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- Arzu AKAN¹ ID
- Semra GÜNAY¹ ID
- Refik BADEMCI² ID
- Necla GÜRDAL³ ID
- Merve Nur GÜVEN³ ID
- Orhan YALÇIN¹ ID

CORRESPONDANCE

¹Arzu AKAN

Phone : +905323951456
e-mail : akanarzu@hotmail.com

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¹ Cemil Tascioglu City Hospital, General Surgery, Istanbul, Turkey

² Medipol University, General Surgery, Istanbul, Turkey

³ Cemil Tascioglu City Hospital, Radiation Oncology, Istanbul, Turkey

RESEARCH

COMPARISON OF BREAST CANCER PATIENTS OVER THE AGE OF 70 AND UNDER THE AGE OF 35

ABSTRACT

Introduction: Although breast cancer is a type of cancer that is mainly seen in advanced ages, its incidence is increasing in early ages in developing countries. While advanced age may create limitations in treatment due to the person's functional capacity and low life expectancy, treatments may be exaggerated at a young age due to the long-life expectancy and expectations from life. In this study, we aimed to examine possible differences in approach in two different age groups diagnosed with breast cancer.

Materials and Methods: The retrospective study included 123 patients over the age of 70 or under 35 who applied to our hospital's breast surgery outpatient clinic between 2016 and 2021 and were diagnosed with breast cancer. The patients' complaints at the outpatient clinic, the histopathological features of the tumor, and the treatments applied were compared.

Results: 64 (52%) of the patients included in the study were over 70 years old, and 59 (47%) were under 35 years old. Patients in both groups were applied to the outpatient clinic with a palpable mass. Histopathologically, invasive ductal cancer constituted the majority in both groups. While the elderly patients were lower grade and Estrogen receptor-positive, the younger patients were high grade, Estrogen receptor negative, and mostly triple negative.

Conclusions: Regardless of age, breast cancer is a cancer type that can have better results with early diagnosis. While making the treatment decision the decision should be made according to the characteristics of the tumor, comorbidity, and life expectancy, regardless of the patient's age.

Keywords: Breast Neoplasms; Aged; Age Distribution; Therapeutics.

INTRODUCTION

Breast cancer is a significant public health problem due to its high incidence; it is one of the most common types of cancer among women, with more than two million new cases diagnosed each year worldwide (1). Globocan, in its statistics for 2020, reported the number of new cases diagnosed with female breast cancer as 2.3 million (11.7%) (2). In addition, the incidence of breast cancer increases with age. For example, breast cancer is seen at a rate of 1/200 under the age of 40 and a rate of 1/14 in those over 70 (3). Breast cancer, which is seen more in advanced ages, starts to be seen at earlier ages. In the United States only %5 to %7 of all breast cancers are diagnosed in patients younger than 40 years (4). Age is one of the important prognostic features in breast cancer, and tumor characteristics and treatment options are other factors that play an important role in the prognosis. When young age and advanced age are compared regarding high mortality reasons, young people are diagnosed at a later stage and have more aggressive tumor characteristics(4). While advanced age is effective in prognosis due to numerous comorbidities and therefore limitations in treatment options, tumor subtypes with more aggressive features determine the prognosis in young people. While advanced age breast cancers sometimes remain under treatment due to comorbidities, younger patients may sometimes receive more treatment due to their expectations (marriage, childbirth, starting a business, long life expectancy). Apart from advanced age, female gender, early menarche, late menopause, late delivery, long-term use of hormones (birth control or hormone replacement), previous breast biopsy, genetic reasons (5-10%) are also among the risk factors of breast cancer(5). In the light of all this information, the diagnosis of breast cancer, which we know as a disease of advanced age, should not be overlooked in younger patients. Additionally, screening and treatment should not be missed also at advanced ages, benefit/harm

calculation should be made when deciding on treatment, knowing that it can occur at an early age, and priorities for early age (pregnancy, long life desire and others) should be known. In this study, we aimed to emphasize the possibility of cancer as well as benign diseases in a very young patient who presents with a breast mass at a very young age, and that they should not be excluded from screening programs early due to the increase in life expectancy in older ages and that their treatment should be done as their comorbidities allow. For this purpose, patients under the age of 35 and over the age of 70 diagnosed with breast cancer who applied to the breast diseases outpatient clinic of our hospital were included in the study, and the patients' complaints, diagnosis stages, tumor location, clinical features of the tumor, pathological features and treatment options were compared. The advantages and disadvantages were evaluated by looking at the differences in the two age groups.

