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ORIGINAL ARTICLE

Clinicopathological features of patients with breast cancer aged 70 years or over

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Summary

Purpose: *The risk of breast cancer (BC) increases in parallel with increasing age. Despite the increased disease burden in elderly patients, there is still a great uncertainty regarding "how to manage'' BC in aging-population. The purpose of this study was to investigate the clinicopathological features and treatment approaches of patients with BC aged 70 years or over.*

Methods: *The medical records of 4413 patients with BC followed between 1994–2015 were retrospectively analyzed. Of the 4413 patients, 238 with stage I to III disease aged 70 years or over at BC diagnosis were enrolled into this study. Patients were divided into 2 groups according to the age as group 1 (70–79 years, N=192) and group 2 (80 or over, N=46). Clinicopathological features of patients including tumor histology, grade, estrogen (ER) and progesterone receptor (PgR) status, human epidermal growth factor receptor 2 (HER2) status, tumor size, lymph node involvement (LNI), lymphovascular invasion (LVI), perineural invasion (PNI), clinical stage, type of surgery, treatments and comorbid diseases were evaluated.*

Results: *The median age was 74 for group 1 (range 70-79) and 82 for group 2 (range 80-92). Excluding tumor size and grade, no statictically significant difference was found between the two groups according to histopathological characteristics. Patients in group 2 had more commonly larger T stage (T4), and less frequently presented with grade I tumor (p=0.014 and p=0.044, respectively). Modified radical mastectomy and adjuvant chemotherapy were more commonly performed in group 1 (p=0.001 and p=0.001, respectively). In contrast, neoadjuvant treatment was more frequently applied in group 2 (p=0.003). There was no difference in disease-free survival (DFS) between the groups (p=0.012), however, median overall survival (OS) was significantly higher in group 1 (p=0.03).*

Conclusion: *Excluding the tumor grade and tumor size, both groups had similar histopathological features. However, patients aged between 70-79 years were likely to receive more agressive treatments for BC, indicating that treatment choice in patients over the age of 80 years was likely to be based on age-related factors rather than tumor characteristics.*

Key words: *breast cancer, elderly, prognosis, survival*

Introduction

BC is the most common cancer in women worldwide. Along with an increase in life expectancy, the incidence of BC is increasing in the aging-population. While 80% of the BC cases are diagnosed in patients aged 50 years or over, 30% of all cases present in patients over the age of 70 years [1]. It is estimated that about three-fourths of the BC cases will be diagnosed in elderly women by 2025 [2]. Despite the increasing incidence of BC in elderly population, the optimal care and treatment management of BC in this group of patients is still unclear and gives rise to compli-

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cated situations for clinicians, leading to disputes concerning the optimal treatment. Although it is expected that the elderly patients with BC are treated in a similar fashion as performed in their younger counterparts, the elderly patients are appearently undertreated [3,4], even after readjustment of some challenging parameters, such as functional status, comorbide disease, and need for social support. For instance, endocrine therapy (ET) can be used in elderly patients with BC as a primary treatment instead of breast surgery, adjuvant chemotherapy (CT), or adjuvant radiotherapy (RT) which are omitted due, in part, to concerns of comorbidities [5]. Different treatment approaches between younger vs older population are likely to be associated with multifactorial reasons including a greater rate of poorer performance status, comorbidities, limited social support, concerns regarding the quality of life, and a decreased life expectancy [6]. Additionaly, the concerns with regard that comorbidity-associated mortality in these patients outweigh the BC mortality [3,7,8] are the major factors leading to this difference in treatment. Therefore, clinical decision-making for optimal treatment in the elderly patients with BC should be individualized based on the following parameters: comorbidities and their effect on therapeutic options, the average life expectancy, and risk/benefit ratio of a proposed treatment strategy.

It has been reported that elderly patients with BC present with favorable tumor characteristics as having an increased hormone receptor expression, decreased HER2 expression, low histologic grade, and low proliferative index [6]. By contrast, elderly patients with BC have been shown to have greater tumor size and increased lymph node involvement at the time of diagnosis [9].

Geriathric evaluations in elderly population are distinguished into 3 stages according to age: stage I senility (65-75 years), stage II senility (75-85 years), and stage III senility (85 years or over) [10]. Herein we aimed to evaluate the elderly patients with BC into 2 subgroups as aged 70-79 vs 80 or over.

