JBUON 2013; 18(2): 328-334
ISSN: 1107-0625 • www.jbuon.com
E-mail: info@jbuon.com

ORIGINAL ARTICLE

Breast cancer in octogenarian women: clinical characteristics and outcome

T. Y. Kuzan[1], E. Koca[1], O. Dizdar[2], C. Arslan[3], T. Eren[4], S. Yalcin[2], N. Kucukoztas[2], S.Aksoy[4], S. Rahatli[2], D. S. Dede[5], O. Altundag[2], N. Zengin[4], O. Ozyilkan[2], K. Altundag[1]

[1]Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara; [2]Department of Medical Oncology, Baskent University Hospital, Ankara; [3]Department of Medical Oncology, Izmir Tepecik Training and Research Hospital, Izmir; [4]Department of Medical Oncology, Ankara Numune Training and Research Hospital, Ankara; [5]Department of Medical Oncology, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

Summary

Purpose: *Breast cancer incidence increases in the elderly but data on treatment and outcomes of elderly patients is limited. We assessed the clinicopathological features and outcomes of our patients with breast cancer aged ≥80 years in comparison with their younger postmenopausal counterparts.*

Methods: *The records of 83 patients diagnosed with breast cancer after the age of 80 (group 1) between 2003 and 2011 in 4 different centers were retrospectively evaluated and the clinicopathological features and outcomes were assessed in comparison with a control group (group 2) of 249 patients aged between 60-70 years.*

Results: *Median ages at diagnosis were 82 years (range 80-95) and 64 years (range 60-70) for group 1 and group 2, respectively. The incidence of invasive cancers other than ductal or lobular type was higher in group 1 than in group 2 (20 vs 8%; p=0.017). More patients in group 1 had Charlson Comorbidty scores ≥1 than those in group 2 (49 vs 36%; p=0.011) . Patients in group 1 had more conservative operations and less axillary node dissections (ALND) and they received chemotherapy, trastuzumab or radiotherapy less frequently compared to their younger counterparts in group 2. Median follow up period was 36 months (range 1-178) in group 1 and 24 months (range 12-217) in group 2. Five-year disease free survival (DFS) was 53.7 and 75.9% (p=0.005), 5-year overall survival (OS) was 61.9% and 80.4% in group 1 and group 2 (p=0.001), respectively. Advanced stage (stage IV vs stage I, II, III, p=0.051) and cerbB2 positivity (p<0.001) were found to be associated with shorter DFS in patients ≥80 years of age.*

Conclusion: *Although the majority of patients were undertreated in our study according to the current guidelines, mortality rates were quite low. Different biology of the disease in the elderly might explain this difference.*

Key words: *breast cancer, elderly, octogenarian, outcome, treatment*

Introduction

Breast cancer is the most frequently diagnosed cancer among women [1-3]. With the longer life expectancy and increasing risk with age, breast cancer has become a major public health problem among older women including those older than 80 [2,3]. However, data on the tumor biology, treatment choices and outcomes are limited in this "oldest old" patient population. These patients are underrepresented in clinical trials. Treatment options for younger patients may not necessarily apply to older ones because of their accompanied comorbidities and vulnerability to toxicities of therapy [4]. There are many studies that have documented that the older patients receive less aggressive treatment compared to younger ones, they are less likely to undergo ALND, radiation after breast conserving surgery and chemotherapy [1-4]. Nevertheless, there are data which propose that older women may do equally well with less aggressive treatment [5-7] and this may be secondary to more favorable tumor characteristics in this population [2] including more tumors

Correspondence to: Kadri Altundag, MD. Department of Medical Oncology, Hacettepe University Institute of Oncology, Sihhiye, Ankara 06100, Turkey. Tel: +90 312 3052954, Fax: +90 312 3242009, E-mail: altundag66@yahoo.com
Received: 20/09/2012; Accepted: 18/10/2012

that express steroid receptors, higher estrogen receptor content, lower proliferative rates and ki67, diploidy, normal p53, and absence of expression of epidermal growth factor receptor and c-erbB2 [6,8,9]. A previous SEER analysis found similar tumor characteristics, less aggressive treatment and higher mortality from breast cancer in women aged 80 years or older compared with younger women [10]. However, this study included only stage I-II patients.

