European Journal of Surgical Oncology 45 (2019) 2009–2015

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

A long-term retrospective comparative study of the oncological outcomes of 598 very young (≤35 years) and young (36–45 years) breast cancer patients

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ARTICLE INFO

Article history:
Received 31 March 2019
Received in revised form
27 May 2019
Accepted 4 June 2019
Available online 5 June 2019

Keywords:
Breast cancer
Very young breast cancer patient
Young breast cancer patient
Overall survival
Disease-free survival

ABSTRACT

Background: Breast cancer diagnosed in very young women (VYWBC; ≤35 years) and young women (YWBC; 36–45 years) tends to be heterogeneous. The current study aimed to compare the clinico-pathological characteristics and long-term clinical outcomes between YWBC and VYWBC subgroups.
Patients and methods: The institutional prospectively led database was retrospectively analysed from 2000 to 2014 at the National Institute of Oncology, Hungary. A total of 297 patients were assigned to the VYWBC group, and 301 patients were assigned to the YWBC group.
Results: The median follow-up period was 69 months for the VYWBC group and 79 months for the YWBC group. Significant differences were observed based on breast cancer subtype. The proportion of Triple-negative and ER-negative patients was higher in the VYWBC group than in the YWBC group (**P = 0.00008**). The incidence of distant metastasis was significantly higher in the VYWBC group **(P = 0.01).** Significant differences in the frequency of chemotherapy (**P = 0.049)** and endocrine therapy (**P = 0.037)** were observed between the two groups. The YWBC group exhibited significantly better overall survival (OS) and disease-free survival (DFS) rates than did the VYWBC group (**P = 0.00005** and **P = 0.00004, respectively**).
Conclusion: Breast cancers in VYWBC are biologically different from those in YWBC and tend to be more aggressive. Younger age was associated with worse OS and DFS. Young women with breast cancer should be subgrouped into VYWBC and YWBC populations, and these subgroups should be targeted by specialized clinical trials and further investigations.

Introduction

Breast cancer in young age has gained increasing attention since the 1st International Consensus Conference for Breast Cancer in Young Women (BCY1) took place in November 2012 in Dublin, Ireland, organized by the European School of Oncology (ESO) [1]. The 2nd conference (BCY2) took place in November 2014 in Dublin, Ireland, and the BCY3 took place in November 2016 in Lugano, Switzerland [2,3]. Consensus recommendations for the management of breast cancer in young women were developed, and areas

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https://doi.org/10.1016/j.ejso.2019.06.007
0748-7983/

of research priorities were identified. Young (from 36 to 45 years) and very young (≤35 years) women with breast cancer (YWBC and VYWBC, respectively) have become a more recent focus, with improvements in diagnosis, treatment, and survivorship [4,5]. According to the literature controversy exists about the definition of very young and young breast cancer and different cut-off have been proposed, it has been shown that younger age is associated with a less favourable prognosis. These findings suggest that young women with breast cancer should be subgrouped into very young and young women populations. The cut-off for young age differed between studies according to the literature and it is unclear whether the survival-age relationship is a linear function across age in premenopausal women. According to the study Han et al. the risk of death rose by 5% for every 1-year reduction in age for patients aged <35 years, whereas there was no significant correlation between risk of death and age for patients aged 35–50 years [6]. VYWBC are more likely to be diagnosed with more aggressive forms of cancer and have a higher mortality rate than older breast cancer patients [7]. Approximately 6.5% of all breast cancers are diagnosed in women <40 years of age, 2.4% are diagnosed in women under the age of 35 and 1% is diagnosed in women under30 years [8].

According to case-control studies, the likelihood that VYWBC had a detectable *BRCA1/2* mutation was 9.4% (compared to a population prevalence of 0.2%) [9,10]. In BRCA1/2 mutation carriers, the breast cancer incidences increased rapidly in early adulthood, 10 years earlier for *BRCA1* carriers, then plateaued to remain relatively constant throughout the remaining lifetime [11], therefore *BRCA1/2*-related inherited syndrome (Hereditary Breast- Ovarian Cancer Syndrome, HBOC) should be considered when developing treatment algorithms for these subgroups. Multimodality treatments such as chemotherapy, endocrine therapy, and local therapies have the potential to significantly impact both the physiologic and psychological health of YWBC and VYWBC as they face a diagnosis of breast cancer. The differences in epidemiology and management options, the unique issues surrounding fertility, sexuality, and pregnancy, and the multidisciplinary approach for the treatment of these two subgroups may also frequently incorporate individuals with other areas of expertise, such as surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, clinical geneticists, gynaecologists, social workers, and plastic surgeons [12,13].