Methods

A total of 4413 patients with BC followed between 1997-2015 at Hacettepe University Cancer Institute were retrospectively analyzed. Of this population, 238 patiens aged 70 years or over were identified and enrolled in this study. Exclusion criteria were as follows: history of secondary primary cancer, unknown ER and PgR status, missing data for margin status, LVI, PNI, LNI and HER2 expression in pathology report. Moreover, stage 0 and stage IV disease were excluded since they might cause statistical errors in DFS and OS analysis. Patients were categorised into 2 groups according to age as group 1 (70-79 years, N=192) and group 2 (80 years or over, N=46). Clinicopathological features including tumor histology, grade, ER and PgR, HER2 status, tumor size (T), LNI, LVI, PNI, clinical stage, type of surgery, adjuvant/neoadjuvant CT, RT, ET and comorbid diseases were evaluated. DFS was defined as the time from the initiation of any treatment to the evidence of disease recurrence on scans or clinical evaluations or death of any cause. OS was defined as the period from the first day of treatment to the date of last follow-up or death.

Statistics

The Statistical Package for Social Sciences (SPSS) version 20 (IBM, Armonk, NY, USA) was used for all statistical analyses. Continuous variables were expressed as median and interquartile range (IQR). Frequencies of distribution between the groups were compared by using Pearson's chi-square or Fisher's-Exact test. DFS and OS were analysed using Kaplan Meier method with log-rank test. P value less than 0.05 was considered as statistically significant

Results

A total of 238 patients (5.3%) aged 70 years or over were identified from a BC population including 4413 patients. The median age was 74 for group 1 (range 70-79) and 82 for group 2 (range 80-92). There were 192 patients in group 1 (80.6%) and 46 patients (19.4%) in group 2. Clinicopathological features of patients are shown in Table 1. Distribution of the histological subtypes in group 1 vs group 2 were as follows: invasive ductal carcinoma (IDC) 66.1% vs 63%, invasive lobular carcinoma 9.4% vs 8.7%, and others 24.5% vs 28.3%, showing no significant difference (p=0.87). Patients in group 2 had an increased rate of higher T stage (T4), compared with those in group 2 (p=0.014). By contrast, patients in group 1 more frequently presented with low-grade (G1) tumor as compared to those in group 2 (p=0.044). No significant difference between the groups was noticed in regard to LVI (p=0.15), PNI (p=0.84), LNI (p=0.68), clinical stage (p=0.24), ER (p=0.71), PgR (p=0.64) and HER2 expression (p=0.09). When stratifying the patients into 2 groups according to the number of accompanying comorbid disease as being ≥ 3 or < 3, no distinct difference was observed between the groups in terms of comorbidity status (p=0.38). Patients in group 1 more frequently underwent modified radical mastectomy (MRM) (p=0.001) and received more adjuvant

Table 1. Patient clinicopathological features

Features	*Total (N=238)* *N (%)*	*Group 1 (N=192)* *N (%)*	*Group 2 (N=46)* *N (%)*	*p value*
Median age (range)	75 (70-92)	74 (70-79)	82 (80-92)	
Tumor histology				
IDC	156 (65.5)	127 (66.1)	29 (63)	
ILC	22 (9.2)	18 (9.4)	4 (8.7)	0.87
Other	60 (25.2)	47 (24.5)	13 (28.3)	
Tumor size (surgical)				
Unknown	5 (2.1)	5 (2.6)	0	
T1	84 (35.3)	71 (37)	13 (28.3)	0.27
T2	110 (46.2)	90 (46.9)	20 (43.5)	0.68
T3	20 (8.4)	15 (7.8)	5 (10.9)	0.55
T4	19 (8)	11 (5.7)	8 (17.4)	0.014
Clinical stage				
Unknown	12 (5)	7 (3.6)	5 (10.9)	
1	59 (24.8)	51 (26.6)	8 (17.4)	0.24
2	102 (42.9)	85 (44.3)	17 (37)	
3	65 (27.3)	49 (25.5)	16 (36.9)	
Nodal status (pathological)				
Unknown	21 (8.8)	10 (5.2)	11 (23.9)	
N0	114 (47.9)	97 (50.6)	17 (37)	0.68
N1	57 (23.9)	45 (23.4)	12 (26.1)	
N2	29 (12.2)	25 (13)	4 (8.7)	
N3	17 (7.1)	15 (7.8)	2 (4.3)	
Tumor focality				
Unifocal	224 (94.1)	181 (94.3)	43 (93.5)	0.74
Multifocal	14 (5.9)	11 (5.7)	3 (6.5)	
Grade				
Unknown	36 (15.1)	25 (13)	11 (23.9)	
1	39 (16.4)	36 (18.8)	3 (6.5)	0.044
2	99 (41.6)	80 (41.7)	19 (41.3)	0.96
3	64 (26.9)	51 (26.6)	13 (28.3)	0.82
ER status				
Unknown	4 (1.7)	3 (1.6)	1 (2.2)	0.71
Positive	188 (79)	150 (78.1)	38 (82.6)	
Negative	46 (19.3)	39 (20.3)	7 (15.2)	
PgR status				
Unknown	3 (1.3)	2 (1)	1 (2.2)	0.64
Positive	167 (70.2)	137 (71.4)	30 (65.2)	
Negative	68 (28.6)	53 (27.6)	15 (32.6)	
HER2 status				
Positive	34 (14.3)	31 (16.1)	3 (6.5)	0.09
Negative	204 (85.7)	161 (83.9)	43 (93.5)	
Triple negative				
Unknown	2 (1.4)	1(1.2)	1(2.3)	0.82
Yes	29 (12.1)	23 (11.9)	6 (13)	
No	206 (86.5)	167 (86.9)	39 (84.7)	