The aim of our study was to assess the clinicopathological features, comorbidities, treatment and therapeutic outcomes of these octogenarian patients with breast cancer. We have chosen a group of patients aged between 60 and 70 as a comparator group because we already know that elderly patients have different tumor and clinical features compared with premenopausal women. However, data on the differences between octogenarians and their younger post-menopausal counterparts is limited.

Methods

Patients who were diagnosed with breast cancer after the age of 80 between 2003 and 2011 in 4 different centers including Baskent University Hospital, Hacettepe University Hospital, Numune Training and Research Hospital and Tepecik Training and Research Hospital were retrospectively evaluated (group 1). Demographic features (age, Charlson Comorbidty Index score), tumor characteristics (size, grade, lymphovascular invasion, hormone receptor, Her2 expression), treatment protocols (surgery, adjuvant chemotherapy, radiotherapy, hormonal therapy and trastuzumab) and clinical outcomes were assessed. The comparator group (group 2) consisted of patients with breast cancer aged between 60-70 years at diagnosis and followed up at Hacettepe University Hospital at the same time period.

Statistics

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Student's t-test or Mann-Whitney U test were used for comparison of numeric variables between the two groups. Chi-square test was used for comparison of ratios between the groups. Kaplan–Meier analysis was performed to examine the influence of predefined factors on survival, with the log-rank test used to compare strata. DFS was defined as the time from the date of diagnosis until first relapse (local, regional or distant) or contralateral breast cancer. OS was measured from the date of diagnosis to the date of death from any cause. Surviving patients were censored at the date of last contact. Because of the small numbers of patients in the study, entry into the multivariate model was conditional on a p value of <0.2. Statistical analysis was performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL) and statistical significance was set at $p<0.05$.

Results

Eighty-three patients aged 80 years and older (group1) and 249 patients aged between 60 and 70 years (group2) when diagnosed were included. Patient and tumor characteristics of both groups are summarized in Table 1. Median ages at diagnosis were 82 years (range 80-95) and 64 years (range 60-70) for group 1 and 2, respectively. There was a trend towards higher grade and earlier stage in group 2 patients compared to group 1, with p values 0.11 and 0.18, respectively. The frequency of invasive cancers other than ductal or lobular type was higher in group 1 than in group 2 (20 vs 8%, p=0.017). In group 1 5 patients (6%) had mucinous carcinoma and 4 (5%) papillary carcinoma. Histologic grade, estrogen and progesterone receptor (ER and PR) status and Her2 expression were similar between the groups. Significantly more patients in group 1 had Charlson Comorbidty scores ≥1 than those in group 2 (49 vs 36%, p=0.011).

Major differences were observed in treatment modalities applied between group 1 and group 2 patients. Chemotherapy and radiotherapy were utilized in 15 (18%) and 21 (25%) of the group 1 patients, respectively, while endocrine treatment was given to 89% of the hormone receptor positive patients. Patients in group 1 had more conservative operations and less ALND and they received chemotherapy, trastuzumab or radiotherapy less frequently compared to their younger counterparts in group 2 (Table 2).

Median follow up period was 36 months (range 1-178) in group 1 and 24 months (range 12-217) in group 2. On follow up, 10 patients relapsed (1 local and 9 distant) and 20 patients died in group 1. In group 2, 47 patients relapsed (5 local and 42 distant) and 32 died. Five-year DFS was 53.7% in group 1 and 75.9% in group 2 (p=0.005). Five-year OS was 61.9% in group 1 and 80.4% in group 2 (p<0.001) (Figures 1 and 2).

