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ORIGINAL ARTICLE

Young age and pathological features predict breast cancer outcome - report from a dual Institution experience in Serbia

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Summary

Purpose: *The aim of this study was to investigate the influence of clinicopathological and biological characteristics on prognosis, disease free survival (DFS) and overall survival (OS), of very young patients (≤35 years of age) with breast cancer.*

Methods: *We retrospectively collected information of 150 women diagnosed with breast cancer, aged ≤35 years, who were operated and treated at two University Hospitals in Serbia between January 2009 and February 2011.*

Results: *After a median follow up of 44 months patients ≤30 had shorter DFS and OS compared to patients aged 31-35 years (p=0.004 and p=0.037, respectively). The differences in DFS and OS were significant with decreased survival associated with higher tumor grade (p=0.005 and p=0.0001, respectively). Tumor size and number of positive nodes were predictors of outcome with decreased survival associated with higher tumor size (p=0.0019 for DFS and p<0.0001 for OS) and increasing number of nodes (p<0.0001 for both). HER 2 receptor did not seem to have a prognostic influence while patients with hormonal receptors (HRs) positive tumors had a better DFS (p=0.034) and OS (p=0.046) than those with HRs negative tumors. In univariate survival analysis, a significant difference in DFS (p=0.0003) and OS (p=0.0003) was found between patients with vs without lymphovascular invasion (LVI).*

Conclusion: *Diagnosis of breast cancer at very young age (≤30) was associated with increased risk of death and shorter DFS than women aged 31- 35. Negative impact on survival was seen in patients with presence of LVI, negative HRs and higher grade and stage at the time of presentation.*

Key words: *breast cancer, Serbia, 35 years-old, young age*

Introduction

Nowadays, breast cancer is the most common malignancy in females, comprising 26% of all cancers occurring in females, with an incidence of 60.8 per 100,000 and mortality of 20.2 per 100,000 in Serbia [1]. However, breast cancer is less common in very young women. It has been assumed that approximately 2% of all cases of breast cancer occur in women under the age of 35 years and also that it is probably biologically different than breast cancer arising in older women. Younger women have less favorable prognosis and higher relapse rates than older women [2,3]. The poor prognosis and tumor's aggressive behavior have been associated with several factors like higher expression of HER 2, lower estrogen (ER) and progesterone receptor (PgR) expression, higher proliferation rate, higher tumor grade and larger size at diagnosis [2,4]. However, young age

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at diagnosis remains an independent risk factor for breast cancer-related death and the risk of death rises by 5% for every year reduction in age for patients aged < 35 years and young age is also an indication for aggressive and more tailored systemic treatment [5-7]. Presentation with larger and higher stage cancer could be attributed to the lack of effective screening and awareness in these women, and also to delayed diagnosis related to the relative rarity of breast cancer in younger women and the common benign breast disorders in this age group [7,8].

The aim of this study was to investigate the influence of clinicopathological and biological characteristics on prognosis, DFS and OS, of very young patients (≤35 years of age) with breast cancer in two University Hospitals in Serbia.

Methods

We retrospectively collected information of 150 women diagnosed of breast cancer, aged ≤35 years between January 2009 and February 2011. All of the patients were operated and treated in two Institutions, the University Hospital Nis and the Oncology Institute of Vojvodina. Each center is an academic comprehensive cancer center at which the majority of surgical and medical oncologists treat breast cancer patients. This study examined the influence of established prognostic factors such as age, tumor grade, T stage, N stage, histology, HRs, HER 2 positivity and LVI on DFS and OS of young patients. The collected information included age at the time of diagnosis, personal history, mammography results, breast ultrasound results, breast MRI results and results of the staging procedures (serum biochemistry, hematological values, bone scan, CT of the chest or chest x-ray and upper abdominal ultrasound examination or CT scan), treatment (chemotherapy, hormonal therapy and biological therapy) and type of surgery. Pathological assessment included tumor size and grade, histological subtype and axillary lymph node status including sentinel node biopsy where applicable, and LVI. Histology was performed on hematoxylin and eosin stained sections using the 2012 WHO classification of breast tumors [9] .Tumor grading was performed according to Elston-Ellis modification of Bloom-Richardson grading system [10]. ER, PgR, and HER 2 overexpression were evaluated immunohistochemically. The threshold for ER and PgR positivity was 1% and was considered positive when either the ER, PgR or both were positive. The Allred et al. scoring system was used to evaluate ER and PR status [11]. HER 2 is being routinely assessed in Serbia since 2007 and tumors were scored according to the intensity and completeness of cell membrane staining in 4 scores (0- no immunoreactivity, 1+: weak and incomplete membrane staining, 2+: borderline and 3+: strong and complete membrane staining). In case of HER 2 2+ (borderline) chromogenic *in situ* hybridization (CISH) was performed. HER 2 positivity was defined as either immunohistochemistry 3+ or 2+ with gene amplification detected by CISH.