Breast cancer in young women tends to develop as more aggressive subtypes (more triple-negative (TN) and more human epidermal growth factor receptor 2 (HER2)-positive disease), presents with a more advanced disease stage at diagnosis and requires individualized treatment plans [14–16]. Mammographic diagnosis in this population is challenging due to increased breast density. Poor sensitivity may lead to missed or misinterpreted lesions in women with dense breast tissue. Therefore, breast cancer in young women usually presents with breast complaints, and clinicians frequently fail to address the possible malignant behaviour of a palpable mass. Women younger than 45 years are less likely to have lower grade breast cancer and are more likely to have oestrogen receptor-negative tumours, nodal metastasis, and larger primary breast tumours [14]. Young age, as a well-known prognostic and predictive factor also impacts local recurrence and overall survival. An analysis of two trial groups, the European Organization for Research and Treatment of Cancer (EORTC) and the National Surgical Adjuvant Breast and Bowel Project (NSABP), revealed a higher risk of local recurrence in patients younger than 35 years [17,18]. Overall survival is also affected in women diagnosed when they are younger than 40 years. Studies have shown higher mortality rates in these subgroups [19].

These differences in breast cancer risk factors, tumour characteristics, and clinical outcomes suggest that breast cancer arising in very young and young women may be a distinct clinical entity. There is only limited data about the clinicopathological differences and outcomes between these subgroups.

The purpose of this study was to compare the clinicopathological characteristics and long-term clinical outcomes between the YWBC and VYWBC subgroups and present the evidence that younger age presents a worse prognosis.

Patients and methods

The current study was performed in accordance with the Research Ethics Committee of the National Institute of Oncology, Hungary (NIO). Written informed consent was always obtained for data collection. The inclusion period was from 1 January 2000 through 31 May 2014. Data were collected from the prospectively led database of the NIO, Budapest. Patients aged ≤35 years were grouped into the VYWBC group, and patents aged between 36 and 45 years were grouped into the YWBC group in a prospectively led database.

According to the updated international European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up, all patients received multimodality oncology treatments and a follow-up at the NIO during the investigation period [20–25]. The diagnosis of breast cancer was based on clinical examination in combination with imaging (mammogram, breast and regional lymph node ultrasound) and was confirmed via pathological (core biopsy or fine-needle aspiration cytology) assessment. MRI was used in most cases because the sensitivity of a mammogram is low in these populations due to the increased density of a young woman's breasts [26]. MRI was also used in cases of breast implants, invasive lobular carcinoma (ILC), the suspicion of multifocality/multicentricity, or large discrepancies between conventional imaging and the clinical examination.

For surgical procedures, breast-conserving surgery (BCS), mastectomy, and sentinel lymph node biopsy (SLNB) with the dual radio-colloid/blue dye technique were used. In sentinel lymph node (SLN)-positive cases or for clinically positive axillary lymph nodes, axillary lymph node dissection (ALND) was performed. In the case of BCS, palpable tumours were resected via a wide excision, and non-palpable tumours were resected via a wide excision using the radio-guided occult lesion localization (ROLL) technique, with a minimum microscopic surgical margin of 1 mm for both invasive and in situ breast cancers. Postoperative pathological assessments included the number, location and size of the tumours removed, the total number of removed and positive lymph nodes, and the extent of metastases in the lymph nodes, such as isolated tumour cells, micrometastases (0.2–2 mm) and macrometastases. The report included the histological type and grade of the tumour, evaluation of the resection margins, vascular invasion, and a biomarker analysis, which included an immunohistochemical (IHC) evaluation of oestrogen receptors (ERs), progesterone receptors (PRs) and HER2 gene expression. HER2 gene amplification for tumours with an ambiguous (2+) IHC score was evaluated using a fluorescent in situ hybridization (FISH) technique. The institutional breast cancer classification into surrogate intrinsic subtypes was based on the IHC assessment of ER, HER2 and Ki67, with a 20% cut-off during the investigation period. Surrogate breast cancer subtypes were classified according to the description of Perou et al. [27]For the purposes of prognostication and treatment decision making, tumours were grouped into surrogate intrinsic subtypes, as defined by routine histology and IHC data [28].