Univariate analysis of factors including stage, Charlson Comorbidity Index, grade, histology, hormone receptor status and c-erbB2 status on DFS revealed advanced stage (stage IV vs stage I,II,III, p=0.051) and c-erbB2 positivity (p<0.001) to be associated with shorter DFS in patients ≥80 years of age (Table 3). Multivariate analysis was not performed because of the high number of missing data.

Table 1. Patient and disease characteristics

Characteristics	*Group 1 (>80 years;N=83) N (%)*	*Group 2 (60-70 years; N=249) N (%)*	*p-value*
Median age, years (range)	82 (80-95)	64 (60-70)	
Charlson Comorbidty Index Point			0.011
0	42 (51)	159 (64)	
I	26 (31)	70 (28)	
II	6 (7)	12 (5)	
III	4 (5)	7 (3)	
IV	3 (4)	1 (0.4)	
V	2 (2)	0 (0)	
T stage			0.048
I	13 (16)	67 (28)	
II	34 (41)	125 (50)	
III	11 (13)	36 (14)	
IV	10 (12)	13 (5)	
Unknown	15 (18)	2 (1)	
N stage			0.243
Nx	27 (33)	14 (6)	
N0	25 (30)	110 (44)	
N1	18 (21)	69 (28)	
N2	9 (11)	26 (10)	
N3	4 (5)	30 (12)	
Stage I-II	32 (39)	152 (61)	0.185
Stage III-IV	27 (32)	87 (35)	
Unknown	24 (29)	24 (11)	
Grade			0.11
I	13 (16)	24 (10)	
II	32 (38)	104 (42)	
III	13 (16)	88 (35)	
Unknown	25 (30)	33 (13)	
Histology			0.017
Ductal	58 (70)	187 (75)	
Lobular	7 (8)	16 (6)	
Mixed	2 (2)	26 (11)	
Other	16 (20)	20 (8)	
ER			0.410
Positive	61 (73)	175 (70)	
Negative	17 (20)	63 (25)	
Unknown	5 (6)	11 (5)	
PR			0.533
Positive	57 (70)	171 (69)	
Negative	17 (20)	62 (25)	
Unknown	9 (10)	16 (6)	
CerbB2			0.149
Positive	9 (10)	41 (16)	
Negative	69 (84)	179 (72)	
Unknown	5 (6)	29 (12)	

ER: estrogen receptor, PR: progesterone receptor

Discussion

In this study, we found that elderly breast cancer patients tend to be more understaged and undertreated compared with their younger postmenopausal Wcounterparts. Indicators of tumor biology including ER, PR, Her2 and histological grade were similar. There was a trend towards lower grade in the older group of patients compared to patients aged between 60 and

70, supporting the assumption that older women with breast cancer have less aggressive tumors. Histological subtypes differed, with higher rate of mucinous and papillary tumors in the older group. OS and DFS rates were lower in octogenarians, but this could be attributed to more advanced age and unfortunately we do not know disease-specific survival rates.

Although infiltrating ductal cancer is still the most common histology of breast cancers in older women, the more indolent histologies, such as mucinous and papillary carcinomas, are also encountered more frequently in older age groups [2,11,12]. Honma et al. found the proportions of mucinous carcinoma and apocrine carcinoma significantly greater in older women (>85 years of age) compared with premenopausal women [13]. Similarly, in our study we found the frequency of invasive cancers other than ductal or lobular type was higher in group 1. Five patients (6%) had mucinous carcinoma and 4 (5%) had papillary carcinoma in group 1.

