

# Breast cancer in the elderly

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## Summary

The study population was derived from 482 patients with breast cancer treated at the Department of Oncology, University Hospital Center Zagreb, between 1992 and 1999. The main purpose of our study was to evaluate differences in breast cancer characteristics and treatment in a population of women with breast cancer older than 65 years compared to younger women group (less than 65 years). We have analyzed disease parameters (stage of the disease, size of primary tumor, tumor differentiation grade and steroid receptor status) and parameters associated to treatment modalities (surgery, radiotherapy, hormonal therapy and chemotherapy) in both age groups. In older women, we found significantly higher rates of tumors grade 1 ( $p = 0.0049$ ), tumors  $> 2$  cm and tumors with a high steroid receptor status ( $p = 0.0013$ ). Evaluation of treatment modalities showed that in older women a significantly higher proportion were treated with hormonal therapy ( $p < 0.001$ ) compared to younger patients. In evaluation of clinical outcome after a median follow-up of 58 months, in older women the cumulative 5-year disease-free survival rate was 65%, while cumulative 5-year survival was 83%, which was not significantly different from the younger women ( $p > 0.005$ ).

*Key words:* Breast cancer; Elderly; Tumor characteristics; Therapy.

## Introduction

Aging is the main characteristic of demographic changes in the whole world. While breast cancer incidence increases with age, in the future we can expect more cases of breast cancer patients older than 65 years. Although the number of elderly breast cancer patients is increasing, knowledge about possible age-related differences in the biology, clinical characteristics and their impact on treatment modalities and clinical outcome is limited [1]. Breast cancer in the elderly is thought to be more slowly growing and indolent than in middle-aged women [2], however evidence-based knowledge about possible differences in the biology and clinical outcome of breast cancer according to age is scarce. Women older than 65 years are not included in clinical trials and specific data mainly come from retrospective studies of selected elderly populations [3, 4]. Due to long-held beliefs that elderly patients have limited life expectancy form comorbid conditions other than breast cancer and that they do not tolerate standard treatment, age is an important decision-making factor in therapy. This study was undertaken to evaluate the tumor characteristics and management differences between breast cancer patients older and younger than 65 years.

## Materials and Methods

Between 1992 and 1999, 668 patients over age 40 were treated for breast cancer at the Department of Oncology, University Hospital Center, Zagreb. As breast cancer patients under age 40 have a worse prognosis and poorer survival compared to older women, they were excluded from the study [5, 6]. The data presented are of 482 patients from whom we obtained and

evaluated all the data relevant for study: histopathology, steroid receptor status (estrogen and progesterone receptor levels), stage of disease, type of the treatments performed, disease-free survival (DFS) and overall survival (OS) data. Patients were separated into two age groups: older women – 65 years or older and younger women – between 40 and 64 years old.

Patients were treated according to our protocol used during the period 1992-1999. All the women with operable breast cancer underwent modified radical mastectomy or lumpectomy with axillary dissection. Indications for lumpectomy or mastectomy depended on the extent of the tumor. Biopsy alone was performed only in patients with locally advanced inoperable disease for histopathology. Patients with positive axillary lymph nodes and high-risk node-negative patients received adjuvant systemic therapy. Chemotherapy or/and hormonal therapy were indicated depending on hormonal receptor status and general state of health. Locally advanced and metastatic breast cancer patients were primarily treated with systemic therapy.

We analyzed disease parameters (stage of the disease, size of the primary tumor, histopathologic type of the tumor, tumor differentiation grade and steroid receptor status) and parameters associated with treatment modalities (surgery, radiotherapy, hormonal therapy and chemotherapy) in women older and younger than 65 years. Follow-up was obtained by records of visits to the operating surgeon, clinical oncologist and breast clinic. We analyzed the data on survival with or without signs of disease.

