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Original Article

What are the clinicopathological features of elderly early-stage breast cancer patients and is there any difference in patients over 70 years of age?

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ABSTRACT

Aim: Although patients over 65 years of age are considered to be elderly patients with breast cancer, the performance status and comorbidity of patients aged 70 and over is not the same as patients aged 65–70 years. The aim of this study was to evaluate the treatment modalities, features of patients and disease in elderly early-stage breast cancer patients.
Material and methods: Data of 87 patients were examined. Demographic data, disease data (tumor size, lymph node involvement, hormone receptor status, Her-2 status), comorbid diseases, and given treatments were evaluated. The patients were divided into two groups as 65–70 years of age and over 70 years of age. All the collected data was compared.
Results: There was no difference in hormone receptor status between 2 groups ($p > 0,05$). Her-2 negativity was found to be significantly higher in patients $\geq$ 70 years (%61 vs %83, $p = 0,024$). There was no significant difference between two groups in terms of surgery ($p > 0,05$). The frequency of chemotherapy and radiotherapy was significantly lower in the older group (%37 vs %17, $p = 0,009$). OS and DFS were significantly shorter in triple negative disease (69.59 months,$p = 0.039$ and 53.95 months,$p = 0.024$ respectively). ER positive subtype has a significantly better DFS (164 vs 47 months, $p = 0,037$) and OS (170 vs 68 months, $p = 0,046$). Additionally, PR positive disease has a significantly better DFS (129 vs 84 months, $p = 0,028$) and OS (190 vs 96 months, $p = 0,006$). HER2-negative subtype had better OS than HER2-positive subtype (172 vs 91 months, $p = 0,016$). DFS was significantly shorter in $\geq$70years patients (161.1 months vs 102.1 months, $p = 0.045$), however OS was not different among the 2 groups. Adjuvant therapy prolongs DFS in both groups(65–70 years 107,5 vs 129,3 months, >70years 86,2 vs 95,7 months $p = 0,034$).
Conclusion: Age is an important and independent risk factor for the treatment of the elderly patients, however patient age alone cannot be decisive. In current study, the pathological features of the tumor and the effects of these features on DFS and OS were similar in young breast cancer patients and patients over 70 years of age. In addition, we found that adjuvant treatment modalities affect OS and DFS positively as in the case of young patients. There is an absolute need for prospective studies involving elderly patients.

1. Introduction

The incidence of cancer in the elderly population increases and will become an important health problem like other chronic diseases.[1] Approximately 40% of breast cancers are seen over 65 years of age; and 25% of them are over 70 years old.[2] According to SEER (Surveillance,Epidemiology and End Results) data between 2004 and 2008, 40% of breast cancer cases were observed in elderly patients. Rates according to the age are as follows; 19.7% of cases in between 65 and 74 years of age, 15.5% of cases in between 75 and 84 years of age, 5.65% of cases in between 85 years of age and over.[3]

Despite this, elderly patients are not frequently involved in clinical trials. Therefore, prospective data about treatment in this

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patient group is very limited. The majority of the data in this patient group were based on retrospective analyzes and the extrapolation of studies with younger patients. However, the data obtained from the extrapolation of the younger breast cancer studies may not be appropriate. Because; the biological behaviour and treatment tolerance of this disease varies with age.[4] In addition, the follow-up period which determines whether treatment has a survival benefit, is not available in most studies.[3] The treatment of patients with metastatic stage was discussed more than the treatment of early stage breast cancer in elderly patients.

Due to age-related physiological changes; side effects are more frequently seen in elderly patients than younger cases. These physiological changes include decreased renal clearance, increased frailty and decreased bone marrow reserve.[1] The chronological age alone does not determine the functional status and life expectancy of the patient.[8] In addition to being elderly, comorbid diseases affect the treatment tolerance.[5] Patients may receive less treatment due to the comorbid diseases, age and short life expectancy. Overall, this affects survival adversely[3]

But adjuvant chemotherapy, radiotherapy and surgical recommendations have not changed since 2007. Questions still remain about the requirement of adjuvant therapy in elderly breast cancer patients. Although patients over 65 years of age are considered to be elderly patients with breast cancer, the performance status and the comorbidity of patients aged 70 and over is not the same as patients aged 65–70 years of age. Do tumor properties and adjuvant therapy efficacy, especially in patients over 70 years of age, have the same characteristics as in patients aged 65–70? Does the need for adjuvant therapy decrease as age increases? In this retrospective analysis, we investigated the treatment modalities, features of patients and disease in early stage elderly breast cancer cases.

