JBUON 2015; 20(3): 723-729
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Breast cancer in postmenopausal patients: Impact of age

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Summary

Purpose: *We analyzed the significance of age together with other classic prognostic parameters on the course of breast cancer in postmenopausal patients.*

Methods: *Our study included 151 postmenopausal patients with primary breast cancer, of which 55% received adjuvant tamoxifen therapy and 45% did not receive any kind of therapy. Probabilities of disease-free interval (DFI) were estimated using the Kaplan-Meier method and were compared by the log-rank test. A p value < 0.05 was considered as statistically significant.*

Results: *In the tamoxifen-treated subgroup, patients with estrogen receptor (ER) or progesterone receptor (PR) concentration ≥5 fmol/mg had favorable course of disease (p<0.01, p<0.04), respectively. Patients ≥66 years of age had a worse disease course compared to those <66 years. Also, patients ≥66 years with pT1 tumors had a worse disease course compared to those <66 years and pT1 tumors. This result was repeated in other groups as well. In pT2 (≥2 cm), ER-positive, PR-positive and invasive ductal carcinoma (IDC) subgroups, patients ≥66 years always had a worse disease course compared to patients <66 years. In the untreated subgroup, patients with ER ≥52 fmol/mg (p<0.01), tumors ≥2 cm (p<0.01), IDC (p<0.01) type or ≥56 years (p<0.04) had statistically more recurrences. Among patients ≥56 years, those with ER-positive or pT2 tumors had shorter DFI compared to ER-negative or pT1. Positive correlation between ER, PR and age of patients was also shown in this subgroup (p<0.03, p<0.02).*

Conclusion: *Age of patients, ER and PR are significant prognostic factors in the tamoxifen-treated subgroup. In the untreated subgroup relevant prognostic parameters are age, tumor size, histological type and ER. The above prognostic factors retained their value in the long-term follow up in both the investigated subgroups of patients.*

Key words: *age, breast cancer, prognosis*

Introduction

The relationship between age at diagnosis and breast cancer prognosis is rather controversial though results coming from recent studies increasingly confirm its significance [1,2]. Statistically, one third of all breast cancers affect patients 65 years or older, while in developed countries this proportion rises to 40% [3]. For postmenopausal patients diagnosed with hormone sensitive breast cancer, increasing age has been associated with worse outcome [4,5]. Due to this age dependence, it is of great importance to distinguish whether breast cancer prognosis varies in different age groups according to classic prognostic parameters at the time of diagnosis.

The aim of this study was to determine whether age is a significant parameter affecting the course and outcome of breast cancer. We conducted a retrospective analysis of 151 primary breast cancer cases aiming to assess possible relationships between age, clinicopathological parameters, classic prognostic factors and disease prognosis during long-term follow up.

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Received: 17/12/2014; Accepted: 14/01/2015

Methods

This study included 151 postmenopausal breast cancer patients with positive steroid receptors (>0 fmol/mg). Adjuvant tamoxifen therapy was administered for 5 years or until disease recurrence in 55% of the patients. After the 5th year no treatment was given. The remaining patients (45%) (without lymph node metastasis), at the time did not receive any kind of therapy because of their favorable clinicopathological characteristics. Patients' follow up was 12 years, or until disease recurrence (development of distant metastasis only). Information on clinicopathological parameters (age, tumor size, nodal status, histological type, steroid receptor status and development of distant metastasis) was obtained from the patients' medical records (Table 1). The patient age ranged from 47 to 81 years (median 59). Histological specimens were reviewed and then classified according to the International Union Against Cancer for TN stages and the histological type. ER and PR quantitative values were measured by the classical biochemical method as recommended by the EORTC [6]. The intra-laboratory quality assessment of steroid hormone receptor levels was performed periodically under the EORTC recommendation. This study was approved by the Institute Ethics Committee.

Statistics

Probabilities of DFI were estimated using the Kaplan-Meier method and were compared by the log-rank test. A p value <0.05 was considered as statistically significant. The primary endpoint was the development of distant metastasis. Correlations between quantitative levels were determined with the Spearman's test. Distribution of quantitative levels between different subgroups of patients was determined using the Mann Whitney U test.

Results

Analysis of DFI according to clinicopathological and steroid receptors in the subgroup of patients who received adjuvant tamoxifen therapy showed a statistically significant difference when patients were stratified on the basis of their steroid receptor status and age (cutoff 66 years) (Table 2). Patients with ER ≥5 fmol/mg, PR ≥25 fmol/mg or ≥66 years of age alone, had a worse course of the disease compared to lower values (ER <5 fmol/mg, PR <25 fmol/mg or <66 years). Other clinicopathological parameters didn't show any statistically significant differences regarding DFI (Table 2). Patients ≥66 years of age had a worse disease course in pT1 (<2cm), pT2 (≥2cm), ER ≥5 fmol/mg, PR ≥25 fmol/mg and IDC subgroups, compared to those aged <66 years (Table 3). Other combinations of clinicopathological parameters didn't show statistically significant results (data not shown).

