breast cancer; for triple-negative breast cancer, anthracycline, taxane, and carboplatin were given. For HER2-positive breast cancer, trastuzumab, pertuzumab, and taxane chemotherapy were given. Adjuvant endocrine therapy was given to hormone-positive patients. All patients were referred to radiation oncology after surgery. Chemotherapy was given according to ER, PR, and HER2 status.

Statistical analysis

The sample size for this study was determined using power analysis with G*power (version 3.1.9.4) software. A power ($1-\beta$) of 0.85 and a confidence level of 95% were considered, resulting in a calculated sample size of 26 patients.

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables and as Mean \pm SD, Median (min-max) for continuous variables. ROC Curve was used to analyze mortality prediction of Post-op CEA, CA15-3, and Ki67 parameters. Kaplan Meier method was used to compare OS and PFS times among the groups of operation type, neoadjuvant treatment status, N stage, tumor localization, HER2 status, molecular subgroups, RT history, ER, PR, and Ki67 parameters. $p < 0.05$ was considered statistically significant.

RESULTS

The study encompassed a total of 101 patients. The median age was 67 (65-81) years. Approximately half of the patients were classified as TNM stage 2. 70% of patients had chronic disease. The majority of them had undergone modified radical mastectomy. 15.8% received neoadjuvant therapy. 84.2% had invasive ductal carcinoma histological subtype. 44% of the patients had T1 tumor size, and approximately half had T2 tumor size. N0 lymph node metastases were present in 53.8% of the patients, N1 in 21.5%, N2 in

18.3%, and N3 in 4.3%. The hormone-positive HER2-negative subtype was present in 72.3% of cases, the HER2-positive subtype in 18.8%, and the triple-negative molecular subtype in 8.9%. 87.1% of the patients received chemotherapy, and 62.4% received adjuvant radiotherapy (Table 1).

Table 1. Clinical and pathological characteristics (n=101)

Variables	N	%
Age		
Median (min-max)	67 (64-81)	
Clinical stage		
Stage-1	24	23.8
Stage-2	50	49.5
Stage-3	21	20.8
Stage-4	8	5.9
Surgery		
No	5	5.0
BCS	18	17.8
MRM	78	77.2
NACT		
No	85	84.2
Yes	16	15.8
Histological subtype		
Invasive ductal	85	84.2
Invasive lobular	5	5.0
Other	3	3.0
Mucinous	3	3.0
Medullary	2	2.0
Papillary	3	3.0
Pathological T stage		
0	2	2.2
1	41	44.1
2	46	49.5
3	4	4.3
Pathological N stage		
0	50	53.8
1	20	21.5
2	17	18.3
3	6	6.5
Molecular Subgroup		
HR+, HER2-	73	72.3
HER2+	19	18.8
Triple-negative	9	8.9
Chemotherapy		
No	13	12.9
Yes	88	87.1
Radiotherapy		
No	38	37.6
Yes	63	62.4

BCS: Breast-conserving surgery, MRM: Modified radical mastectomy, HR+: Hormone receptor-positive, NACT: Neoadjuvant chemotherapy

The predictive effect of postoperative CEA (Carcinoembryonic Antigen), CA15.3 (Cancer Antigen 15-3), and ki-67 values on mortality was examined. Both sensitivity and specificity were low

and not significant, suggesting that these markers may not be reliable indicators of mortality risk in breast cancer patients (Table 2).

Table 2. Analysis of predictive values of various index values in distinguishing mortality

Variables	AUC	%95 CI	Sensitivity (%)	Specificity (%)	P
Post-op CEA	0.549	0.307-0.792	55.6	50.6	0.628
Post-op CA15-3	0.589	0.375-0.803	55.6	62.1	0.379
Ki-67	0.569	0.408-0.731	54.5	53.5	0.456

AUC: Area under the curve, CI: Confidence interval CEA: Carcinoembryonic Antigen, CA15.3: Cancer Antigen 15-3

Receiving or not receiving neoadjuvant treatment, tumor localization, HER2 status, molecular subgroups, radiotherapy, ER and PR percentage, ki-67, and tumor markers were insignificant in OS. The 5-year survival rate was 61.7% in patients with N3

pathological lymph nodes, 91% in those with N2 pathological lymph nodes, and 100% in patients with N1 or N0 pathological lymph nodes. Survival was significantly lower in pathological lymph node metastasis N3 (Table 3).