2. Material and method

In this retrospective study, histologically confirmed, early stage breast cancer patients who were older than 64 years of age were enrolled. Clinical information on each patient was obtained from the medical records of the database of Aydın Atatürk State Hospital and Selçuk University Medical Faculty Medical Oncology outpatient clinics between 2015 and 2018. All of the patient files which were accessible were included in the study. Only 87 CRC patients' data could be reached. The demographic data of the patients, disease data (tumor size, lymph node involvement, hormone receptor status, Her-2 status), comorbid diseases, and the treatments received were recorded. Patients were divided into 2 groups according to age; first group 65–69 years of age and the second group 70 years of age and older. All the collected data was compared.

Ethical Considerations: Permission to conduct the research was obtained from Selcuk University Faculty of Medicine in 2018. The research protocol was approved by the Ethics Committee for Clinical Research and Counseling of Selcuk University Medical Faculty.

Statistical Analysis: All analyses were conducted by www.e-picos.com, New York, NY. Categorical variables were described by frequencies and percentages; continuous variables were described by means and standard deviations values. Chi-square Test was used to find out the relationship between categorical variables. Correlation Analyses were performed by Spearman Correlation Test. Kaplan Meier analysis was performed with Breslow test and Log Rank test to compare prognostic factors. A COX regression analysis was run to understand multivariate interaction of prognostic factors. A p-value less than 0.05 was considered as statistically significant.

3. Results

The mean age was 71,26 ± 5966 (65–92). Patient and disease characteristics are summarized in Table 1.

Patients were divided into 2 groups according to age; the first group includes patients between 65 and 69 years of age and the second group includes patients with 70 years of age and older. Differences between the groups are summarized in Table 2.

In our study, hormone receptor status was not different between 2 groups (ER p = 0,76 PR p = 0,74). However, Her-2 negativity was found to be significantly higher in patients ≥ 70 years compared to the first group (p = 0,024). There was no significant difference between two groups in terms of surgery (p = 0,27). However, we found that the frequency of chemotherapy and radiotherapy was significantly lower in the older group (p = 0,009).

Correlation analysis between patient age, disease subtype, chemotherapy status, recurrence status and stage were performed. Her2 positivity, triple negative disease percentage, the frequency of chemotherapy treatment and the frequency of recurrence were increased as the disease stage increased (p < 0.05). The number of patients who received chemotherapy was found to be higher in the Her2-positive and triple-negative subtype (p < 0.05).

Survival Analysis: Estimated Overall survival(OS) was 159.0(95%

Table 1
Patient and disease characteristics.

	Number of patients	%
Age		
<70 years	46	52,9
65–70 years	41	47,1
Pathology		
IDC	76	86,4
ILC	2	2,3
Mixt	1	1,1
Other	9	10,2
Type		
Luminal A	27	30,7
Luminal B	27	30,7
Her 2	23	26,1
Triple negative	11	12,5
Stage		
1	19	21,6
2	39	44,3
3	30	34,1
ER		
Positive	67	76,1
Negative	23	23,9
PR		
Positive	63	71,6
Negative	25	28,4
Comorbid disease		
Present	56	63,6
Absent	32	36,4
Operation		
MRM	54	61,4
BCS	34	38,6
Adjuvant chemotherapy		
Present	62	70,5
Absent	26	29,5
Adjuvant radiotherapy		
Present	63	71,6
Absent	25	28,4

IDC: infiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma, ER: estrogen receptor, PR: progesterone receptor MRM: modified radical mastectomy, BCS: breast conservating surgery.

Table 2
Differences between age groups.

	1st group: 65–70 years		2nd group: ≥ 70 years		p-value
	Number of patients	%	Number of patients	%	
ER					
Positive	31	75,7	36	78,2	0,76
Negative	10	24,3	10	21,8	
PR					
Positive	29	70,7	34	74	0,74
Negative	12	29,3	12	26	
Her-2					
Positive	16	39	8	17	***0,024***
Negative	25	61	38	83	
Type					
Luminal A	10	24	17	37	0,49
Luminal B	11	27	16	35	
Her-2	16	39	6	13	
Triple negative	4	10	7	15	
Type					
Stage I	12	29	7	15	0,12
Stage II	14	34	25	54	
Stage III	15	37	14	31	
Operation					
MRM	22	54	31	67	0,27
BCS	19	46	15	33	
Adjuvant chemotherapy					
Absent	6	15	19	41	***0,009***
Present	35	85	27	59	
Adjuvant radiotherapy					
Absent	7	17	17	37	***0,038***
Present	34	83	29	63	

IDC: infiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma, ER: estrogen receptor, PR: progesterone receptor MRM: modified radical mastectomy, BCS: breast conservating surgery.

