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At what rate does advanced age affect decision-making on neoadjuvant therapy?

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Abstract

Introduction: Increasing numbers of patients with breast cancer receive neoadjuvant therapies. We investigated differences in survival rates between geriatric and non-geriatric patient groups following administration of neoadjuvant therapies. **Materials and Method:** We examined 166 patients who received neoadjuvant therapy for breast cancer between 2007 and 2016. Patients <70 years were in Group 1 and those ≥70 years were in Group 2. We retrospectively compared age, sex, treatment, tumour stage and localisation, status of oestrogen and progesterone receptors, involvement of axillary lymph nodes, systemic treatment complications, treatment compliance and survival rates using a variety of parametric and non-parametric statistical tests. **Results:** The mean ages of patients in Group 1 [*n* = 136] and Group 2 [*n* = 30] were 44.6 ± 8.92 and 76.7 ± 5.48 years, respectively. The most common tumour location was the upper-outer quadrant. All patients received treatment consisting of 4AC [doxorubicin-cyclophosphamide] + 4 taxane or 4AC [doxorubicin-cyclophosphamide] + paclitaxel for 12 weeks. Neither group exhibited mortality or complications requiring treatment interruption. Breast-conserving surgery was performed in 88 [53%] patients. Complete response was achieved in 14 [8%] patients after surgery. Mean tumour diameters in Groups 1 and 2 were 26.8 mm [±27.59] and 28.5 mm [±40.23], respectively. Five-year general survival rates were % 69,7 in Group 1 and % 70 in Group 2[*p* = 0.94]. **Conclusion:** Neoadjuvant therapy is a reliable treatment option in patients ≥70 years who are candidates for chemotherapy, since complication and mortality rates did not increase compared with younger patients.

Keywords: Geriatry, breast cancer, neoadjuvant therapy; mortality.

Introduction

For females in both developed and developing countries, breast cancer has the second highest mortality rate after lung cancer. More than 1.3 million individuals are diagnosed with breast cancer each year, and the mortality rate is 60% in developing countries [1-2]. Some studies have reported that in American women, the probability of developing breast cancer is 12.3% [3]. Presently, various factors such as genetic predisposition, hormones, lifestyle and age play an etiological role in this disease [4].

Approximately 7% of patients with breast cancer are diagnosed before age 40 years [5] and the risk for breast cancer increases with age.

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The most critical factors affecting the survival of patients with breast cancer are early diagnosis, tumour stage and age [3,6,7].

Neoadjuvant therapy can reduce tumour size and may provide a higher chance for breast-conserving surgery [BCS]. Additionally, and perhaps more importantly, achieving pathological complete response of 50%–60% in axillary-positive patients may allow the performance of sentinel node biopsy instead of axillary dissection in patients with axillary downstage. Thus, lymphoedema due to axillary dissection, restricted shoulder range of motion, numbness and reduced quality of life are potentially prevented. Also, treatment modification may be performed by *in vivo* monitoring of chemotherapeutic responses of an existing tumour. Studies report high rates of pathological complete responses and, consequently, remarkable survival advantages in patients who received neoadjuvant therapy Consequently, neoadjuvant therapy appears to be a good treatment option for some patients as it increases the chances that BCS [rather than

mastectomy] can be performed by reducing tumour size [2,5-7]. This less drastic, surgical approach holds both psychological and cosmetic advantages [4].

In Literacy prognosis of premenopausal patients with breast cancer was worse than that of postmenopausal females.[8] Despite these findings, administration of neoadjuvant therapies associated with favourable outcomes in younger patients is generally considered more deliberately in elderly patients [2,9]. Various studies on the effects of neoadjuvant therapy have been conducted; however, these focused on patients <65 years [10,11], and there are little outcomes data pertaining to neoadjuvant therapy in older patients. We sought to investigate differences in survival rates between geriatric and non-geriatric patient groups following administration of neoadjuvant therapies for breast cancer.

Materials and Method

Study profile and data collection

We retrospectively analysed patients who were followed up between 2007 and 2016. Patients <70 years old were designated as Group 1 and those ≥70 years were Group 2. This study was approved by the Istanbul University Ethical Committee approval.

Patient characteristics

Patients were treated with the following protocol: 4AC [doxorubicin-cyclophosphamide] + 4 taxane or 4AC [doxorubicin-cyclophosphamide] + paclitaxel for 12 weeks. Patients were followed for hematologic toxicity [neutropenia, thrombocytopenia], hepatic toxicity, nephrotoxicity, nausea and vomiting associated with chemotherapy drugs, deterioration of the general condition of the patient, decrease in functional capacity during treatment. Routine clinical and radiological examinations [mammography, breast ultrasound and breast magnetic resonance imaging] were completed prior to and following treatment to determine treatment response. Herceptin was added to the treatment regimen of HER2-positive patients. HER 2 positive patients took Trastuzumab during neodjuvan therapy and after the surgery.