MATERIALS AND METHODS

Patients under the age of 35 and over 70 who applied to our hospital's breast diseases outpatient clinic between January 2016 and December 2021 and were diagnosed with breast cancer were retrospectively included in the study. Patients who were outside this age range, male gender, previously diagnosed with breast cancer, presenting with recurrence, and whose follow-up files could not be reached were excluded from the study. Information about the patients was obtained from the patient registry files and the hospital information system. The hospital ethics committee approved the study with the date of 08.08.2022 and approval number 241.

The patients were divided into two groups under 35 years old and over 70 years old. The complaint of admission to the outpatient clinic (mass, pain) and the location (right/left) of the mass were recorded. Tumor characteristics were classified according to the TNM system (primary



tumor size, axillary lymph node, and presence of distant metastases) according to the American Joint Committee on Cancer (AJCC) criteria. Tumor size was determined by ultrasonography (T1, T2, T3, and T4). Other radiological methods used for diagnosis (mammography, magnetic resonance), additional radiological methods (PET-CT), and the radiological status of the axilla were evaluated. According to the biopsy results, tumor histological type (in situ, invasive ductal, invasive lobular, and other), grade (I, II, or III), estrogen (ER), progesterone receptor (PR) status, and Her2 status were determined. All patients were discussed in the tumor council, and additional examinations and treatments were decided. Patients receiving neoadjuvant and/or adjuvant therapy were classified according to their treatment regimen. The type of surgery, breast-conserving surgery (BCS), simple mastectomy (SM), reconstructive procedures, sentinel lymph node sampling to the axilla (SLNB), and axillary dissection (AD) were classified in patients who received surgical treatment. Patients' hormone therapy and radiotherapy treatment status (whether they received it or not) were also categorized.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA). Variables are presented as mean \pm SD or median (range, interquartile range [IQR]) for continuous data and as a proportion for categorical data. Categorical parameters were analyzed with the Chi-square test. The conformity of continuous variable to normal distribution was assessed with the Kolmogorov-Smirnov test. The area under the curve (AUC), sensitivity and specificity values were calculated. Values of $p < 0.05$ and $p < 0.01$ were taken as significance levels. Two-sided p values < 0.05 were considered statistically significant.

RESULTS

While 64 of the 123 patients included in the study were in an advanced age group, the rest 59 patients were in the younger age group. The characteristic features of the patients are given in Table 1. The mean age was 75 ± 4.5 in the advanced age group and 31 ± 3 in the younger age group. Considering the family histories, breast cancer was present in the first-degree relatives of 10 patients in the advanced age group and 9 patients in the younger age group. Genetic tests were performed only in the young patients, and it was determined that three patients had BRCA 1 and three patients had BRCA 2 mutations. Breast cancer was detected more in the left breast in both groups. It was observed that both groups applied to outpatient clinics more frequently with a palpable mass. T2 (20-40 mm) was more common in the advanced age group (32 patients), and also T2 was more common in the younger age group (31 patients). In the axilla examination, the younger group came to the outpatient clinic with clinical and radiological positive results.

When the tumor histological types were examined, both groups had a high probability of invasive ductal cancer. It was found to be 78.1% above the age of 75 and 88.1% under the age of 35, respectively. When looking at other cancer types, mucinous cancers were also found in the advanced age group. When the molecular subtype was evaluated, ER positivity was mostly positive in the advanced age group (84.3%), while it was positive in 55.9% of the young age group, and this was observed to be statistically significant ($p < 0.01$). Considering the progesterone receptor positivity, 71.8% was positive in the advanced age group, while this rate was 34.4% in the young age group, which was significantly different ($p < 0.01$). Her2 receptor positivity was found to be lower in advanced age, and a statistical difference was observed ($p < 0.01$). Triple negative was positive in 54 patients (84.3%) in the advanced-age breast cancer patients, it was positive