Table 3
Survival analysis.

	OVERALL				DİSEASE FREE			
	Median	95% CI		p	Median	95% CI		p
		Lower	Upper			Lower	Upper	
Age								
65–70years	167.9	108.9	226.9	0.22	161.1	97.59	224.6	**0.045**
≥70years	120.6	102.1	139.1		102.1	82.14	122.0	
Type								
Luminal A	199.4	148.5	250.3	**0.039**	137.0	109.3	164.6	**0.024**
Luminal B	139.5	139.5	139.5		109.5	77.31	141.7	
HER2	92.97	75.35	110.5		102.3	86.63	118.0	
Triple Negative	69.59	58.63	80.55		53.95	36.47	71.43	
ER								
Negative	68.39	60.92	75.87	**0.046**	64.22	55.08	73.35	**0.037**
Positive	170.6	126.7	214.5		147.8	108.3	187.3	
PR								
Negative	96.84	66.20	127.4	**0.006**	84.18	67.41	100.9	**0.028**
Positive	190.4	142.5	238.4		129.3	110.4	148.3	
HER2								
Negative	172.3	127.4	217.2	**0.016**	146.5	106.9	186.2	0.09
Positive	91.95	73.76	110.1		87.47	67.30	105.6	
CT								
Absent	130.8	117.4	144.2	0.91	110.9	82.91	139.0	0.86
Present	165.8	120.8	210.7		143.1	101.4	184.5	
RT								
Absent	129.8	113.6	145.9	0.63	116.0	95.83	130.3	0.92
Present	160.2	114.3	206.1		145.8	101.0	190.5	
Operation								
MRM	123.2	108.1	138.2	0.65	117.3	101.4	133.2	0.38
BCS	214.4	191.8	237.0		137.3	74.44	200.2	

RT:radiotherapy, CT: chemotherapy, ER: estrogen receptor, PR: progesterone receptor MRM: modified radical mastectomy, BCS: breast conservating surgery.

Confidence Interval 118.0–200.0 months, Std. Error:20.9)months. Estimated DFS value was 139.0(95% Confidence Interval 101.7–170.4 months, Std. Error:17.7)months. Some subgroups showed significantly different results in OS and DFS. DFS was significantly shorter in ≥70years patients($p = 0.045$). OS and DFS was significantly shorter in triple negative disease ($p = 0.039$ and

Table 4
Survival analysis between age groups.

OVERALL	1st group: 65–70 years			2nd group: ≥ 70 years			
	Median	95% CI		Median	95% CI		p
		Lower	Upper		Lower	Upper	
ER							
Negative	75.5	74.8	76.1	61.1	49.9	72.3	0.07
Positive	175.4	113.5	237.4	129.6	111.2	148.1	
PR							
Negative	75.5	74.8	76.1	98.1	66.5	129.8	**0.02**
Positive	174.7	112.6	236.7	143.1	132.5	153.7	
HER2							
Negative	167	104.6	229.3	138.3	126.9	149.8	**0.03**
Positive	110.5	97.3	123.8	53.1	44.4	61.9	
CT							
Absent	92.6	66.6	118.7	129.1	111.1	147.0	0.53
Present	164.6	105.0	223.8	116.6	90.3	142.8	
RT							
Absent	95.1	72.6	117.7	127.0	103.7	150.3	
Present	161.4	101.9	220.9	116.6	90.3	147.8	0.91
Operation							
MRM	126.2	105.5	146.9	120.6	98.3	142.9	
BCS	231.2	231.2	231.2	109.4	82.2	136.7	0.80
DISEASE FREE							
ER							
Negative	70.3	60.2	80.4	46.3	28.9	63.8	0.02
Positive	132.9	110.4	155.4	100.7	74.5	126.9	
PR							
Negative	71.1	62.3	79.9	63.6	38.5	88.7	**0.02**
Positive	132.3	109.1	155.4	116.0	87.6	144.3	
HER2							
Negative	136.6	113.1	160.2	102.0	75.3	128.8	**0.01**
Positive	102.5	83.6	121.4	50.9	39.4	62.4	
CT							
Absent	107.5	107.5	107.5	86.2	65.5	106.9	**0.03**
Present	129.3	107.2	151.5	95.7	65.5	125.8	
RT							
Absent	97.0	80.2	113.8	81.6	61.8	101.4	
Present	128.0	104.9	151.2	107.3	79.5	135.2	0.90
Operation							
MRM	112.4	88.2	136.6	101.3	73.5	129.1	
BCS	141.9	109.4	174.4	66.6	46.2	87.0	0.48