Modified radical mastectomy was the major type of surgery in our study. We did not assess

Table 2. Treatment modalities

Treatment modalities	*Group 1 (>80 years; N=83) N (%)*	*Group 2 (60-70 years; N=249) N (%))*	*p-value*
Surgery			
Modified radical mastectomy	44 (53)	175 (70)	0.001
Simple mastectomy	9 (10)	4 (2)	
Lumpectomy	14 (17)	57 (23)	
Median number of dissected lymph nodes (range)	10 (0-41)	18 (0-53)	<0.001
Chemotherapy			
Adjuvant chemotherapy	14 (16.9)	130 (52.2)	<0.001
Anthracycline	10 (12)	101(40.6)	<0.001
Taxane	5 (6)	93 (37.3)	<0.001
Radiotherapy			
Yes	21 (25)	153 (62)	0.001
No	54 (75)	93 (38)	
Hormone therapy			
Tamoxifen	15 (18)	27 (11)	0.11
Aromatase inhibitor	44 (53)	161 (65)	
None	10 (12)	12 (5)	
Trastuzumab	3/9 (33)	29/41(71)	

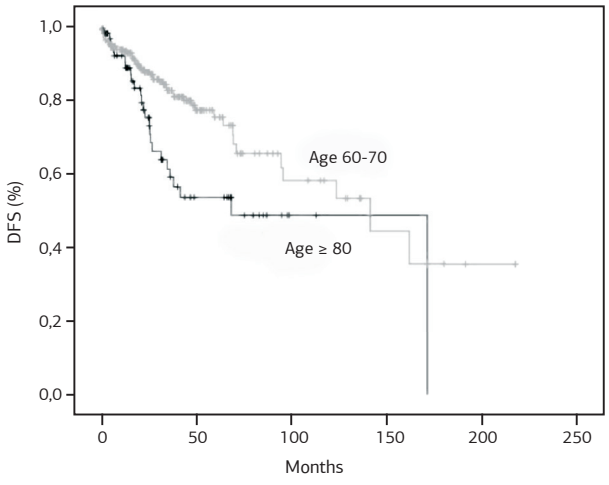

Figure 1. Disease free survival of patients in group 1 and group 2 (53.7 vs 75.9% at 5 years, respectively, p=0.005).

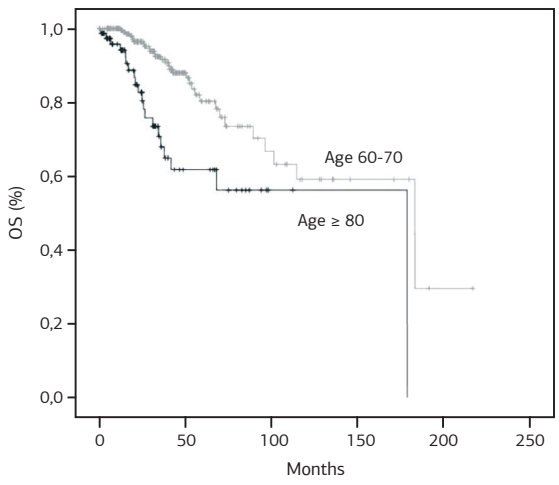

Figure 1. Overall survival of patients in group 1 and 2 group (61.9 vs 80.4% at 5 years, respectively, p<0.001).

Table 3. Univariate analysis of factors significantly associated with disease free survival of patients ≥80 years of age

Factors	*Disease free survival at 3 years (%)*	*p-value*
Stage		0.051
I-III	62	
IV	0	
CerbB2		0.001
Positive	19	
Negative	66	

Analysis also included Charlson Comorbidity Index, grade, histology and hormone receptors status all of which showed no statistical significance

complication rates but previous studies reported acceptable rates of morbidity and mortality [14]. ALND was not performed in 33% of ≥80 years patients in our study. The median number of lymph nodes dissected was also lower. ALND was not associated with DFS or OS in a previous study in elderly patients with T1N0 tumors [7]. The role of ALND is primarily prognostic. Cumulative incidence of local recurrence was found to be 5.9 % in one series among patients with T1-T2 tumors and clinically uninvolved axilla [15]. Furthermore, morbidity of ALND in this patient population may be more disabling [6]. Previous studies have also reported lower rates of ALND in the elderly [4,12]. Thus ALND needs not be routinely performed and should be reserved for patients in whom lymph node involvement would influence the management of the patient.