Table 1. The characteristic features of the patients

	Group I	Group II	p
n	64	59	
Age*	75 (± 4.5)	31(± 3)	
Family history	10	9	
BRCA I/II	0	6	
Pathological diagnosis n(%)			
Ductal carcinoma	50	52	
Lobular carcinoma	1	5	
Other	13	2	
T n(%)			0,615
T1	9	14	
T2	39	28	
T3	14	17	
T4	2	0	
Tumour grade n(%)			
G1	25	8	
G2	30	41	
G3	9	10	
ER positivity n(%)	54	33	p<0.01
PR positivity n(%)	46	21	p<0.01
Molecular subtype n(%)			
Luminal A	30	16	
Luminal B Her2 +	19	14	
Her2 -	8	16	
Her2 +	7	13	p<0.01
Triple -	54	33	p<0.01
Axillary metastatic lymph node n(%)	32	34	
Surgical procedure n(%)			
- breast coservative surgery	41	42	
- modified radical mastectomy	23	17	
SLNB			p<0.01
pozitif	12	15	
negative	29	23	
Neoadjuvant chemotherapy	13	31	p<0.01
Hormonotherapy	50	31	p<0.01

* MEAN±SD, SLNB: Sentinel lymph node biopsy, ER: Estrogen receptor, PR: Progesterone receptor



in 33 patients (67.7%) in the younger age group, and a statistical difference was again observed ($p < 0.01$). While patients in the advanced age group were mostly Grade I (39%), it was observed that more Grade II (69.4 %) and III (16.9%) tumors were found in the younger age group.

While the neoadjuvant treatment was 52.5% in young people, this rate was 20.3% in the advanced age group. Also, hormone therapy was significantly higher in the advanced age group (78%), and it was determined to be 31(52.5%) patients in the younger age group. Considering the chemotherapy regimens, there was no difference in treatment in both groups. Cardiotoxic drugs were avoided only in elderly patients with insufficient cardiac function (usually by echo testing). On the other hand, especially in patients planning pregnancy, the gonadotropin-releasing hormone agonists (GnRHa) were given to 34.4% of the patients in the young age group.

Considering the surgical treatment options, breast-conserving surgery (71.1%) was preferred more in younger patients, while reconstructive procedures were added to 6 out of 17 patients who underwent a mastectomy. However, when the older patients were compared with the younger age group, mastectomy was more common (35.9% and 28.8%, respectively). While all patients treated with breast-conserving surgery received radiotherapy, only two elderly patients, due to comorbidity and two patients due to good tumor characteristics, did not receive radiotherapy. In the advanced age group, 27 patients continued their treatment with only hormone therapy after surgery (42.1%), while 21 patients continued their treatment with both hormone therapy and chemotherapy (32.8%).

DISCUSSION

We know that breast cancer, which we know as a disease of old age, is now more common in younger ages. However, with the prolongation of

life expectancy, we should not exclude the elderly population from follow-up since the success is achieved with early and complete treatment in breast cancer. With this study, we aimed to emphasize that there are no significant differences in the examinations and treatments performed at the onset of the disease between the advanced age and the young age, and that we should not neglect the treatment of elderly patients due to possible comorbidities.

In preventing breast cancer, besides the risk factors that we can change, there are risk factors that we cannot change such as age and genetics risk factors. Although breast cancer was previously considered as a disease of advanced age, follow-up should be started early in cases with a genetic predisposition. Today, with the sensitivity of individuals and health personnel, early diagnosis has increased, and mortality rates have started to decrease with innovations in treatment. While mortality in young patients with breast cancer is due to cancer, it is due mainly to comorbidities in older patients. However, elderly patients should undergo surgical treatment just like younger patients, as with other cancers (6).