Tumors were grouped according to their HR and HER 2 status into 4 subtypes HR+/HER 2-, HR +/HER 2+. HR-/HER 2 +, HR-/HER 2-. Ki 67 was not routinely assessed at that time in Serbia so we couldn`t classified tumors in luminal A and luminal B subgroups. TNM classification was made according to the American Joint Committee on Cancer (AJCC) staging system [12].

Treatment data included type and duration of neoadjuvant chemotherapy, breast-conserving surgery or mastectomy (Madden's technique), adjuvant chemotherapy, radiation therapy and hormonal therapy. Follow-up data included information about local and distant sites of recurrences. Additional follow-up information was collected by phone calls made to patients or their families, when necessary.

Statistics

The primary endpoints were DFS and OS. DFS was calculated from the date of surgery to the first documented local or distant disease relapse. OS was calculated from the date of surgery to the date of death from any cause or the date of the last follow-up. Survival curves were generated using the Kaplan-Meier method and log-rank test was used for comparison of survival between groups. Multivariate analyses using Cox's proportional hazard model were performed in order to characterize prognostic factors of various clinical and histopathological characteristics of the tumor on OS and DFS. Factors included in multivariate analyses were tumor size, nodal status, tumor grade, ER and PgR status, LVI and age ≤30.

Results

Patients and treatment characteristics

Tables 1 and 2 show the baseline patient and tumor characteristics and all treatments performed.

The median age at presentation was 32 years (range 24-35). Breast ultrasound was performed in 55 (36.7%) patients, breast MRI in 32 (21.3%), mammography in 25 (16.7%) and clinical examination only in 27 (18%) patients. Histological examination revealed that in 101 (67.3%) patients the tumor was invasive ductal carcinoma, in 22 (14.6%) invasive lobular, ductal carcinoma in situ (DCIS) in 7 (4.6%), mixed in 14 (9.3%), medullary in 5 (3.3%) and squamous cell in 1 (0.6%). The clinical stage of the tumors in terms of size and nodal involvement is shown in Table 1. Triple negative breast cancer (TNBC) was found in 26 (17.3%) patients while HR positive/HER 2 negative disease

Table 1. Baseline patient and tumor characteristics

Characteristics	*Patients N (%)*
Age, years	
≤ 30	38 (25.4)
31-35	112 (74.6)
Grade	
G1	15 (10)
G2	69 (46)
G3	62 (41.3)
Unknown	4 (2.7)
T stage (cm)	
≤ 2 (pT1)	46 (30.7)
2-5 (pT2)	77 (51.3)
>5 (pT3/4)	15 (10)
Unknown	12 (8)
N stage	
N0 (0 nodes)/ N1 (1-3 nodes)	66 (44) / 29 (19.3)
N2 (4-9 nodes)/ N3 (≥ 10 nodes)	31 (20.7) / 24 (16)
Stage	
I/II	27 (18)/ 65 (43.3)
III/IV	49 (32.6)/ 8 (5.3)
Lymphovascular invasion	
Positive/Negative	59 (39.3)/ 45 (30)
Unknown	46 (30.7)
Hormone receptor	
Positive/Negative	98 (65.3) / 52(34.7)
HER 2	
Positive/Negative	45 (30) / 98 (65.3)
Unknown	7 (4.7)