Table 1. Clinicopathological characteristics of 151 patients with breast carcinomas for a follow-up period of 12 years

Parameters	*Patients N*	*%*
Recurrence	151	100
No recurrence	70	46
Recurrence	81	54
Tumor size (cm)		
pT1 (<2)	78	52
pT2 (<2)	69	47
Unknown	4	1
Axillary lymph nodes		
N0	77	51
N+	64	42
Unknown	10	7
Histological type		
IDC	66	44
ILC	53	35
Rare and mixed	32	21
Histological grade		
I	19	13
II	114	75
III	17	11
Unknown	1	1
Therapy		
Treated with tamoxifen	84	55
Untreated	67	45

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

In the subgroup of patients which did not receive any kind of therapy, those with ER concentration ≥52 fmol/mg had a shorter DFI and worse disease course compared to patients with concentrations <52 fmol/mg. When patients were stratified according to other clinicopathological parameters, patients with tumors ≥2 cm (pT2) (compared to <2 cm - pT1) or IDC type (compared to ILC – invasive lobular carcinoma) had a worse disease course (Table 4). Patients ≥56 years had a higher rate of recurrence compared to <56 years. Those with pT2 tumors or ER ≥52 fmol/mg had shorter DFI and higher rate of recurrences in the subgroup of ≥56 years of age compared to <2 cm or ER <52 fmol/mg (Table 5). There were no statistically significant differences according to clinicopathological parameters in the subgroup of patients younger than 56 years. Positive correlation was found between ER, PR and age of patients (Table 6).

Table 2. Disease free interval probabilities according to clinicopathological variables and molecular biomarkers for the period of 12 years (patients on tamoxifen therapy)

Parameters	*Patients N*	*Recurrence N*	*Recurrence %*	*p value**
Tumor size				
pT1	40	25	63	0.10
pT2	42	30	71	
Axillary lymph nodes				
N0	10	6	60	0.70
N+	64	39	61	
Histological type				
IDC	37	26	70	0.90
ILC	32	20	63	
Histological grade				
I	10	5	50	0.30
III	15	11	73	
Age (years)				
<66	59	35	59	0.01
≥66	25	20	80	
Estrogen receptor				
ER-low (<5 fmol/mg)	12	10	83	0.01
ER-high (≥5 fmol/mg)	72	45	63	
Progesterone receptor				
PR-low (<25 fmol/mg)	45	33	73	0.04
PR-high (≥25 fmol/mg)	38	19	50	

*log rank test. For abbreviation see footnote of Table 1

Table 3. Disease free interval probabilities in subgroup of patients according to age (66 years) and ER, PR, size of tumor, histological type for the period of 12 years (patients on tamoxifen therapy)

Parameters	*Patients N*	*Recurrence N*	*Recurrence N%*	*p value**
<66 ER-high	52	30	58	0.040
≥66 ER-high	20	15	75	
<66 ER-high	52	30	58	0.001
≥66 ER-low	5	5	100	
<66 PR-high	45	26	58	0.001
≥66 PR-high	23	19	83	
<66 pT1	29	16	55	0.04
≥66 pT1	11	9	82	
<66 pT1	29	16	55	0.001
≥66 pT2	13	11	92	
<66 pT2	30	19	63	0.01
≥66 pT2	12	11	92	
<66 IDC	27	17	63	0.05
≥66 IDC	10	9	90	

*log rank test

Discussion

Cancer is a disease of ageing. Of all breast cancers 35-50% are diagnosed in women aged 65 or older [7]. There is an evident problem concerning the medical treatment of elderly patients. This is reflected by the report from Allemani and colleagues who showed that elderly patients receive below-standard medical care [8]. For example, age restrictions applied in many clinical studies during selection of study participants result in poor representation and evaluation of this patient age group [9]. One possible explanation for the existing underrepresentation of elderly patients in clinical studies is the physiological and clinical diversity in this age group [10]. Due to changing demographics, increased life expectancy and the nature of cancer itself, this patient group is on the rise and it is therefore imperative to have its careful assessment in both clinical and research

Table 4. Disease free interval probabilities according to clinicopathological variables for the period of 12 years (only patients without therapy)