Patients were tested by appropriate routine diagnostic processes to detect any mutation in highly penetrant genes, namely, *BRCA*1 or *BRCA*2 cancer predisposition genes routinely from 2009

according to the ESMO recommendation [29]. The current study was approved by the Institutional Review Board at the NIO. Informed consent was obtained from all patients. Germline DNA was extracted by a standard procedure from the blood of patients diagnosed with breast cancer at the NIO. In Hungary, genetic testing for the presence of germline mutations of *BRCA1/2* genes has been conducted at the Department of Molecular Genetics, National Institute of Oncology since 1995 [30–32]. *Sanger sequencing* (1995-present), *denaturing high-performance liquid chromatography* (DHPLC) (2004–2012), and *multiplex ligation-dependent probe amplification* (MLPA) (2004-present) were the molecular diagnostic methods used. From 1995 to 2004 samples were pre-screened by *heteroduplex analysis* (HDA) or *Single-Strand Conformation Polymorphism* (SSCP) analysis, but mutations were identified by *Sanger sequencing* or MLPA. From 2013 onward, next-generation sequencing (NGS) is performed on a MiSeq instrument (Illumina Inc., San Diego, CA) using the platform-installed MiSeq Reporter's workflow. Women were offered testing if their family and personal history fulfilled the selection criteria of Breast Cancer Linkage Consortium or NCCN Clinical Practice Guidelines for Genetic/Familial High-Risk Assessment [30–32]. [33].

During the investigated period and according to the updated international European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up, the chemotherapy regimen was based on FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide) and taxanes. Chemotherapy was indicated in triple-negative, HER2-positive breast cancers and in high-risk luminal HER2-negative tumours. Depending on the individual recurrence risk and the selected regimen, chemotherapy was usually administered for six cycles. Endocrine therapy (ET) was based on tamoxifen or aromatase inhibitors with an LHRH agonist in luminal cases for five years after the surgery. After 2005, all HER2-positive patients with pT1c or larger tumours received adjuvant trastuzumab therapy, which was administered once per week during treatment with other chemotherapy medications and then once every 3 weeks after treatment with the other medications for up to 52 weeks. Radiotherapy (RT) was performed using CT-based three-dimensional treatment planning. The adjuvant radiotherapy started 4–8 weeks after surgeryor 3–4 weeks after adjuvant chemotherapy. Patients who received BCS were given whole breast radiotherapy and tumour bed boost irradiation. Postmastectomy radiotherapy (PMRT) to the chest wall was administered to patients with pT3–T4 pN0-1mi tumours. Locoregional PMRT was indicated for patients with lymph node metastatases >2 mm (pN1a, pN2a, pN3a). Doses used for local and/or regional adjuvant irradiation were 50 Gy in 25 fractions of 2.0 Gy with a typical boost dose of 16 Gy in 2 Gy single doses.

Medical records and pathology reports were reviewed, and information on the HER2, ER and PR status of the patients, as well as data on the age at diagnosis, histological grade, stage, and other clinical covariates, was collected from the institutional database retrospectively. The TNM classification was defined by the American Joint Cancer Committee (AJCC) and the Union for International Cancer Control (UICC) Breast Cancer Staging 7th Edition [34].

Patients with missing information were excluded. All patients were followed up, and their status was checked from their medical records. The follow-up period was managed by regular visits with physical examinations every 3 months during the first 2 years, every 6 months from years 3–5, and annually thereafter. Annual mammography with ultrasound was performed. For cases of local, regional or distant relapse suspicion in the CT scan, PET/CT scans or MRI was used. For *BRCA* mutation holders, mammography, ultrasonography and breast MRI was alternated every six months.