## Results

The study group included 482 breast cancer patients over age 40. They were separated into two age groups: older and younger, while 65 years of age was determined as the discriminating value. The older group of patients were women aged 65 and older ( $N = 113$ ; 23%), with a median age of 69 years and mean age of 70 years (range 65-86 years). The younger patients ( $N = 369$ ; 77%) were aged between 40 and 64 years, with a mean and median age of 52 years (range 40-64 years).

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Distribution of patients by stage of the disease is shown in Table 1. No. significant differences between older and younger patient groups were found ( $p = 0.693$ ). Most patients over ( $N = 53$ , 64.6%) and under ( $N = 214$ , 58%) 65 years had Stage II disease. Invasive ductal carcinoma (IDC) was the predominant histologic type in both age groups; 86% ( $N = 304$ ) of younger and 82.6% ( $N = 90$ ) of older patients had IDC. Of lesions in the younger patient group 7.5% ( $N = 27$ ) were described as lobular invasive carcinoma (LIC), which was not significantly different from 5.5% ( $N = 6$ ) found in older patients. A comparison of tumor size was statistically different between the study groups: 42.73% ( $N = 144$ ) of women under age 65 had tumors 2 cm and smaller (T1) whereas older women had 70.3% ( $N = 71$ ) of tumors larger than 2 cm (Table 2). Sixty percent ( $N = 12$ ) of older women had grade 1 tumors compared to 57.7% ( $N = 30$ ) grade 2 tumors in younger women ( $\chi^2 = 10.64$ ,  $DF = 2$ ,  $p = 0.0049$ ) (Table 3). Distribution of the patients by steroid receptor status is summarized in Table 4. According to estrogen receptor (ER) and progesterone receptor (PgR) status patients were distributed into three subgroups: positive (ER+ PgR +), intermediate (ER+ PgR- or ER-PgR+) or negative (ER-PgR-). Positive receptor status (ER+PgR+) was recorded in 37.5% of patients older than 65 years and in 21.4% of younger women ( $p = 0.0013$ ,  $\chi^2 = 13.296$ ).

Table 1. — Distribution of patients by stage of disease.

AGE		Stage of the disease <sup>1</sup>							All
		0	I	IIA	IIB	IIIA	IIIB	IV	
< 65 years	N	6	92	107	107	27	21	9	369
	%	1.6%	24.9%	29.0%	29.0%	7.3%	5.7%	2.4%	100%
≥ 65 years	N	1	19	31	42	2	13	5	113
	%	0.9%	16.8%	27.4%	37.2%	1.8%	11.5%	4.4%	100%
All	N	7	111	138	149	29	34	14	482
	%	1.5%	23.0%	28.6%	30.9%	6.0%	7.1%	2.9%	100%

$\chi^2$  (correction to Yates) = 0.16,  $p = 0.693$ ; <sup>1</sup>Stage of the disease according to the American Joint Committee on Cancer and the International Union Against Cancer (AJCC/UICC).

Table 2. — Distribution of patients by tumor size.

AGE		Tumor size (cm)			All
		≤ 2	2-5	> 5	
< 65 years	N	144	162	31	337
	%	42.73%	48.07%	9.20%	
≥ 65 years	N	30	59	12	101
	%	29.70%	58.42%	11.88%	
All	N	174	221	43	438

Table 3. — Distribution of patients by histologic grade.

AGE		Histologic grade			All
		1	2	3	
< 65 years	N	15	30	7	52
	%	28.8%	57.7%	13.5%	100%
≥ 65 years	N	12	3	5	20
	%	60%	15%	25%	100%
All	N	27	33	12	72
	%	37.5%	45.8%	16.7%	100%

$\chi^2 = 10.64$ ,  $DF = 2$ ,  $p = 0.0049$ .

Table 4. — Distribution of patients by receptor status.