Statistical analysis

Study data were evaluated using descriptive statistical methods, such as averages, standard deviations, frequencies and percentages, whereas variable distributions were assessed using the Kolmogorov–Smirnov test. Student's *t*-tests and Mann–Whitney *U*-tests were used to analyse quantitative data while qualitative data were analysed using the Chi-square test. Kaplan–Meier analysis was used to determine survival rates, and the log-rank test was used to perform comparisons. SPSS 24.0 software was used in the analysis of study data. The level of statistical significance was accepted as $p < 0.05$.

Results

Our study included 166 patients. Group 1 [<70 years] consisted of 136 patients, whereas Group 2 [≥70 years] consisted of 30 patients. The mean age of the study group was 49.50 ± 13.42 [26–89] years. Breast tumour was most commonly found in the right breast and upper-outer quadrant. BCSs were performed in 88 patients. Demographic data are shown in Table 1.

Table 1: Demographic data

		Group 1 <70		Group 2 ≥70		p
Mean age		44.60 ± 8.92		76.73 ± 5.48		0,005
Mean ASA		1.13 ± 0.34		2.4 ± 0.81		<0.001
Presence of comorbidity		19		30		
		N	%	n	%	
Operation	**BCS**	73	53.7	15	50	0.434
	Mastectomy	63	46.3	15	50	
Quadrant	**Lower outer**	19	14	6	20	0.960
	Lower inner	14	10.3	3	10	
	Upper outer	57	41.9	12	40	
	Upper inner	18	13.2	3	10	
	Overlapping	11	8.1	3	10	
	Central	17	12.5	3	10	
Pathological regression rate		65.89 ± 32.9		68 ± 34.87		0.557

ASA: American Society of Anesthesiologists classification BCS: Breast conserving surgery

One hundred and thirty-nine patients were administered the 4AC-4T treatment regimen, and no statistically significant difference was found between the results of the administered treatment regimens [p > 0.05]. In the content of these treatment regimens, 4AC + 12p treatment protocol was performed instead of 4AC + 4T in elderly patients. Pathological regression rates were 66% and 68% in Groups 1 and 2 patients, respectively [p>0.05]. There were no differences between the clinical stages of patients prior to chemotherapy. Pathological examination revealed no tumour in 20 patients who underwent surgery after neoadjuvant therapy. The patients most commonly received surgery during the cT2 stage. Pathological complete response rates [pCRs] were 8% in Group 1 patients and 30% in Group 2 patients [p=0.01]. [Table 2].

Table 2: Postoperative stages

		Group 1 <70		Group 2 ≥70		p
		n	%	n	%	
T stage	0	11	8.1	9	30	0.01
	1	12	8.8	3	10	
	2	59	43.4	6	20	
	3	38	27.9	9	30	
	4	16	11.8	3	10	
N stage	0	24	17.6	12	40	0.001
	1	84	61.8	15	50	
	2	25	18.4	0	0	
	3	3	2.2	3	10	

In Group 1, 81 patients [59%] were oestrogen receptor-positive and 59 [43%] were progesterone receptor-positive. In Group 2, 15 patients [50%] were oestrogen receptor-positive and three patients [10%] were progesterone receptor-positive [p = 0.224 and p = 0.001, respectively]. Lymphovascular invasion was found in 69 patients [Table 3].

Table 3: Pathological data

	Group 1 <70	Group 2 ≥70	p
Residual Tumour Size	26.81 ± 27.59	28.50 ± 40.23	0.020
Oestrogen receptor [+]	81 [59%]	15 [50%]	0.224
Progesterone [+]	59 [43%]	3 [10%]	0.000
Lymphovascular invasion [+]	57 [41%]	12 [40%]	0.508
Necrosis [+]	17 [12%]	3 [10]	0.493
HER2 [+]	17 [12%]	3 [10%]	0.493

No patient died during treatment and there were no toxicity events that required the interruption of chemotherapy in either group. No differences between groups were found in surgical complications [hematoma,wound infectionand seroma]. Mean survival duration was 79.103 ± 4.057 [71.152–87.054] months. Disease relapse was determined in 24 and 3 patients in Groups 1 and 2, respectively. Median 45-month [1–116 months] follow-up revealed disease-free survival rates of 92.599 ± 4.22 [Group 1] and 86.500 ± 5.20 [Group 2; p = 0.184]. Five-year overall survival rates were were %69,7 in Group 1 and % 70 in Group 2. An evaluation of mean survival rates between the groups showed no statistically significant difference, although survival rate of Group 1 patients was slightly higher [p = 0.94].