Continued on next page

Groups	*Total (N=238) N (%)*	*Group 1 (N=192) N (%)*	*Group 2 (N=46) N (%)*	*p value*
LVI				
Yes	61 (25.6)	53 (27.6)	8 (17.4)	0.15
No	177 (74.4)	139 (72.4)	38 (82.6)	
PNI				
Yes	29 (12.2)	23 (12)	6 (13)	0.84
No	209 (87.8)	169 (88)	40 (87)	
Surgery				
No/unknown	18 (7.6)	6 (3.1)	12 (26.1)	
BCS	78 (32.8)	62 (32.3)	16 (34.8)	0.75
MRM	142 (59.6)	124 (64.6)	18 (39.1)	0.001
Chemotherapy				
Unknown	2 (1)	2 (1.1)	0	
Yes	73 (30.6)	68 (35.4)	5 (10.8)	0.001
No	163 (68.4)	122 (63.5)	41(89.2)	
Radiotherapy				
Unknown	6 (2.2)	5 (2.7)	1 (2.2)	
Yes	128 (53.7)	109 (56.7)	19 (41.3)	0.052
No	104 (44.1)	78 (40.6)	26 (56.5)	
Endocrine therapy				
Yes	197 (82.8)	156 (81.2)	41 (89.1)	0.20
No	41 (17.2)	36 (18.8)	5 (10.9)	
Comorbidity				
≥3	91 (38.2)	76 (39.6)	15 (32.6)	0.38
<3	147 (61.8)	116 (60.4)	31 (67.4)	
Adjuvant therapy	208 (87.4)	174 (90.6)	34 (73.9)	0.001
Neoadjuvant therapy	25 (10.5)	14 (7.3)	11 (23.9)	0.003

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ER: estrogen receptor, PgR: progesterone receptor, LVI: lymphovascular invasion, PNI: perineural invasion, BCS: breast concerving surgery, MRM: modified radical mastectomy

CT (p=0.001), whereas neoadjuvant treatment was more frequently applied in group 2 (p=0.003). The rates of RT, breast-conserving surgery (BCS) and ET were similar between the groups (p=0.052 for RT, p=0.75 for BCS, and p=0.20 for ET).

Survival analysis

At a median follow up time of 41.2 months (range 3.68-173.47), median OS and DFS of all patients were 122.58 months (95% CI, 82.78 - 162.38) and 72.25 months (95% CI, 40.89 - 103.61), respectively (Figures 1 and 2). During follow up, a total of 50 (21%) patients developed recurrence, with a similar rate for group 1 and group 2 (group 1; N=40, 20.8% vs group 2; N=10, 21.7%, respectively). DFS did not differ between the groups (group 1; 87.82 months, 95% CI, 54.54 - 121.10 vs group 2; 47.05 months, 95% CI, 41.26 - 52.83; p=0.12). However, OS was significantly better in group 1 (122.58 months vs not reached) (95% CI, 91.68-153.48); p=0.03) (Figures 3 and 4). There were 38