AGE		Steroid receptor status <sup>1</sup>			All
		negative <sup>2</sup>	intermediate <sup>3</sup>	positive <sup>4</sup>	
< 65 years	N	207	79	78	364
	%	56.9%	21.7%	21.4%	100%
≥ 65 years	N	45	25	42	112
	%	40.2%	22.3%	37.5%	100%
All	N	252	104	120	476
	%	52.9%	21.8%	25.2%	100%

$p = 0.0013$ ,  $\chi^2 = 13.296$ , <sup>1</sup>estrogen receptor (ER) and progesterone receptor (PgR), <sup>2</sup>ER-PgR-; <sup>3</sup>ER+PgR- or ER-PgR+, <sup>4</sup>ER+PgR+.

Surgical treatment did not differ statistically between the study groups: 53.1% ( $N = 60$ ) of older and 60.7% ( $N = 224$ ) of younger patients underwent modified radical mastectomy (MRM). Breast conserving surgery (quadrantectomy and tumorectomy) was the initial treatment for 36.3% ( $N = 41$ ) of patients over 65 years, and it was not statistically different from the younger group (33.3%,  $N = 123$ ). Younger patients (5.6%,  $N = 21$ ) and older patients (7.1%,  $N = 8$ ) with locally advanced or metastatic disease were submitted to excisional biopsy only. There was no statistical difference found in adjuvant postoperative radiotherapy after MRM or breast conserving surgery between the study groups ( $\chi^2 = 1.96$ ,  $p = 0.1613$ ). Both older (81.4%,  $N = 92$ ) and younger patients (86.7%,  $N = 320$ ) received postoperative radiotherapy. Hormonal therapy with tamoxifen in an adjuvant or neoadjuvant setting was given to all patients with steroid receptor positive tumors (ER and PgR high and intermediate score). Patients older than 65 years (51.3%,  $N = 58$ ) were treated with tamoxifen, while only 29.8% ( $N = 110$ ) of women in the younger group received hormonal therapy (Table 5). The difference was due to the

Table 5. — Distribution of the patients with hormonal therapy.

AGE		Hormonal Therapy		All
		yes	no	
< 65 years	N	259	110	369
	%	70.2%	29.8%	100%
≥ 65 years	N	55	58	113
	%	48.7%	51.3%	100%
All	N	314	168	482
	%	65.1%	34.9%	100%

$\chi^2$  (corrected to Yates) = 16.70,  $p = 0.001$ .

different hormonal receptor status between the study groups and was found to be statistically different:  $\chi^2$  (correction to Yates) = 16.70,  $p < 0.001$ . The  $\chi^2$  test did not find any statistical difference in application of chemotherapy (comparing treatment with chemotherapy vs none, adjuvant vs neoadjuvant chemotherapy, regimens with or without anthracyclines) between study groups.

The results of our study suggest that there were no significant differences in stage of the disease and histopathological type between older and younger patients. In older women, we found significantly high rates of grade 1 tumors ( $p = 0.0049$ ), tumors larger than 2 cm and tumors with a high steroid receptor status ( $p = 0.0013$ ).

Local and systemic therapy for breast cancer did not

differ according to age. Evaluation of treatment modalities did not show any significant differences in surgery, chemotherapy or radiotherapy. In the older group, a higher proportion of those treated with hormonal therapy ( $p < 0.001$ ) was found compared to younger patients group.

Survival analyses were based on data of breast cancer-associated survival and disease-free survival. After a median follow-up of 58 months, in older women the cumulative 5-year disease-free survival rate was 65% and cumulative 5-year survival was 83%, not significantly different from the younger women ( $p > 0.005$ ). We did not find any survival differences according to stage of disease between older and younger patients. Breast cancer-associated death occurred in 65 (17.3%) younger patients and in 19 (16.8%) patients over age 65. Overall, the death rate did not increase with age.

## Discussion

Elderly women present a large population of women with breast cancer. The literature referring to natural history of breast cancer in the elderly is not undivided in biology, tumor characteristics and behavior [7, 8]. Age at diagnosis is a controversial prognostic factor for breast cancer. Several studies have demonstrated indolent tumor behavior with lower proliferative activity, but others also greater aggressiveness [6, 9]. Zenon *et al.* found lower production of growth and angiogenic factors [10, 11].