Parameters	*Patients* *N*	*Recurrence* *N*	*Recurrence* %	*p value**
Tumor size (cm)				
pT1 (<2)	38	10	26	0.01
pT2 (≥2)	27	15	55	
Histological type				
IDC	29	6	20	0.01
ILC	21	12	57	
Histological grade				
I	9	4	44	0.9
III	2	1	50	
Age (years)				
<56	15	2	13	0.04
≥56	52	24	46	
Estrogen receptor				
ER-low (<52 fmol/mg)	41	11	26	0.01
ER-high(≥52 fmol/mg)	26	15	57	

*log rank test. For abbreviations see footnote of Table 1

Table 5. Disease free interval probabilities according to age (cut off 56 years) and ER, tumor size and histological type for the period of 12 years (patients without therapy)

Parameters	*Patients* *N*	*Recurrence* *N*	*Recurrence* %	*p value**
≥56 ER-high	24	15	62	0.01
<56 ER-low	13	2	15	
≥56 ER-high	24	15	62	0.03
≥56 ER-low	28	9	32	
<56 pT1	13	2	15	0.01
≥56 pT2	25	15	60	
≥56 pT1	25	8	32	0.04
≥56 pT2	25	15	60	
<56 IDC	11	1	9	0.01
≥56 ILC	20	11	55	

*log rank test. For abbreviations see footnote of Table 1

Table 6. Spearman's rank order correlation test between age of patients and ER, PR (patients without therapy)

Parameter		*PR*	*Age*
ER fmol/mg	Correlation coefficient	0.48	0.268
	p value*	<0.001	0.03
	Number of patients	67	67
PR fmol/mg	Correlation coefficient	-	0.276
	p value*	-	0.02
	Number of patients	-	67

*Spearman's rank order correlation

settings.

The disease course and prognosis in patients of different age groups is still questionable. These connections are described in several articles, one of which is a large study involving 9,766 postmenopausal breast cancer patients with hormone-sensitive disease. These patients were included in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial [4,11]. There was one study in which the influence of age on prognosis was analyzed [12]. In contrast to the claims that cancer is indolent in older patients, some tumor types are more

aggressive in elderly population, contributing to increased mortality from breast cancer [5].

Our research covers 12 years of follow-up of two patient groups with different clinicopathological parameters and therapeutic approaches. The focus of our study was to define the prognostic significance of age in postmenopausal patients. The biological specificity that governs the disease course in this group is still unknown. We investigated the group of postmenopausal patients treated with adjuvant tamoxifen for 5 years.

Tamoxifen is standard therapy for ER-positive breast cancer patients. Postsurgical treatment of breast cancer patients with tamoxifen for 5 years reduces recurrence and disease-specific mortality by 41% and 33%, respectively [13]. However, a large fraction of patients does not respond to therapy, underlining the need for further classification of ER-positive breast cancer patients and more individually tailored endocrine therapy [14].

In the tamoxifen-treated group, patients with higher ER and PR protein concentration (≥5 fmol/mg and ≥25 fmol/mg, respectively) had a lower chance of developing recurrence. Previous researches suggest that the value of a prognostic factor decreases over time, depending of the length of follow-up [15,16]. Also, it has been reported that ER expression loses its prognostic value in the first 5-10 years after diagnosis [17]. In contrast, our study involving 84 tamoxifen-treated patients revealed that ER (≥5 fmol/mg) retains its important prognostic value for a period of 12 years. Analysis of other clinicopathological parameters shows that only patient's age is significantly correlated to disease course, allowing for differentiation of two distinct age subgroups. Patients aged 66 years or older had a significantly higher probability of disease recurrence. This age limit (≥66 years) has been reported as a cut off value in other studies as well [18]. It is well known that breast cancer incidence rises with age [11], and more than 40% of newly diagnosed breast cancers arise in the population group of ≥65 years of age [7]. Our results show that age can be used as prognostic factor in the long-term follow-up. So among ER ≥5 fmol/mg, PR ≥25 fmol/mg, IDC or patients with tumor size <2 cm or ≥2 cm, patients aged ≥66 years always have a shorter DFI compared to those <66 years (Table 3). This age cutoff can be used as prognostic parameter which can additionally classify initially favorable subgroups, above all ER ≥5 fmol/mg, PR ≥25 fmol/mg and pT1. Patients with unfavorable characteristics may be taken into consideration for new therapy approaches. In the present study, assessment of the combination of age with lymph node status, as most important prognostic parameter, did not reach statistical significance.