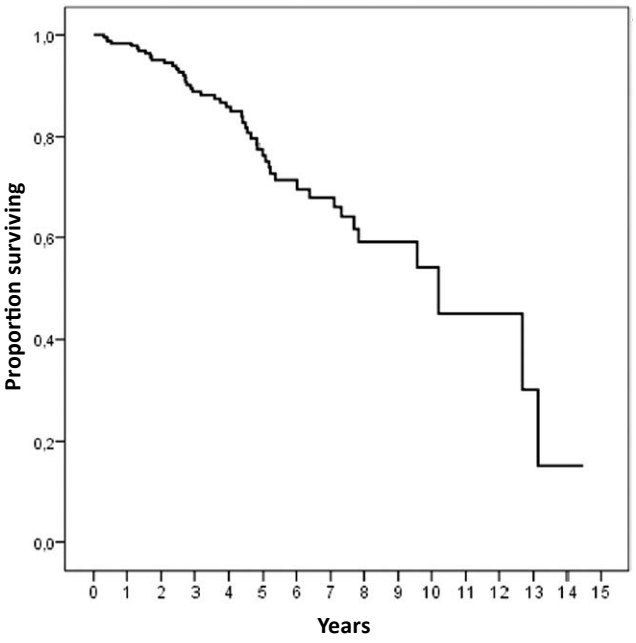

Figure 1. Kaplan-Meier estimates for overall survival in all groups. Median 122.58 months (95% CI 82-162.38).

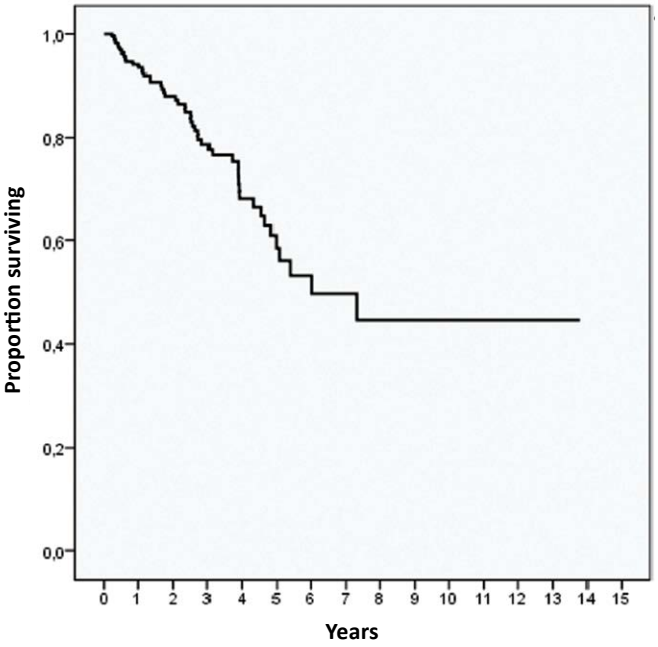

Figure 2. Kaplan-Meier estimates for disease-free survival in all groups. Median 72.25 months (95% CI 48.89-103.61).

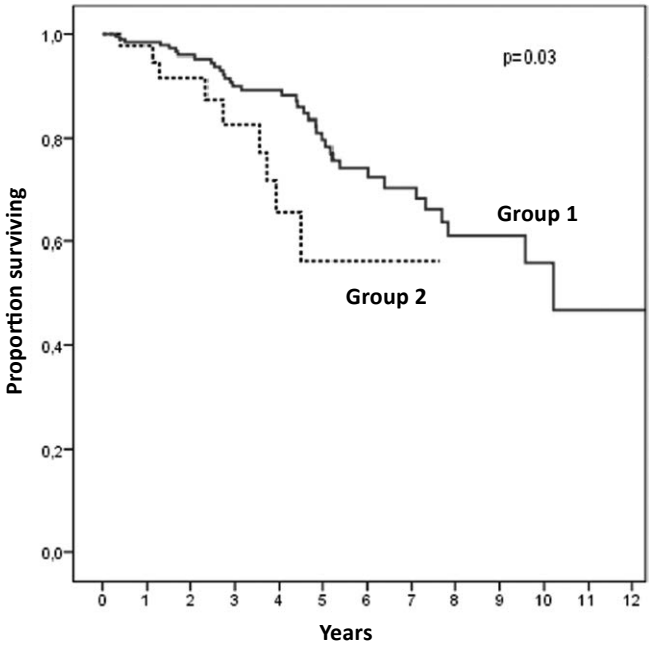

Figure 3. Kaplan-Meier estimates showing overall survival differences between two groups. Median for group 1 122.58 months vs group 2 not reached.