Table 2. Treatment characteristics

Characteristics	*Patients N (%)*
Type of surgery	
Breast conserving	62 (41.3)
Mastectomy according to T stage	82 (54.7)
Unknown	6 (4)
Mastectomy according to T stage	
T1	18/46 (39.1)
T2	50/77 (64.9)
T3	14/15 (93.3)
(Neo)Adjuvant therapy (+trastuzumab for HER 2 pos)	136 (90.7)
ET[a]	8 (5.9)
A[b] +/- ET	64 (47)
A/T[c] +/- ET	62 (45.6)
CMF [d]	2 (1.5)
Hormonal therapy	77 (51.3)
TAM[e]	29 (37.7)
TAM(or AI[f])+OS[g]	48 (62.3)
1st line metastatic disease	49 (32.7)
ET	9 (18.7)
Anthracycline-based	3 (6.1)
Taxane-based	24 (49)
Capecitabine	10 (20.4)
Taxane/Platinum	2 (4)

[a]endocrine therapy, [b]anthracycline-based, [c]anthracycline/taxane, [d]cyclophosphamide + methotrexate + fluorouracil, [e] tamoxifen, [f] aromatase inhibitors, [g]ovarian suppression (LHRH analogues)

in 72 (48%) cases. HER 2 positive tumors were found in 45 (30%) cases (HR+/HER 2+ in 13.3% and HR-/HER 2+ in 16.7%).

All patients received adequate local treatment (breast conserving surgery [BCS] or total mastectomy), plus axillary sentinel lymph node biopsy (SLNB) or complete axillary dissection. BCS was done in 62 (41.3 %) patients, while in more than half of the patients (54.7%) total mastectomy was done. Radical mastectomy according to tumor size was done in 39.1% (T1), 64.9% (T2) and 93.3% (T3), respectively. For patients with endocrine responsive disease, adjuvant endocrine therapy alone was given (combination of tamoxifen for 5 years plus LH-RH analogue for 3 years or tamoxifen alone) (Table 2).

Endocrine therapy alone, as adjuvant therapy, was administered in only 8 patients for low risk stage I breast cancer, while hormonal therapy was added to chemotherapy for stage II or III. For stage II, as adjuvant treatment, the majority of the patients (60.6%) received anthracycline-based chemotherapy ± endocrine therapy according to hormone receptor positivity, while 39.4% received anthracycline- and taxane-based chemotherapy sequentially. For stage III 75.6% of the patients received anthracycline- and taxane-based chemotherapy sequentially.

In patients at higher risk (LVI, younger age, large tumors) and/or with features of uncertain endocrine responsiveness (e.g. low levels of ER positivity, lack of PgR expression) and overexpression of HER 2, chemotherapy was added. Nearly the same number of patients received anthracycline-containing chemotherapy (47%) and anthracycline followed by taxanes (45.6%) was considered as the best option in patients with higher risk. Due to comorbidities 2 patients received classic CMF (oral cyclophosphamide, methotrexate and fluorouracil).

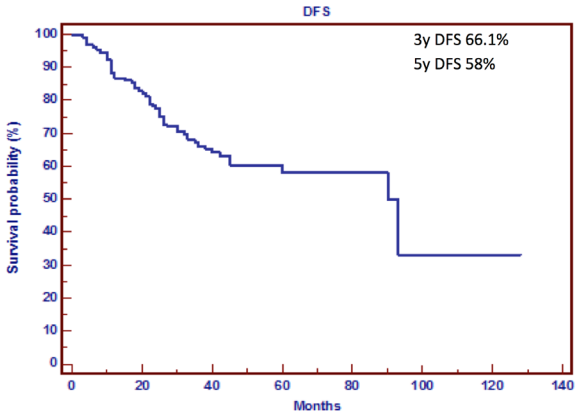

Figure 1a. Disease-free survival.

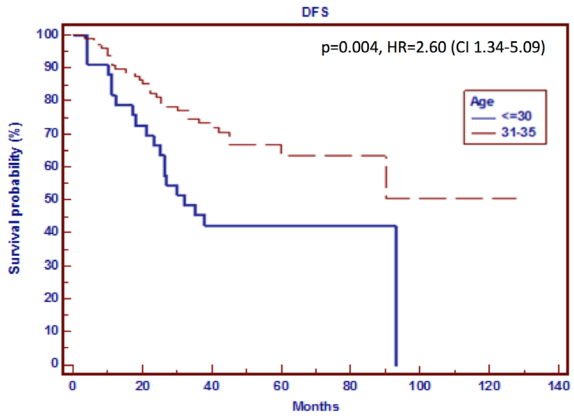

Figure 2a. Disease free survival according to patient age.