Table 3. Overall survival analysis

	2 years %	5 years %	P
General	97	94.5	
Surgery			
No	40	40.0	<0.001
BCS	-	100	
MRM	100	96.6	
NACT			
No	97.6	96.2	0.235
Yes	93.8	84.4	
Pathological N stage			
0	100	100	<0.001
1	100	100	
2	100	91.7	
3	100	66.7	
HER2 status			
Positive	94.7	88.4	0.980
Negative	97.6	96.1	
Molecular subgroup			
HR+, HER2-negative	98.6	96.9	0.809
HER2+	94.7	88.4	
Triple-negative	88.9	88.9	
Radiotherapy			
No	92.1	92.1	0.656
Yes	100	96	
Estrogen receptor			
<%50	92.9	89.1	0.519
>%50	98.4	96.4	
Progesterone receptor			
<%50	95.2	93.3	0.174
>%50	100	95.5	
Ki-67			
<20	100	97.1	0.544
≥20	95.7	93.5	

BCS: Breast-conserving surgery, MRM: Modified radical mastectomy, NACT: Neoadjuvant chemotherapy

PFS was lower in patients receiving neoadjuvant therapy, with pathological N3 lymph nodes, and in HER2-positive patients (Table 4).

Table 4. Progression-free survival analysis

Variable	2 years %	5 years %	P
Generall	95.5	87.9	
NACT			
No	97.5	90.6	0.008
Yes	83	71.1	
Pathological N stage			
0	98	92.9	0.006
1	100	93.8	
2	100	91.7	
3	100	-	
HER2 status			
Positive	88.5	82.2	0.019
Negative	97.1	89.3	
Radiotherapy			
No	100	100	0.111
Yes	93.1	80.9	
Estrogen receptor			
<%50	92.3	88.3	0.446
>%50	96.1	83	
Progesterone receptor			
<%50	94.6	83.3	0.130
>%50	95.7	95.7	
Ki-67			
<20	93.4	85.3	0.711
≥20	97.6	89.8	

NACT: Neoadjuvant chemotherapy, HER2: human epidermal growth factor receptor 2

DISCUSSION

Clinical studies on breast cancer treatment in elderly patients are few. Elderly populations are often excluded from clinical trials due to poor performance, comorbidities, and frailty. Age should not be taken alone as a criterion in choosing a breast cancer treatment modality. A multidisciplinary geriatric evaluation should include life expectancy, comorbidities, and performance status⁵. Life expectancy has increased in recent years. For this reason, breast cancer is diagnosed more frequently in the elderly. As with other cancers, early diagnosis gives better results in breast cancer. Elderly patients

must be encouraged to implement cancer screening programs, which can significantly improve their outcomes. They may experience cognitive impairment because they are alone in coping with stress and lack social support. Frailty, which consists of weight loss, exhaustion, weakness, tiredness, and insufficient physical activity, increases with age. Frail patients have lower OS. A study of geriatric patients diagnosed with breast cancer found that the presence of frailty was associated with mortality similar to that of patients with nodal involvement, even in the absence of nodal involvement⁷. Identifying frail patients before treatment is essential to reduce morbidity and mortality.

It has been observed that, with increasing age, radical mastectomy is preferred by clinicians, regardless of tumor size, despite surgical complications^{7,11}. In a multicenter prospective study in the United Kingdom, researchers found that age, frailty, and comorbid diseases influenced the decision to undergo mastectomy and axillary dissection¹². In our study, 77.2% of the patients had undergone mastectomy. The 5-year survival of patients who underwent lumpectomy was 100%, while the 5-year survival of patients who underwent mastectomy was 96.2%. In our study, lumpectomy was performed instead of mastectomy for patients with lower stages and smaller tumor sizes. The 5-year survival rate was 40% for patients who could not undergo surgery.

Studies conducted in recent years have recommended surgery without axillary lymph node dissection (ALND) in elderly patients with clinically lymph node-negative early-stage breast cancer. They found that performing ALND in stage-1 breast cancer patients had adverse effects on lymphedema, arm pain, and shoulder movement limitation¹³.