Considering the complaints of the patients who applied to the clinic, it was seen that both age groups applied with a higher rate of palpable mass. This situation shows that self-examination is essential in the diagnosis of breast cancer. However, there are also opposing views to this view. Breast examination may increase anxiety in individuals, or unnecessary biopsies may be performed by mistaking it for a false positive mass. Diagnosis is usually delayed since, in our country, routine mammography screenings are not performed under the age of 40, and also that the breasts become extremely dense in the 40s. The thought that palpable masses on physical examination may be more benign in patients under 35 years of age also leads to a late diagnosis. It is an advantage for older patients to be included in screening mammograms.

Thus, they are diagnosed at an early stage and receive less aggressive treatments. However, today's life expectancy has increased, and the removal of advanced-age patients from follow-up in the early period causes them to present with more advanced cancer stages later on (3). Although there are no studies on mammography screenings in advanced age group (over 75 years) patients, observational studies suggest that continuing screening is crucial in the early diagnosis of breast cancer. It has also been reported in these observational studies that it is beneficial to continue screening every two years in patients with an expected life expectancy of more than ten years (7). According to breast cancer screening programs in our country, patients between the ages of 40-69 are followed up with mammography once every two years (8). On the other hand, in international screening programs, screening starts at the age of 35-40 and is conducted once a year. Therefore, in the advanced age group, each patient should be evaluated individually, and the benefits and disadvantages of the screening should be determined. Furthermore, regardless of age group, self-examination should be taught (9,10).

Tumors were mostly detected in the left breast in both groups. In addition, in both groups, the upper outer quadrant was the most common tumor localization, and it is seen in the literature that the upper outer quadrant is the most common location (11).

While the axilla is positive with delayed diagnosis in elderly patients, we encounter axilla positivity in young patients due to the aggressive features of the tumor (3). In our patients, 50% of the advanced age group and 57.6% of the young age group were diagnosed as axilla positive at the time of application.

Considering the histological features of the tumor, the most common type of breast cancer in both groups was invasive ductal cancer, which was consistent with the literature. Lobular cancers are

the second most common breast cancer, primarily seen in the younger age group. In the advanced age group, mucinous cancers, known to have a better prognosis, were the third most frequent after ductal and lobular cancers. When we look at the tumor's molecular characteristics, lower grade, ER/PR positive, and Her2 negative cases are more common in the advanced age group. In comparison, triple-negative or Her2-positive tumors and tumors with a higher grade are seen more commonly in younger patients (4). In our study, the grade was higher in young patients and lower in elderly patients, which was consistent with the literature. A study by Kroman et al. with 10,356 women from Denmark found that breast cancer patients younger than 35 years had a higher lymph node positivity rate (51%) (12). In a study, ER positivity increases with increasing age (83% between the ages of 55-64, while 91% over the age of 85) (3). Again, in a study by Zhang et al. in which elderly and young breast cancers were compared, ER positivity was found to be more prominent in the advanced age group (13).

Today, neoadjuvant chemotherapy is an inevitable option for the patient with the proper indication. It has significant benefits such as protecting the patient's breast, seeing the response to treatment, saving time for genetic tests, and, most importantly, reducing the possibility of axillary dissection. Neoadjuvant treatments come to the forefront of cancer treatment, as younger patients have more aggressive histopathological features and usually present with axilla positivity.

When deciding on treatment in young patients, the patient's expectations due to the patient's age, social status, marriage, or birth status are considered. Genetic counseling should be conducted in young patients with a family history, bilateral breast cancer and triple-negative cancers (14). Considering that there may be a pregnancy plan in early-stage young breast cancer patients, embryo, mature/immature oocyte, and ovarian tissue preservation



can be provided. Each method has its advantages and disadvantages. GnRHa, is still an experimental treatment, is a noninvasive, easily applicable method that does not require a donor (sperm) and does not cause chemotherapy delay either (15). As it was still an early stage, ovarian preservation with GnRHa was achieved to 21 of our patients who were planning pregnancy.