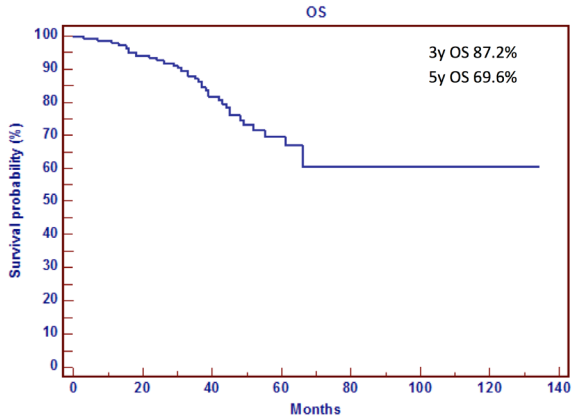

Figure 1b. Overall survival.

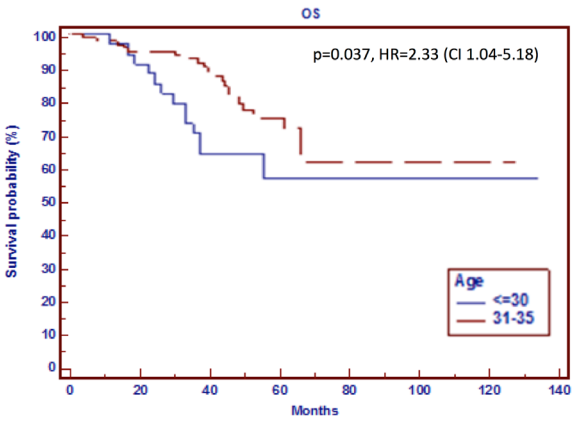

Figure 2b. Overall survival according to patient age.

Disease free survival and overall survival

After a median follow up of 44 months (range 3-134), long-term results are satisfying. The median DFS for all the patients was 90 months with 3-year DFS of 66.1% and 5-year DFS 58% (Figure 1a), while the 3-year OS was 87.2% and the 5-year OS 69.6% (Figure 1b). Patients aged ≤30 years had shorter DFS compared to patients with 31-35 years (p=0.004, Figure 2a). The difference in 3-year OS was also significant with 70.7% (≤35 years) and 91.5% (31-35 years), respectively (p=0.037, Figure 2b). No significant difference in DFS (p=0.624, HR=0.82, 95% CI 0.37-1.79) and OS (p=0.549, HR=0.75, 95% CI 0.29-1.89) was observed either in patients with ductal invasive cancer or with lobular invasive cancer (only clear ductal and lobular histologies were taken into account). The Kaplan-Meier results for DFS and OS for different tumor grades showed that the 3-year DFS rate was 72.6% in G1, 78.2% in G2 and 51.5 % in G3 tumors. The differences in DFS and OS were significant with a decreased survival associated with higher tumor grade (p=0.005 and p=0.0001, respectively). The difference in DFS and OS according to tumor size and number of positive nodes was highly significant with decreased survival associated with the larger tumor size (p=0.0019 and p<0.0001, respectively) and increasing number of nodes (p<0.0001 for both). As expected, similar situation was with stage of disease (Figure 3a,b), where 3-year OS and DFS rates were highly significant related with tumor stage (p<0.0001).

HER 2 receptor did not seem to have a prognostic influence on DFS (p=0.271, HR=1.45, 95% CI 0.74-2.82) and OS (p=0.184, HR=0.69, 95% CI 0.77-3.67). A similar situation was observed in relation to the different tumor subtypes (p=0.136 for DFS, p=0.092 for 3-year OS), while patients with HR positive tumors had a better DFS (p=0.034, HR 0.54, 95% CI 0.27-0.95) and OS (p=0.046, HR 0.47, 95% CI 0.22-0.98) than those with negative HR.