Radiation therapy is usually well tolerated even in elderly patients [16]. However, those with limited mobility may have difficulties in complying with the schedule. The Cancer and Leukemia Group B trial randomly assigned 636 women older than 70 years with ER-positive tumors ≤2 cm to tamoxifen with or without RT. At a median follow-up of 10.5 years, local recurrence rates were lower but there were no significant differences in metastasis-free survival, breast cancer-specific survival, or rates of salvage mastectomy for local failure [17]. The risk of a local recurrence is lower in older women, and the benefits of radiotherapy may decline with age [18,19]. Thus, treating all elderly patients, particularly those >80 years of age, may not be necessary, given the low recurrence rates and the effectiveness of endocrine treatment. In our study adjuvant radiotherapy was applied to only one fourth of our elderly patients compared with 62% in the younger age group, consistent with previous studies [1,4].

Systemic chemotherapy and trastuzumab were used at lower rates in patients >80 years in our study. Previous studies showed similar benefit with chemotherapy in older patients compared with younger ones. However, other series of octogenarian patients also yielded low utility of chemotherapy in the elderly. Schonberg et al. reported that less than 40% of the patients with lymph node-positive, ER-negative stage I-II breast cancer received chemotherapy [10]. The rate was 2.2% in another series [4] of octogenarians (among all patients). Comorbidities and life expectancy are key factors in chemotherapy decision and must be carefully weighed against the benefit. Trastuzumab was reported to be used in 1 out of 11 (10%) of Her2 amplified octogenarian breast cancer patients in a previous study [12]. Three out of 9 (33%) Her2 amplified patients had received trastuzumab in our series. Classically Her2 positivity is associated with poor prognosis in breast cancer but after trastuzumab started to be used, the prognosis substantially improved. A retrospective series from MDACC revealed women with Her2/neu-positive disease who received trastuzumab had improved prognosis compared with women with Her2/neu-negative disease [20]. Recently, a review of two prospective randomized trials reported that there is a significant 47% relative risk reduction in elderly patients (> 60 years) receiving trastuzumab compared to chemotherapy alone [11]. However, as the majority of our patients had not received trastuzumab, it is not surprising to observe ominous prognosis in these patients.

OS in patients >80 years was unexpectedly high in our and previous studies, and median OS survival was not reached in our series after 36 months follow up, and in 2 other studies after 34 and 70 months follow up [4,12]. Among postmenopausal women with hormone receptor-positive breast cancer, disease-specific mortality was found higher in patients aged 75 years or older [21], although opposite association was also observed in other studies [22-24]. Differences in tumor biology, histological subtypes and undertreatment may account for these differences. Nevertheless, more than half of the patients were alive at a median follow up period > 30 months in 2 studies [4,12] including ours. As stated by Evron et al. [4] "Living to an old age may predict living to a very old age". Charlson Comorbidity Index score was not associated with survival in our study, but this may be secondary to the insufficiency of medical records because only 11%

of the patients had Charlson Comorbidity Index score 3+. Schonberg et al. found an estimated 5-year mortality of 72% for women with Charlson Comorbidity Index score of 3+ and 36% for women with Charlson Comorbidity Index score 0 in women aged 80 or older with early stage breast cancer [25]. Another cohort study of 62591 Danish women with breast cancer showed that, compared with patients without comorbidity (Charlson Comorbidity Index 0), the presence of comorbidity increased the risk of dying from breast cancer as well as other causes [26].

In conclusion, although the majority of the patients were undertreated in our study according to the current guidelines, mortality rates were quite low. Therefore, the treatment modalities applied might not actually be undertreatment. Future randomized studies targeting these patients are needed to determine an optimum treatment algorithm.