RT:radiotherapy, CT: chemotherapy, ER: estrogen receptor, PR: progesterone receptor MRM: modified radical mastectomy, BCS: breast conservating surgery.

p = 0.024 respectively). ER positive subtype has a significantly better DFS (164 vs 47 months, p = 0,037) and OS (170 vs 68 months, p = 0,046). Also PR positive disease has a significantly better DFS (129 vs 84 months, p = 0,028) and OS (190 vs 96 months, p = 0,006). HER2-negative subtype had better OS than HER2-positive subtype (172 vs 91 months, p = 0,016) (Table 3). In cox regression analysis, relaps status and stage were found as independent prognostic factors.

We examined whether there is OS or DFS difference between the 1st and 2nd groups in terms of pathological and treatment methods(Table 4). PR negative and Her-2 positive groups' had worse OS in ≥70 years old patients than the first group (p = 0.02, p = 0.03 respectively). DFS was worse in ER or PR negative and Her-2 positive groups' in ≥70 years old patients than first group (p = 0.02, p = 0.02 and p = 0.01, respectively). In addition, we examined the effect of adjuvant treatment on DFS and OS in two groups (patients with 65–70 years of age and patients with 70 years of age). Adjuvant treatment did not prolong OS (p = 0,53) but adjuvant treatment prolonged DFS and it was statistically significant in both groups(65–70 years 107,5 vs 129,3 months, >70years 86,2 vs 95,7 months p = 0,034). There was no statistical difference between 2 groups in terms of adjuvant RT and operation type.

4. Discussion

The incidence of breast cancer increases with age.[5] However, older patients are less frequently involved in the studies, and comorbid diseases adversely affect the prognosis.[3] Since prospective studies are not sufficient in elderly patients, data is limited about the treatment[1] and therefore it is frequently obtained from retrospective analysis as in the case of our study.

In many clinical studies, it was found that breast cancer in elderly patients was less aggressive and the risk of recurrence was lower.[9] Unlike younger patients, hormone receptor positive disease is more common in elderly patients. This rate is 60% in patients aged between 30 and 34 and 85% in patients aged between 80 and 84[4]. In our study, the rate of ER and PR positivity was 76.1% and 71.6%, respectively. Her2 positivity rate was 22% in patients under 40 years of age and 10% in patients over 70 years of age.[4] According to the San Antonio Breast Cancer Database and Surveillance, Epidemiology and End Results data, the frequency of hormone receptor positive breast cancer is as follows: 83% in patients over 65 years old, 85% in patients aged between 65 and 74, 91% in patients over 85 years of age.[10] In Inal et al. study, the disease was more frequently ER and PR positive, Her-2 negative which is similar to the studies found in the literature.[9] In the retrospective analysis of Oran et al., breast cancer biology has more favourable features in patients over 65 years of age compared to younger ones.[11] In our study, hormone receptor status was not different between 2 groups. However, Her-2 negativity was found to be significantly higher in patients ≥ 70 years than the first group (p = 0,024). Her2 positivity rate was 27% in all patients and 17% in patients > 70 years. It was higher compared to the results reported in literature.

Tumor size increases with age and patients are diagnosed at a more advanced stage. In the study of Barthelemy et al., data of patients over 70 years of age were studied. In patients over 85 years of age, 75% of breast cancer was diagnosed with a physical examination, while this rate was 42% in patients aged between 70 and 74 years of age.[2] In our study, the patients were diagnosed most frequently at stage 2 (44.3%). In other studies, older patients were diagnosed with larger tumor size.[4,12] This may indicate that the older population is more informed about the breast cancer over time.

In our study, patients underwent a higher rate of radical surgery (MRM ratio was 61.4% and BCS rate was 38.6%). The frequency of radical surgery among age groups has not changed. The type of surgery in the elderly patient group is similar with the young cases; BCS and then-radiotherapy or MRM ± sentinel lymph node sampling and then radiotherapy in selected cases.[5] It is wrong to consider only the age when making the surgical decision. Because; it is the comorbid conditions rather than the age that affects the mortality rate.[6,10] Similar to these findings, the type of surgery did not affect OS and DFS in our study(p = 0,65 vs p = 0,38). However, OS was found to be significantly longer in the BCS (123 vs 214 months). In the subgroup analysis, there was no statistically significant difference between the 1st and 2nd group according to the type of operation. In other words, MRM did not increase OS or DFS in patients over 70 years of age.