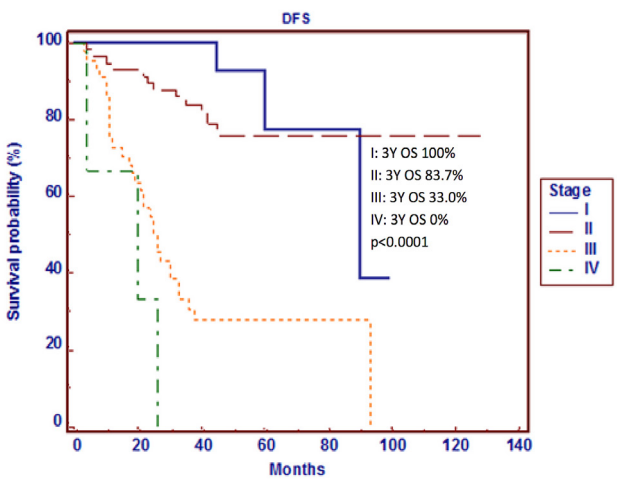

Figure 3a. Disease free survival according to stage of disease.

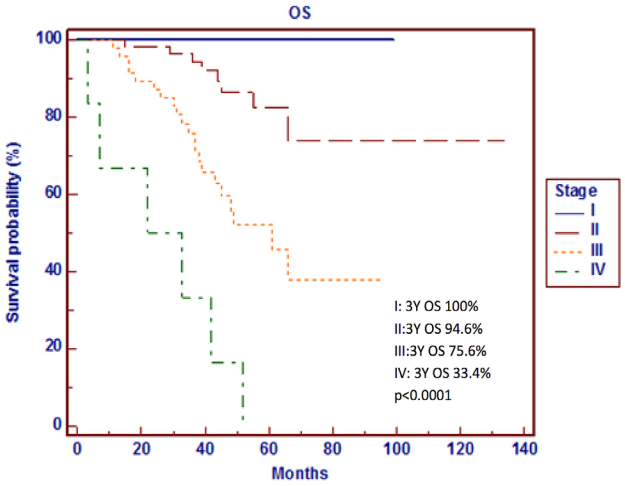

Figure 3b. Overall survival according to stage of disease.

Univariate and multivariate analyses

In univariate survival analysis, a significant difference in DFS (p=0.0003, HR=0.27, 95% CI 0.13-0.55) and OS was found between patients with or without LVI (p=0.0003, p=0.0003, HR=0.21, 95% CI 0.09-0.49).

In multivariate analysis, clinical stage and LVI positivity influenced DFS and OS in patients with higher clinical stage vs early stage (p<0.0005 for DFS; p=0.01 for OS) and in patients with LVI vs without LVI (p=0.03 for DFS; p=0.03 for OS).

Discussion

Breast cancer that develops at a young age is usually considered as a different entity from the breast cancer arising in older patients and it has been generally accepted that young age at diagnosis correlates with unfavorable prognosis and worse clinical outcome [2,13]. The tricky question is whether we really know the effect of young age on outcome. Many studies propose that this is a reflection of prognostic pathological features, such as higher grade of differentiation, presence of LVI, higher proliferation rate, lower ER or PR expression, higher HER 2 expression and also higher rates of axillary lymph node involvement and higher tumor size [14-17]. Azim et al. examined the influence of different gene expressions between different age groups on outcome and the conclusion was that gene expressions might play a crucial role in the treatment decision for young women in the future [18]. The issue remains controversial because a few studies from developing countries found that young age did not have an adverse effect on survival of breast cancer patients [19]. A recently reported population-based study from Switzerland showed no effect of young age on survival when standard of care offered to young patients, but this study had limited value because only a minority of patients (3%) were below 35 years [20]. In any case, knowing the true impact of age on outcome is necessary, because if it is actually an independent factor, then young women might benefit from more aggressive treatment than older patients with the same clinical and pathological features.

A few studies noticed that young breast cancer patients usually present with higher stage of disease than older women [15,17,21]. A retrospective study from Denmark on 10,356 women reported that 51% of the patients aged ≤35 years at diagnosis were node-positive [17], which is in line with the 56% reported in our analysis. Gajdos et al. [15], who examined 732 non-metastatic breast cancer patients from Mount Sinai Medical Center, New York, showed that 50% of patients younger than 35 years had nodal involvement, and were more likely to be diagnosed with stage II or III cancer (60%), while in our study this figure was higher, nearly 76%.