Not much is known about the impact and value that prognostic factors way have in the group of postmenopausal patients without lymph node metastasis, and clinical trials investigating the issue are rare [19]. One of the main reasons for this lack of knowledge is the changes in therapeutic protocols in the last 20 years as well as serious ethical concerns over patient recruitment and randomization with no-treatment arm involved. Though adjuvant systemic therapies can improve the quality of patients' lives and delay or prevent disease recurrence, toxicities originating from such therapies are major risk factors. For that reason the cost/benefit ratio must be evaluated on individual basis [20]. In this study, analysis of DFI in the node negative subgroup revealed that standard clinicopathological parameters such as tumor size, histological type, age and hormone receptor status were significant in the long-term follow-up. Patients with pT2 tumors (p=0.01) or IDC (p=0.01) had a higher chance of recurrence compared to patients with pT1 or ILC tumors. Other studies confirmed that tumor size is the most relevant prognostic factor for this subgroup [20]. According to Warwick et al. tumor size can have a long-lasting prognostic significance over time [15], maintaining its significance, together with old age, up to 10 years following diagnosis [16,21]. Once again, in our study, patient age at the time of diagnosis has been shown to have prognostic value. In the untreated subgroup patients aged ≥56 years had a 3-fold higher recurrence rate, resulting in shorter DFI. When analyzing both tumor sizes with age at diagnosis, we found that patients with pT2 tumors, in the age group ≥56 years, had higher probability of recurrence compared to pT1. Additional therapy can improve the disease course in these patients (Table 5). Since there is a small number of patients in the group aged <56 years for analyzing by tumor size, further studies are needed.

Interestingly, the results of the long-term follow-up analysis regarding ER content in the untreated group are exactly the opposite of those in the tamoxifen-treated group. We found a cut-off value for ER tumor content at 52 fmol/mg. Patients with ER content above this cutoff (≥52 fmol/mg) had higher recurrence rate (p=0.01), even in the subgroup of ≥56 years and would probably benefit from the adjuvant therapy (Tables 4,5). These results may suggest that among ER-pos-

itive postmenopausal patients that tend to have more indolent disease course, higher ER levels call for more aggressive ER directed tumorigenesis. This may be due to increased membrane or non-genomic ER functions as opposed to lower ER tumor content. As ER has been found in lipid rafts along with EGFR, integrins, IGF1R and other surface receptors involved in the control of growth and proliferation, it would be of interest to identify a prevalent mode of ER function and signaling in these tumors, as well as ER binding partners. As the patients of one of the analyzed groups have not received systemic treatment after surgery, the course of disease progression was unaffected, reflecting in a more adequate way the natural history and progression of the disease itself. Addressing mechanistic aspects governing growth and progression of high ER content tumors in this patient group may be of interest. Unlike normal mammary gland tissue, malignant cells continuously increase ER expression after menopause [22]. This was confirmed by our analysis, where we found that ER concentration rises with the patient age (Table 6). Our data showed that patients aged ≥56 years had a shorter DFI. Higher aggressiveness of tumors in patients ≥56 years could be partially explained by higher concentration of ER and PR (data not shown). Also, it is important to mention that ER-positive breast cancers are more frequently diagnosed in older women [7,23]. The levels of estrogen in postmenopausal women are reduced dramatically compared to premenopausal ones [24]. But, this low serum concentration of estrogen does not necessarily reflect the local situation in the mammary gland tissue. Today it is considered that the predominant influence comes from estrogens synthesized intratumorally [25]. The levels of the enzyme aromatase, that is responsible for conversion of androstenedione and testosterone into estrone and estradiol, are increased in postmenopausal women by the breast adipose and stromal cells. This age-related increase in the production of aromatase is present to such an extent that estrogen levels in the postmenopausal mammary gland could be almost the same as those in premenopausal women [26]. In this way, intratumorally produced estrogen can exert a great impact on tumor growth through its receptors, and finally contribute to worsening the disease course in this untreated subgroup.

Other possible causes for poor outcome of disease in elderly patients are deterioration in the genome integrity, increased gene silencing by methylation of gene promoter, general genetic instability and accelerated proliferation resulting from a combined effect of cumulative mutational load and telomere dysfunction [27]. One additional possible reason may be the influence of aging stroma due to its great impact in remodeling of the extracellular matrix and promoting invasion and growth of premalignant epithelial cells [28].

In conclusion, according to our analysis, patients ≥56 years in the untreated group and ≥66 years in the adjuvant tamoxifen group both had a higher chance of developing recurrence compared with untreated patients <56 years and treated patients <66 years. Tumors in older postmenopausal patients tend to be more aggressive than in younger postmenopausal patients, so this should be taken into account when deciding the therapeutic approach. The underlying molecular mechanisms of the aggressive nature of tumors in older patients are still unknown. It may be speculated that the molecular and cellular processes that take part in aging could be also responsible for increased cancer aggression and progression.

Acknowledgement

This work was supported by Grant No. 175068 "Molecular biomarkers of breast cancer and changes of their significance depending on the follow-up of the disease" from the Ministry of Science and Environment Protection of the Republic of Serbia.

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