Overall survival (OS) and disease-free survival (DFS) were calculated from the date of surgery until the date of death and the diagnosis of the first locoregional or systemic recurrence, respectively. In cases of incomplete events, OS and DFS were calculated for the entire investigated period until the last visit. Survival analyses were performed using the Kaplan-Meier method. The comparison between survival functions for different strata was assessed with log-rank statistics. Qualitative variables are expressed as a number and percentage, and quantitative variables are expressed as the median with minimum and maximum values. For the comparison of qualitative data, a chi-square test or Fisher's exact test was applied. Asymmetric numerical data were analysed using a Mann-Whitney test. Statistical significance was confirmed when P values were <0.05. Data analysis was performed using Statistica 13.4 (TIBCO Software Inc., Palo Alto, CA) and PAST version 1.86b [35].

Results

During the investigation period, a total of 420 patients were assigned to the VYWBC group, and 390 patients were assigned to the YWBC group. Patients with missing information or those who were lost to follow-up were excluded. In total, we analysed data from 297 patients in the VYWBC group and 301 patients in the YWBC group. The median follow-up period was 69 months (range, 1–198 months) for the VYWBC group and 79 months (range, 1–170 months) for the YWBC group. The general characteristics of the two groups are presented in Table 1. Significant differences in the clinical characteristics were observed based on breast cancer subtype (**$P = 0.00008$**). The proportion of TN patients was higher in the VYWBC group than in the YWBC group. The proportion of luminal A type tumours was significantly higher than the luminal B type tumours in the YWBC group compared to the VYWBC group (Table 1). Significant differences in ER % **($P < 0.000001$)**, PR % **($P < 0.000001$)**, HER2 status **($P = 0.017$)** and Ki67 value **($P < 0.000001$)** were observed between the two groups (Fig. 1) (Table 1). Significant differences only in the frequency of chemotherapy and endocrine therapy were observed (Table 2**)**.

Positive family history was noted in 88 (29.6%) patients in the VYWBC group and in 87 (28.9%) patients in the YWBC group, although the difference was not significant. *BRCA* mutation testing was performed only in 35.3% ($n = 105$) of patients in the VYWBC group and 24.2% ($n = 73$) patients in the YWBC group (Table 1).

The YWBC group exhibited significantly better OS rates than did the VYWBC group (**$P = 0.00005$**; log-rank) (Fig. 2). The *BRCA 1/2* mutation holders did not exhibit significantly worse OS or DFS rates than those with negative results (**$P = 0.749$**; log-rank) (Fig. 3).The YWBC group exhibited significantly better DFS rates than did the VYWBC group (**$P = 0.00004$**; log-rank) (Fig. 4).

Discussion

Compared to young breast cancer patients, very young breast cancer patients have poorer outcomes, which are in part attributed to more aggressive tumours and less favourable tumour subtypes [16]. The current study showed a significantly higher mortality rate among women ≤35 years of age compared with women 36–45 years of age. Very young women in our study were not diagnosed with more advanced pT and pN disease compared with young women, but the frequency of distant metastasises was significantly higher in the younger group. According to a Danish study designed by Kroman et al. [36], where data from 10356 premenopausal women with breast cancer were analysed, the frequency of the pT1 category was lower in women aged under35 years than in women aged 35–45 years (49.7% vs. 54.7%), and the frequency of the pT2 category was higher in the younger group (38.1% vs. 34.3%). In our study, the rates of pT1 and pT2 categories in VYWBC vs. YWBC were

Table 1
The general characteristics of the VYWBC and YWBC groups.