Figure 1: Overall survival

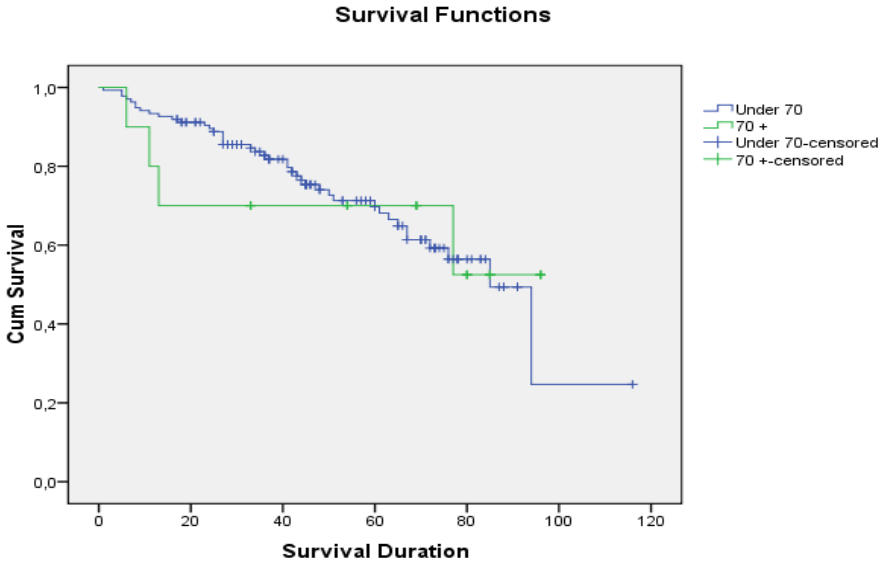
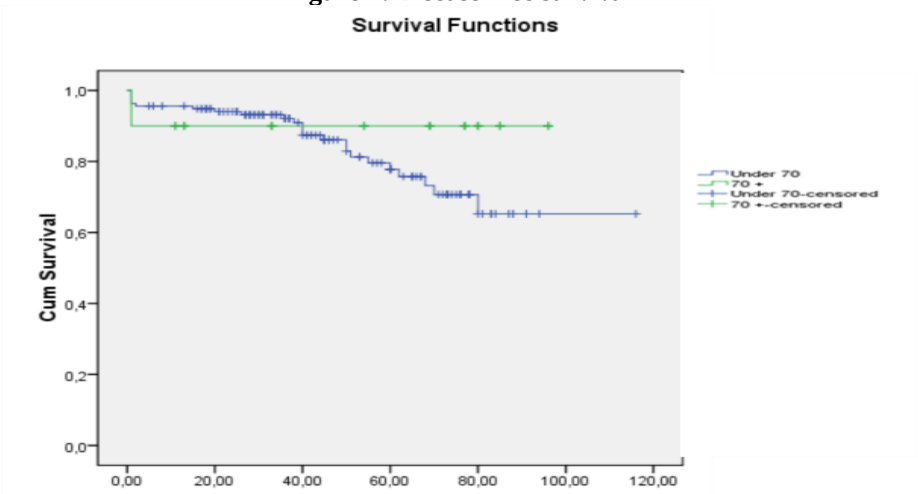


Figure 2: Disease-free survival



Discussion

Follow-up and treatment of breast cancer is an important public healthcare problem and, despite diagnostic and treatment advances, is more complicated in elderly patients than in younger patients. Patient age is a critical risk factor for breast cancer. A study out of the United States of America indicated that geriatric patients frequently present with invasive breast cancer. Approximately 50% of the new cases were among older patients [5,6]. Age 70 is an important cut point for breast cancer risk. The risk of developing breast cancer is higher in women ≥70 years, and breast cancer treatment is a more complicated proposition in this population because of comorbidities [5,7,12]. Patients ≥70 years are considered "geriatric"; therefore, we sought to compare treatment outcomes between patients with breast cancer who were <70 years and those aged ≥70 years.

Survival rates of patients with breast cancer improve depending on early diagnosis, treatment model and accurate regulation of follow-up visits. Developments in early diagnosis and treatment reduced annual mortality rates related to breast cancer to <36% [3,12]. Many studies that examined survival in patients with breast cancer focused on the relationship between survival and early diagnosis or tumoural invasion. Studies that examined treatment response relative to age were usually associated with younger patients;

existing data on treatment responses among geriatric patients is limited [7,12]. The present study contributes novel insights to this topic since we analysed responses to neoadjuvant therapy in geriatric patients with breast cancer compared with those in younger patients with breast cancer.