Comorbidities, and life expectancy, regardless of age, should be considered when planning treatment in elderly patients. Anesthesia risks should be determined, and the treatment decision should be made accordingly. In elderly patients, when the treatment decision is made based on age alone, the patient may receive inadequate treatment. In patients at risk of receiving chemotherapy due to the possible toxic effects of chemotherapy (cardiac, hepatic, etc.), In one analysis of women >70 years receiving chemotherapy, the rate of febrile neutropenia was 19% and the treatment discontinuation rate was 23%. Adjuvant trastuzumab is associated with cardiac toxicity (16)

Treatment can also be started with hormone therapy in appropriate indications. Older women are more likely to have ER-positive disease, which is associated with improved prognosis and is treatable with adjuvant endocrine therapy. (16) However, in a review comparing surgery and hormone therapy (tamoxifen) in which seven randomized controlled studies were summarized, there was no difference in overall survival. However, there was a significant difference in progression-free survival (10).

Regarding surgical treatment options, breast-conserving surgery (BCS) is more prominent in young patients. At the same time, mastectomy comes to the forefront in elderly patients to reduce the possibility of lactation and radiotherapy. When breast-conserving surgery is performed in the early stage and estrogen receptor-positive patients in the advanced age group, locoregional recurrence is not high. Adding hormone therapy and/or radiotherapy to the treatment further reduces the possibility of

recurrence. In our patients, BCS was chosen in 71.7% of young patients, while mastectomy was chosen in 35.9% of elderly patients. Since local recurrences are more common after BCS than mastectomy in young patients with aggressive tumor characteristics, radiotherapy should be inevitable in this age group, especially during treatment (17). Again, since there may be aesthetic concerns in this age group, the patient should be informed about the surgical and reconstructive procedures (repair with implant, expander, flap). In our patients, reconstruction was performed with implants in 2 patients and flaps in 4 patients in the young age group.

Axillary approach is essential in the treatment and prognosis. Today, axilla interventions are very minimal. Regardless of age, sentinel lymph node sampling (SLNB) can be performed by controlling the response to treatment in patients with positive axilla before neoadjuvant therapy (18). Axillary dissection with severe comorbidities such as lymphedema is avoided. While lymphedema is seen in 21.4% of axillary dissection, it is seen in 0-7% with SLNB (19,20). Considering the recent studies in patients with advanced age and comorbidities, if the axilla is thought to be clinically and radiologically negative, it is shown that treatment can be continued without any intervention for the axilla in patients with early-stage and estrogen receptor-positive, and it does not have a negative effect on survival (21). Since the elderly patient group is a heterogeneous group, treatment planning should be done by considering the center and the facilities of that center while planning the treatment.

Radiotherapy is inevitable after BCS and can be added according to the patient's stage in patients who have undergone mastectomy (22). There are studies in which advanced-age patients were ignored because of complications such as cardiac morbidity, secondary malignancies, rib fracture, and tissue necrosis. In the CALGB 9343 study, when BCS patients who received only tamoxifen without radiotherapy and BCS patients who received both

radiotherapy and tamoxifen were compared, local recurrence was found to be more common in the group that did not receive radiotherapy. However, both groups had no difference in overall survival and distant metastasis (23). Another study stated that only endocrine treatment could be given in patients over 65 years, with tumors smaller than 3 cm, node-negative, and hormone receptor-positive (24).

Many studies have shown that, except for rare cases, breast cancer has a good prognosis in older patients, while it has a worse prognosis in younger patients. Although the duration of local recurrence could not be evaluated in our study due to the short follow-up period, recurrence is seen in the literature at a higher rate in patients under 45 years of age. Again, it was shown that the probability of locoregional recurrence increases by 7% with each decrease in age under 40 years (25).

Our study showed that screening programs should be started at an earlier age in our country in order to diagnose at an earlier stage. Individuals who cannot enter screening programs at a young age should be taught the importance of self-examination, competent health personnel should be taught about the importance of examination, and it is necessary to prevent elderly patients from leaving screening programs in the early period due to the prolongation of their life span. Due to the increase in life expectancy today, treatment should not be planned incompletely by looking only at age, even in elderly patients who do not have comorbidities. In patients with comorbidities, less invasive surgeries (breast conserving surgery or sentinel lymph node sampling) or medical treatments that may have fewer side effects (such as hormone therapy) can be applied. Perhaps, it may be a mandatory health policy to control whether mammography is performed in patients who come for their routine follow-ups (such as blood pressure or blood sugar measurements). We hope that future studies and developing technological methods will provide an earlier diagnosis.

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