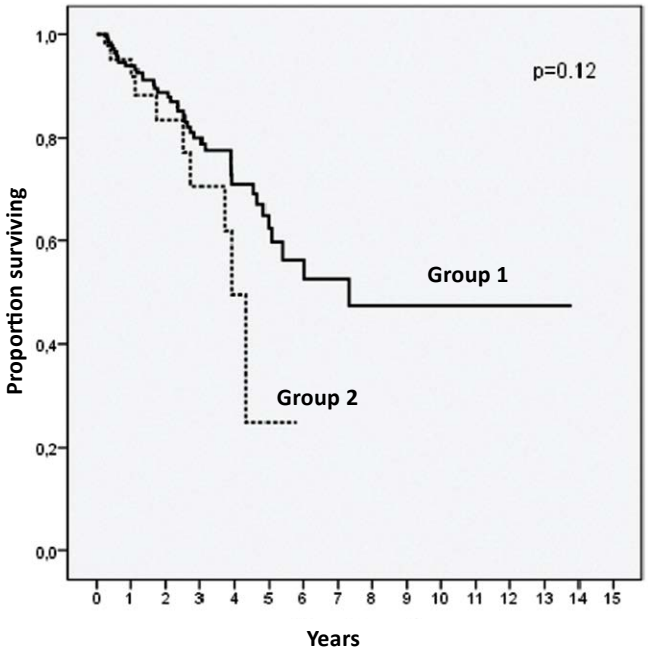

Figure 4. Kaplan Meier estimates showing disease-free survival differences between two groups. Median for group 1 87.82 months vs 47.05 for group 2.

(19.8%) deaths in group 1 and 9 (20 %) in group 2.

Discussion

Elderly women with BC are likely to be diagnosed with more advanced stages since they remain underrepresented in screening populations. Moreover, they are less likely to be aware of BC, and more likely to delay reporting their complaints regarding breast lesions. Similarly, in our study, patients in group 2 were more commonly presented with larger T stage (T4) than those in group 1. Previous reports have indicated that older patients with BC were likely to have a higher frequency of tumors with favorable histologies along with overall favorable biologic tumor features such as higher rate of ER-positive tumors, however, elderly patients were also reported to have higher incidence of greater T stage and LNI [9], with no significant difference in clinical stage [11]. In most cases, lymph node staging in elderly patients with BC is generally ignored. Previous data have shown that lymph node staging in cases aged over 70 years is performed with an estimated rate of 22-42.4% [12-14] compared to 76.1-91.2% in patients enrolled into this study.

A decrease in proliferation markers and HER expression are also common features of BC in the elderly population [15]. Likewise, in our study, patients in group 2 were less likely to have HER2 expression, however, the difference was not significant (p=0.09). Hormone receptor positivity has also been reported to change in elderly patients, with an increasing tendency. In one study [16], the rate of ER-positive tumors increased from 83 to 87% in patients aged 55-64, to 90% in patients

aged 65-74, to 91% in patients aged 75-84, and to ≥ 91% in patients aged over 85. In another study, the rate of hormone positivity in patients aged 80-85 has increased to 85% compared to 60% in corresponding patients aged 30-35 [17]. However, in our study, ER positivity in group 1 vs group 2 was 78.1 vs 82.6%, respectively, with no significant difference.

Although it has been reported that elderly patients with BC more frequently present with lower tumor grade [6], we found that grade I tumor, but not grades II and III, were significantly more common in group 1.

As previously noted, older women with BC were more likely to be diagnosed in advanced stages, hence they were less likely to be treated with surgery, CT and RT. Considering the surgical techniques performed for patients with BC, elderly patients can be good canditates for MRM and BCS as well as their younger counterparts, suggesting that the most important factors affecting the surgery is the comorbid status rather than the chronological age [18]. In our study, MRM was more commonly performed in group 1 (p=0.001), however, there was no significant difference in regard to BCS between the groups (p=0.75). On the contrary, one study showed that MRM, but not BCS, was more frequently preferred in patients aged over 80 years [19]. Of note, the rate of BC mortality with BCS plus RT vs MRM was found similar in elderly patients [20]. However, studies including small group of patients reported a favorable quality of life for BCS vs MRM in patients aged 70 years or over [21]. Patients who are medically unfit for surgery or would not pursue for surgery should be offerred ET. In a Cochrane metaanalysis of 7 randomized trials including patients aged over 70 years [22], patients medically fit for surgery were treated with either surgery or tamoxifen alone, and the study results showed a significant difference in PFS but not in OS.