	VYWBC group, n (%)	YWBC group, n (%)	P value
Median age (range)	33 ys (20–35)	40 ys (36–45)	**<0.01**[a]
Median follow-up (range)	69 ys (1–198)	79 ys (1–170)	**0.136**[a]
pT category			**0.16**[b]
pTis	18 (6%)	20 (6.7%)	
pT0	17 (5.8%)	6 (1.9%)	
pTmi	3 (1%)	5 (1.6%)	
pT1	116 (39%)	138 (45.9%)	
pT2	101 (34%)	98 (32.6%)	
pT3	33 (11.1%)	30 (9.9%)	
pT4	8 (2.8%)	4 (1.4%)	
NA	1 (0.3%)	0 (0%)	
pN category			**0.135**[b]
pN0	148 (49.9%)	158 (52.5%)	
pNmi	10 (3.3%)	7 (2.3%)	
pN1	77 (25.9%)	87 (28.9%)	
pN2	47 (15.9%)	28 (9.3%)	
pN3	14 (4.7%)	19 (6.4%)	
NA	1 (0.3%)	2 (0.6%)	
M status at the time of diagnosis			**0.01**[c]
M0	286 (96.3%)	300 (99.7%)	
M1	9 (3%)	1 (0.3%)	
Histological grade			**0.004**[b]
Grade I	11 (3.7%)	32 (10.7%)	
Grade II	76 (25.6%)	98 (32.5%)	
Grade III	151 (50.8%)	142 (47.2%)	
NA	59 (19.9%)	29 (9.6%)	
BRCA 1/2 mutation testing	105 (35.3%)	73 (24.2%)	**0.045**[b]
BRCA 1/2-positive	41 (39.0%)	18 (24.7%)	
BRCA 1/2-negative	64 (61.0%)	55 (75.3%)	
BRCA 1 carriers	31 (29.5%)	4 (5.5%)	**0.132**[b]
BRCA 2 carriers	10 (9.5%%)	14 (19.2%)	
BRCA 1/2-negative	64 (61.0%)	55 (75.3%)	
HER2 expression			**0.6761** [b]
HER2-negative	228 (76.8%)	224 (74.5%)	
HER2-positive	60 (20.2%)	54 (17.9%)	
NA	9 (3%)	23 (7.6%)	
IHC surrogate subtypes			**0.00008**[b]
Luminal A	87 (29.3%)	143 (47.6%)	
Luminal B (Ki67 > 20%)	58 (19.5%)	48 (15.9%)	
Luminal B (HER-2+, ER/PR+)	35 (11.8%)	32 (10.7%)	
Triple-negative	92 (31%)	51 (16.9%)	
HER2 +, ER-, PR-	25 (8.4%)	22 (7.3%)	
NA	0 (0%)	5 (1.6%)	

ys: years.
IHC: immunohistochemical.
HER2: human epidermal growth factor 2.
ER: oestrogen receptor.
PR: progesterone receptor.
NA: not available.
[a] Mann-Whitney tes**t**.
[b] Chi-square test.
[c] Fisher's exact test.

similar to that observed in the Danish study (39% vs. 45.8% and 34% vs. 32.5%, respectively). According to our statistics, the incidence of pT3 tumours was higher in both subgroups compared to those described in the Danish study (11.1% vs. 8% for very young women and 9.9% vs. 7.7% for young women). Our results are also comparable to a Swedish study designed by Fredholm [15], where data from 22017 women with breast cancer were analysed, and the incidence of pT1, pT2 and pT3 tumours in women aged under 35 years and women aged 35–39 years (pT1: 46.1% vs. 53. 7%; pT2: 36.5% vs. 33.6%, pT3: 7.4% vs. 6.6%) showed similar trends to our results.

According to our findings, the incidence of regional lymph node involvement did not show a significant difference between the two groups. The incidence of negative lymph nodes was 49.8% in the very young group and 52.4% in the young group, which is comparable to the Danish (45.1% vs. 51.1%, respectively) and Swedish (49.7% vs. 47.8%, respectively) studies [15,36].Histological grade was significantly less favourable in the VYWBC group compared to the YWBC group (Table 1). Similar results were observed in the Swedish study, where the amount of grade I tumours was less than 10% in both groups (3% and 4.9%) [15].

Only minorities of the patient were tested for *BRCA* that is a limitation of the study and no significant conclusion can be drawn. Despite of the low rate of genetic testing, differences in *BRCA* genotyping data of the two age groups were detected. The incidence of *BRCA* mutations was significantly higher in VYWBC, and