The frequency of adjuvant chemotherapy was 70.5% in all study groups. When patients were grouped according to age, the frequency of chemotherapy treatment in patients over 70 years of age decreased significantly (31% vs 40%, p < 0.05). In some studies, the frequency of adjuvant chemotherapy decreased as the age increases, similar to our data. The characteristics of elderly patients undergoing adjuvant chemotherapy in these studies include larger tumor size, lymph node involvement, angioinvasion and Her-2 positivity.[2,4,9] In the current study, correlation analysis showed Her2 positivity, triple negative disease percentage, the frequency of

chemotherapy treatment and the frequency of recurrence were higher as the disease stage increased ($p < 0.05$). The number of patients who received chemotherapy was higher in the Her2-positive and triple-negative subtype ($p < 0.05$). These results are consistent with the literature.

According to our findings, adjuvant treatment did not prolong OS and DFS (all patients' survival analysis $p = 0,91$, all patients' DFS $p = 0,86$). However, when we compared 2 groups, we found that the adjuvant treatment prolonged only DFS and it was statistically significant in both groups(DFS: 65–70 years 107,5 vs 129,3 months, ≥70years 86,2 vs 95,7 months $p = 0,034$, OS: 65–70 years 92,6 vs 164,6 months, ≥70years 129,1 vs 116,6 months $p = 0,53$). However, adjuvant therapy increased OS in the first group, but no effect was observed in the ≥ 70 years of age group. Based on these results, adjuvant chemotherapy decision should not be given according to age. Other important factors besides age include life expectancy,benefit from treatment, treatment tolerance, patient and relative preference. According to many studies, adjuvant chemotherapy was the most beneficial in patients with positive lymph node and negative hormone receptor status.[4,6] Additionally, studies recommended that trastuzumab therapy should be added to the treatment in Her-2 positive cases.[7] According to our data, PR negative and Her-2 positive groups' had worse OS in ≥70 years old patients than the first group ($p = 0.02$, $p = 0.03$ respectively). DFS was worse in ER or PR negative and Her-2 positive groups' in ≥70 years old patients when compared to the first group ($p = 0.02$, $p = 0.02$ and $p = 0.01$, respectively). These results show that the treatment received according to the Her-2 condition and hormone status, is beneficial in patients over 70 years of age, which is even more beneficial when compared with the 1st group.

Radiotherapy indications in elderly patients include locally advanced disease, tumor near the surgical margin, tumor larger than 5 cm, lymph node involvement of more than 4, and the life expectancy over 10 years.[5] As in the case of chemotherapy, we found that the frequency of radiotherapy was significantly lower in the older group ($p = 0,038$). However, the effect of RT on OS and DFS could not be shown($p = 0,63$ vs $p = 0,92$). In subgroup survival analysis, there was no statistical difference between 2 groups in terms of adjuvant RT(DFS $p = 0.90$, OS $p = 0.91$). We think that the lower number of patients affected the statistical significance.

Studies show that although elderly patients received the standard treatment less frequently, survival data was similar to younger patients.[11] In this study, there was no significant difference between age groups in OS, however DFS was shorter in ≥70years patients. According to the survival analysis, triple negative, ER or PR negative, HER-2 positive patients lived shorter and DFS was found to be compatible with these results except HER-2 status. These results did not change in the >70-year-old group, despite the high incidence of additional diseases. The pathological features of the tumor and the effects of these features on DFS and OS were similar with young breast cancer patients over 70 years of age. In addition, we found that adjuvant treatment modalities affect OS and DFS positively as in the case of young patients.

In conclusion age is an important and independent risk factor for under treatment of the elderly patient. Other factors were ethnicity, sociocultural level, comorbid conditions, patient's distance from the hospital and patient's relatives preference.[4,7,13,14] The expected benefit, expected survival, and side effects should be taken into consideration while making a decision about treatment in the elderly patient. All these factors affect the clinician's decision.[1] Patient age alone can not be decisive. Various geriatric assessment tools are available. The parameters in these tools are; comorbid conditions, socioeconomic, cultural and emotional conditions, functional capacity, nutritional status and polypharmacy.[6] There is also an absolute need for prospective studies involving an increased number of elderly patients.

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