Difference in response rates to neoadjuvant therapies between younger and older patients is an important issue. In our study, pCR was higher in geriatric patients than in non-geriatric patients. Tumour biology revealing higher PR-negative and higher HER2-positive levels in geriatric patients receiving neoadjuvant therapy may explain the higher complete response rates. The fact that pCR in geriatric patients was not worse than that observed in non-geriatric patients is an important finding that may support the use of neoadjuvant therapies in geriatric patients.

Adjuvant chemotherapy may not be preferred for use in geriatric patients because of concerns including medication side effects or the potential for chemotherapeutic resistance, which may develop during treatment [10,13]. Neoadjuvant therapies should also be considered as potential treatments in geriatric patients with breast cancer; however, studies on this subject are limited. Of note, neoadjuvant therapy increases survival rates in addition to its known advantages including monitorisation of treatment response. Additionally, adjuvant therapy may increase the chance of BCS in patients with pCR [10]. In our study, the 5-year survival rate was 76% in patients who received neoadjuvant therapy and 66% in geriatric patients. Although survival may vary depending on many factors, our outcomes are in agreement with existing literature [2,1,14-16].

The term “geriatric oncology” was first suggested in 2003 and has received increasing attention in recent years [17]. According to the WHO data, individuals aged 66–79 and 80–99 years are considered of “middle” and “elderly” ages, respectively. Even as the human lifespan continues to lengthen, the accepted age ceiling for neoadjuvant therapy remains 70 years in the current common practice. Prior to 1980’s, elderly patients were often excluded from studies, whereas outcome data increasingly include that of elderly patients [18]. The assertion that chemotherapy provides better responses in younger patients is inconsistently supported by existing data. Some studies report milder side effects of chemotherapy in younger than in elderly patients. On the other hand, another study found that biological age was more important than chronological age when examining tolerance to standard chemotherapy in elderly patients. According to several studies, elderly patients present to oncologists during earlier tumour stages. Distant metastases develop more frequently in elderly patients than in younger patients with the same tumour stage who receive the same treatment [19,20]. This outcome suggests that more aggressive therapy may be indicated in elderly patients. The treatment protocols set forth by the NCCN Oncology Outcomes Database for Breast Cancer can be used to minimise toxicity; however, cancer treatment should be individualised. During the decision-making process, the patient’s biological characteristics should be taken into account in addition to tumour-associated factors [21]. Patient preference is another important consideration. Age should not be taken as the sole restrictive factor during the decision-making process. The patient’s biological age, disease stage, tumour characteristics, expected response after chemotherapy, disease-free survival duration and preferences require consideration in addition to the chronological age.

The positive effects of the postmenopausal period on treatment also require attention [8,10]. Neoadjuvant therapy improves life quality by helping the patient psychologically and facilitating adaptation to life circumstances. Additionally, it can reduce tumour size, thereby helping conserve breast tissue by BCS and increasing the chance of cure [5,15,17,22]. Bleyer et al. found that younger female patients had a higher chance of survival than elderly female patients across all disease stages [23]. However, another study found that the rate of local relapse after mastectomy was nine-fold higher in young female patients than that in elderly female patients [9]. All in all, young and elderly patients may show different survival rates; however, this can be attributed to the biological status of both age groups [5]. The outcomes of our study suggest that neoadjuvant therapy may provide favourable results not only in the treatment of patients with breast cancer aged <70 years old but also in geriatric patients ≥70 years. Breast preservation may also afford psychological benefits.

Presently, a commonly preferred neoadjuvant treatment regimen without age limit is anthracycline, cyclophosphamide and taxane-based chemotherapy [10]. We preferred this treatment regimen for most of the patients in our study. Besides this regimen, several studies reported that administration of weekly paclitaxel as a taxane treatment is easier and safer in patients with comorbidities. In our study, there were no differences in complications that required treatment interruption and in treatment responses between the administrations of weekly paclitaxel and docetaxel once every 3 weeks [$p>0.05$]. Nevertheless, there are many studies which have reported that paclitaxel can be administered weekly, is well-tolerated and is associated with similar response rates in elderly patient with comorbidities.

In conclusion, geriatric patients with breast cancer who received neoadjuvant therapy showed similar treatment results compared with non-geriatric patients with breast cancer. Since many studies published on this subject have shown that there were no differences between the outcomes associated with either adjuvant or neoadjuvant therapy, neoadjuvant therapy may help improve the quality of life for geriatric patients and should stand as a treatment option for these individuals.

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