In elderly patients, it is recommended to omit adjuvant radiotherapy even if breast-conserving surgery is performed in the stage 1 hormone-positive and HER2-negative group. They found no difference in survival during the 5-year follow-up period despite a slightly higher locoregional recurrence rate in the non-irradiated group¹⁴. Kinj et al. used a single dose fraction instead of the long cure APBI (accelerated partial breast irradiation). They found this method safe¹⁵. A study of patients over 70 years of age with ER-positive HER2-negative stage 1 breast cancer investigated the effect of omitting radiotherapy after lumpectomy on recurrence and overall survival.

Although omitting adjuvant radiotherapy increases the local recurrence rate, it has not been observed to affect OS negatively. In the Prime 2 study, adjuvant radiotherapy had no survival benefit in patients over the age of 65 who were lymph node-negative, hormone receptor-positive, HER2-negative, and had a tumor size of less than 3 cm¹⁴. In our study, we investigated the effect of whether or not patients received radiotherapy on OS and PFS, and we found that radiotherapy did not provide additional benefits.

Adjuvant and neoadjuvant chemotherapy treats micrometastatic disease and reduces the risk of recurrence and mortality. A randomized clinical study showed a contribution to OS in patients given adjuvant or neoadjuvant chemotherapy¹¹. Although data on adjuvant chemotherapy in the elderly are limited, it is thought to be beneficial in selected patients despite the risk of toxicity and in a study conducted on 592 patients with comorbid diseases and diagnosed with lymph node-positive breast cancer, administration of adjuvant chemotherapy resulted in better survival compared to patients who did not receive chemotherapy¹⁶. Due to advanced age, comorbid diseases, and toxicity, caution should be exercised when administering chemotherapy. In cases of lymph node-negative, hormone receptor-positive, or triple-negative breast cancer smaller than 1 cm, the less toxic docetaxel and cyclophosphamide may be preferred instead of an anthracycline-based regimen¹⁷. Prophylactic G-CSF (granulocyte-stimulating growth factors) was given to every patient receiving chemotherapy to prevent hospitalizations and reduce the risk of febrile neutropenia in elderly patients. Our study examined the effect of neoadjuvant chemotherapy on PFS and OS. Neoadjuvant chemotherapy provided better PFS. However, OS was not significant.

The rate of trastuzumab-induced cardiotoxicity in HER2-positive disease is approximately 5%. Cardiotoxicity is more common when trastuzumab is used with anthracyclines, so anthracyclines should be avoided as much as possible¹⁸. In our study, cardiac side effects of patients receiving Trastuzumab were reversible and manageable. HER2-negative patients had better PFS than HER2-positive patients. However, HER2 status was not significant for OS.

Early-stage breast cancers in older women are often hormone receptor-positive. Adjuvant endocrine therapy should be recommended to all patients regardless of age. Compared to tamoxifen, aromatase inhibitors have been associated with fewer

thromboembolic events, less endometrial thickening, and less bleeding. It has been reported that aromatase inhibitors provide longer recurrence-free survival than tamoxifen¹⁹. Tamoxifen may be recommended in cases where aromatase inhibitors are not used due to complications or osteoporosis²⁰. In elderly patients who are not suitable for surgery but do not want to receive chemotherapy, neoadjuvant endocrine therapy can be given for up to 6 months to reduce the tumor size if the hormone receptor is positive and HER2 is negative²¹. In our study, most patients were in the hormone receptor-positive HER2-negative subgroup. No difference in 5-year OS was found between molecular subgroups.

The main limitations of this study include its small sample size, short median follow-up period, retrospective design, and being conducted at a single center.

In conclusion, breast cancer is a significant health problem in the geriatric population. Given the increasing frequency of breast cancer diagnoses in patients over the age of 65, it is important to provide the most appropriate treatment for older breast cancer patients. In our study, pathological N3 lymph nodes resulted in lower progression-free survival and overall survival. Patients who are well-off, not frail, and have no comorbidities should receive treatment similar to younger patients, regardless of age. More studies are needed to evaluate the efficacy and toxicity of chemotherapy and radiotherapy in elderly patients.

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