Many believe elderly women often present with more advanced disease. However, Chu *et al.* reported no difference in classification at diagnosis, although the elderly are sometimes not classified at all [12, 13]. Our data indicate that elderly patients do not necessarily always present with more locally advanced disease. Most patients in our study – elderly (64.6%) and younger (58%) women were classified as having Stage II disease, as is also reported in most other case series [1, 3, 14]. We did not find a statistically different percentage of patients in advanced stages (III and IV) according to age. In agreement with Diab *et al.* we found a statistical difference in tumor size between the older and younger group. However, previous publications by Buch, Singletary and Davis did not show age-related differences in tumor size [1, 3, 12, 14, 15]. Of patients younger than 65, 42.3% had tumors  $< 2$  cm compared to only 29.7% of tumors of the same size in the older women's group ( $p = 0.0048$ ). There have also been different reports about pathohistology types of breast cancer occurring in older women. Busch and Bonnier did not find any differences, while Fisher *et al.* reported a lower incidence of medullary and inflammatory breast cancer and a higher incidence of colloid, papillary and lobular invasive cancer in older patients [12, 13, 16]. Our results support the work of Busch, finding 82.6% of ductal invasive carcinoma in older women and 84% in younger patients. A higher frequency of undifferentiated tumors (grade 3) and negative

hormone receptor status have been observed and described in younger breast cancer patients [3, 9, 14, 17]. In our work the incidence of well differentiated tumors (grade 1) was significantly higher in older women ( $p = 0.0049$ ). It is commonly reported that older women have a higher likelihood of having endocrine-dependent tumors [18-20]. Our analysis showed that there was a significant difference in receptor status. Positive receptor status (ER+PgR+) was observed in 37.5% of older patients and in 21.4% of younger women ( $p = 0.0013$ ,  $\chi^2 = 13.296$ ).

Management decisions for elderly patients with breast cancer are still controversial. They are often screened inadequately, have incomplete workups for definitive staging and are likely to receive less than standard therapy [4, 5, 6, 10, 21]. Part of the reason for this situation is the historic exclusion of women older than 65 years from the trials. The main characteristic of breast cancer surgery for older women is dichotomy. They usually have less than standard surgery and conversely mastectomy is frequently the procedure of choice, regardless of the stage. In our study there was no difference in the breast cancer surgery approach to the younger and older patients, both having similar percentages of MRM and breast conserving surgery ( $p = 0.6804$ ). Adjuvant radiotherapy after surgery for breast cancer is less frequently used in the elderly [12, 17, 21]. This approach would simplify the treatment but results in a higher local recurrence rate of 15-25% [22, 23]. Our data showed no difference in delivering adjuvant radiotherapy to younger or older breast cancer patients ( $p = 0.1613$ ). The recommendation of the use of adjuvant systemic therapy for elderly woman is the same as for postmenopausal women of younger age [24]. Older women with breast cancer are less likely to be referred for chemotherapy because of the fear of the toxicity and the question of relative benefit. In our work there was no significant difference ( $p = 0.0134$ ) in application of chemotherapy in the study groups (comparing treatment with chemotherapy vs none, adjuvant vs neoadjuvant chemotherapy, and regimens with or without anthracyclines). Hormonal therapy is often suggested in treatment of elderly patients because it is well tolerated and the elderly often have more steroid receptor positive tumors. A higher proportion (51.3%) of women in the older study group were treated with adjuvant hormonal therapy compared to only 29.8% patients in the younger group ( $p < 0.001$ ). Hormonal therapy is the only treatment field for elderly breast cancer patients where consensus is achieved.

Because of the demographic changes in the world and ageing of the population, our results suggest further evaluation on this subject. The most important finding in our study is that the disease-free survival and overall survival were not influenced by age. Including older women in prospective clinical trials will create standard protocols for diagnostics, therapeutic procedures and follow-up regimes as well as improve the quality of life of older women with breast cancer.

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