As with the surgery, patients in group 2 less frequently received CT (p=0.001), in corcodance with similar literature findings [23,24]. This is likely due in part to the fear of concerns regarding the comorbidities, CT side effects, limited social support, decreased life expectancy, and decreased quality of life in elderly patients [25,26]. However, the fact that no significant difference between the groups in terms of comorbid disease was found (p=0.38) suggests that chronological age was the main parameter affecting the treatment choice. As a matter of fact, this situation in elderly patients should not be accepted as a treatment contraindication. In addition, aging population was previously shown to be able to tolerate the CT succesfully even with comorbid status, particularly in case of being treated with appropriate treatment options [20]. Overall, we still don't know completely why elderly patients are less likely to receive surgery and RT for BC than their younger counterparts. Nevertheless, elderly women with BC should be informed regarding the advantages of surgery, particularly patients who are medically fit for surgery.

RT has also remained a therapeutic challenge in elderly patients since it may cause serious side effects [27]. In our study, 53.7% of all patients received RT. Different studies have reported that RT was not sufficiently used in elderly patients [28,29]. In this context, during the decision-making for postmastectomy RT in elderly patients, the International Society of Geriatric Oncology recommends the use of the same criteria used for younger counterparts [30].

The rate of ET in group 2 was more frequent, but unlike the literature [12,31,32], the difference was not significant (p=0.20).

Despite the lack of sufficient data regarding the neoadjuvant CT in elderly population [30], patients with locally advanced tumor or with larger tumor may be treated in the neadjuvant setting. Neoadjuvant CT was more frequently applied in group 2 (p=0.003). This is simply due to the fact that patients in group 2 had more locally advanced tumor, or more frequently presented with larger T stage. On the contrary, adjuvant CT was significantly more common in group 1 (p=0.001), suggesting that patients in this group were likely to have a better ECOG performance score, compared to those in group 2.

Considering survival, there was a statistically significant difference in regard to OS, but not in DFS, between the groups (p=0.12 for DFS, and p=0.03 for OS). The possible reason of OS difference in the absence of DFS difference may be attributed to fact that patients in group 2 were less likely to receive adjuvant CT, and less likely to undergo surgery for concerns regarding toxicity and higher risk in mortality, thus leading to a decrease in OS. Moreover, elderly patients with BC tend to be diagnosed with more advanced disease [23], since they are likely to remain underrepresented in screening populations due to lack of sufficient data suggesting the survival advantages of screening methods in these group of patients [31].

Overall, despite favorable clinical features, elderly patients with BC have appearently poorer

than expected survival outcomes, compared with their younger counterparts. Comorbidity is suggested as the most important factor that plays the main role in this sophisticated outcome [30], leading to ineffective and insufficient treatment due to the aforementioned concerns in elderly patients.

Set aside its retrospective nature, the major limitiations of this study were as follows: the study was limited by small sample size; the impact of comorbid disease on treatment choice could not be clearly detected; BC-spesific mortality could not be estimated.

Conclusion

Elderly patients with BC tend to be diagnosed with more advanced stages as these patients are more likely to remain underrepresented in screening populations due to lack of sufficient data suggesting the survival advantages of screening methods in these group of patients. Moreover, these patients are less likely to receive adjuvant CT, and less likely to undergo surgery for concerns regarding toxicity and higher risk in mortality, thus leading to decreased OS. Therefore, clinical decision-making for the elderly patients with BC should be individualized based on several factors including comorbidities and their impact on the therapeutic options, the average life expectancy, and risk/benefit ratio of a proposed treatment strategy. Of note, chronological age should not be the only parameter to determine the treatment choice because elderly patients, even with comorbid status, may succesfully tolerate the CT as well as their younger counterparts, particularly in case of being treated with appropriate treatment options.

Conflict of interests

The authors declare no confict of interests.

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