References

1. Bouchardy C, Rapiti E, Fioretta G et al. Undertreatment Strongly Decreases Prognosis of Breast Cancer in Elderly Women. J Clin Oncol 2003; 21: 3580-3587.
2. Kimmick G, Muss HB. Breast Cancer in Octogenarians. Semin Oncol 2004;31: 234-248.
3. Schonberg MA, Silliman RA, McCarthy EP, Marcantonio ER. Factors noted to affect breast cancer treatment decisions of women aged 80 and older. J Am Geriatr Soc 2012; 60:538-544.
4. Evron E, Goldberg H, Kuzmin A et al. Breast Cancer in Octogenarians. Cancer 2006;106:1664–1668.
5. Bergman L, Kluck HM, Van Leeuwen FE et al. The influence of age on treatment choice and survival of elderly breast cancer patients in south-eastern Netherlands: A population-based study. Eur J Cancer 1992; 28A: 1475-1480.
6. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000; 92: 550-556.
7. Gajdos C, Tartter PI, Bleiweiss IJ et al. The consequence of undertreating breast cancer in the elderly. J Am Coll Surg 2001; 192:698-707
8. McCarty KS Jr, Silva JS, Cox EB et al. Relationship of age and menopausal status to estrogen receptor content in primary carcinoma of the breast. Ann Surg 1983; 197: 123-127.
9. Pujol P, Daures JP, Thezenas S et al. Changing estrogen and progesterone receptor patterns in breast carcinoma during the menstrual cycle and menopause. Cancer 1998; 83: 698-705.
10. Schonberg MA, Marcantonio ER, Ngo L et al. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival.J Clin Oncol 2010; 28: 2038-2045.
11. Brollo J,Curigliano G, Disalvatore D et al. Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: A systematic review of randomized controlled trials. Cancer Treat Rev 2012 Apr 26. [Epub ahead of print]
12. Cyr A, Gillanders WE, Aft RL, Eberlein TJ, Margenthaler JA. Breast Cancer in Elderly Women (80 Years): Variation in Standard of Care? J Surg Oncol 2011; 103: 201-206.
13. Honma N, Sakamoto G, Akiyama F et al. Breast carcinoma in women over the age of 85: distinct histological pattern and androgen, oestrogen, and progesterone receptor status. Histopathology 2003; 42: 120-127.
14. Chatzidaki P, Mellos C, Briese V, Mylonas I. Perioperative complications of breast cancer surgery in elderly women (≥80 years). Ann Surg Oncol 2011;18: 923-931.
15. Martelli G, Miceli R, De Palo G et al. Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilla? Cancer 2003; 97: 1156-1163.
16. Deutsch M. Radiotherpay after lumpectomy for breast cancer in very old women. Am J Clin Oncol 2002; 25:48-49.
17. Hughes KS, Schnaper LA, Berry D et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer: a report of further follow-up (abstr). Rresented at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 14, 2006. (Abstract available online at www.sabcs.org/SymposiumOnline/index.asp#abstracts, accessed January 5, 2007).
18. Smith BD, Gross CP, Smith GL et al. Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst 2006; 98: 681-690.
19. Veronesi U, Luini A, Del Vecchio M et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 1993; 328:1587-1591.
20. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol 2010; 28: 92-98.
21. Van de Water W, Markopoulos C, van de Velde CJ et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA 2012;307: 590-597.
22. Du XL, Fox EE, Lai D. Competing causes of death for women with breast cancer and change over time from 1975 to 2003. Am J Clin Oncol 2008;31:105-116.
23. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH et al. .Overall survival and cause-specific mortality of patients with stage T1a,bN0M0 breast carcinoma. J

Clin Oncol 2007; 25: 4952-4960

24. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 2004; 96: 1311-1321.
25. Schonberg MA, Marcantonio ER, Ngo L et al. Does Life Expectancy Affect Treatment of Women Aged 80 and Older with Early Stage Breast Cancers?. J Geriatr Oncol 2012; 3: 8-16.
26. Land LH, Dalton SO, Jensen MB, Ewertz M. Impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990-2008. Breast Cancer Res Treat 2012;131:1013-1020.