It is well established that there are at least 4 main subtypes of breast cancer based on different gene expression, and that they have a significant impact on prognosis [22,23]; however, we didn't find that different subtypes had a prognostic influence on DFS and OS. In a study conducted by Collins et al. [24] on 399 breast cancer patients below 40 years, 57% of the patients aged 31–35 years and 64% of the patients ≤30 years had high

grade tumors. In the present study 41% of the patients had high grade tumors which was independent prognostic factor for decreased DFS and OS (p=0.005 and p=0.0001, respectively). Concerning the proportion of HR positive tumors in our series, this was in line with data reported in other studies (ranging from 44% to about 60-65%) [25 ,26].

Collins et al. have reported that the very young patients (≤30 years) do not appear to have poorer prognostic features compared to young women aged 31-40 years with breast cancer [24], but our data suggests that patients ≤30 years had 3-year DFS rates of 45.75% compared to 73.45% in patients aged 31-35 years, the difference being significantly lower for DFS (p=0.004) and OS (p=0.037). Anders et al. [16] also reported no significant differences in DFS between <30, 30-34, and 35-39 years age groups. Interestingly, in the same study the authors found 367 significant gene sets among young women's tumors that specifically distinguished them from tumors arising in older women, concluding thus that breast cancer in young women is definitely a unique biologic entity. Of note, Cancello et al. found no difference in DFS (p=0.79) and OS (p=0.99) in three age groups (<25, 25-29 and 30-34) of young breast cancer patients [27].

We found a significant difference in DFS and OS rate in patients ≤30 years compared to patients aged 31-35 years. In line with our data, a recent large series of the Korean Breast Cancer Society Registration Program between 1992 and 2001 showed that patients in the <30 years age group had worse survival than patients aged 30-34 years. In the group of patients aged <35 years, the risk of death rose by 5% for every 1-year reduction in age, whereas there was no significant change in the risk of death with age in patients aged 35-50 years [7]. The results of de la Rochefordiere et al. study showed that the relationship between recurrence and age was continuous for every year of increase in age [28].

A large prospective cohort of 2,956 breast cancer patients less than 40 years diagnosed between 2000-2008 in 126 UK hospitals reported a 5-year OS of 82% [26], which is promising and higher than in our data (69.6%). At the Institut Curie in France, it was shown that even after equalizing for tumor size, nodal involvement, histological grade, HR, locoregional treatment procedure and adjuvant systemic therapy, both OS and DFS continued to be lower in the younger age group [28].

Our study has some limitations. Having no information of Ki 67 index for all of the patients we were not able to separate breast cancer subtypes, especially luminal A and luminal B. Canellos et al. [27] showed that even within subtypes, there was striking heterogeneity among tumors and different genomic features in young patients, therefore ongoing research is necessary to additionally characterize what appears to be a concrete biologic expression of breast cancer among young patients that might explain the prognostic significance of age [27]. Indeed, Anders et al. [16] demonstrated that considering treatment programs, decisions should be driven by subtype biology and performance status, and much less by age. Nowadays this might suggest that, as breast cancer continues to be better characterized at the genomic level and as therapies are selected to target molecular subtypes for individual patients, the importance of age on prognosis may eventually disappear [16].

Conclusion

In conclusion, this study showed that diagnosis of breast cancer at very young age (≤30) was associated with increased risk of death and shorter DFS than in women aged 31-35. Negative impact on survival was seen in patients with positive lymph nodes, presence of LVI, negative HRs and higher grade and stage at the time of diagnosis. These call for more aggressive treatment modalities and the need for closer monitoring and follow-up.

Young age adds extra biological complexity, which is independent of differences in breast cancer subtype distribution. The underlying biology of breast cancer in young females needs to be resolved and development of personalized treatments for this patient population is crucial. Treatment modalities for this patient group definitely need the presence of a therapeutic multidisciplinary team and also such patients should be referred to a fertility specialist as early as possible, prior to initiating systemic therapy. Therapists should not neglect that young women with breast cancer are at high risk for psychological disorders. Prophylactic contralateral mastectomies are increasingly carried out, but it is still controversial if they really improve survival. In the future, the discovery of more prognostic biomarkers and factors might weaken the correlation between age and outcome.

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