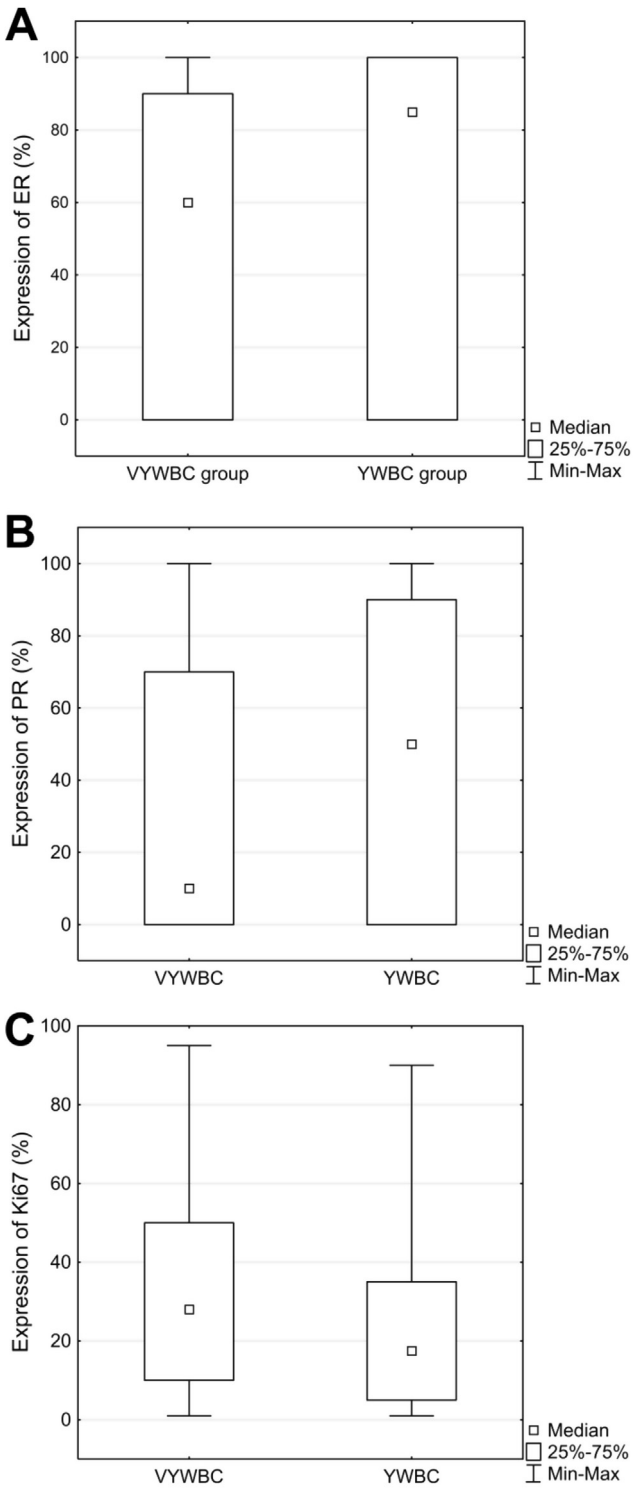

Fig. 1. Significant differences in ER %, PR % and Ki67 value between the two groups. A: P < 0.000001 Mann-Whitney B: P < 0.000001 Mann-Whitney C: P < 0.000001 Mann-Whitney.

BRCA 1 mutations were mainly diagnosed in this subgroup (Table 1). According to our findings, the *BRCA* mutation carriers did not show worse OS or DFS compared to non-holders (Fig. 3a and b). Similar results were concluded in a recent study designed by Copson et al. [37].

The VYWBC group had tumours characterized by more unfavourable biological parameters compared to the YWBC group. VYWBC had tumours that were more likely to be of a higher grade, ER-negative, PR-negative and with a higher Ki67 value (Table 1) (Fig. 1). According to the Danish and Swedish studies, women aged older than 35 years presented higher ER-positive rates compared to younger women (57.8% vs 51.2% and 60.3% vs. 46.5%) [15,36] According to our results, the VYWBC group presented less favourable subtypes with varying prognostic implications that are associated with more aggressive tumours and a poorer prognosis [14,38–40]. The basal-like subtype has been associated with poor clinical outcomes, possibly attributed to its high proliferative capacity, lack of oestrogen receptors, and over-expression of HER2, while the luminal A subtype has been shown to have the best prognosis [14]. Contrary according to the study of Cancello et al. very young patients with Triple Negative, Luminal B or HER2-positive breast cancer have a worse prognosis when compared with older patients with similar characteristics of disease [7].

According to our results, VYWBC exhibited significantly lower OS and DFS rates (Figs. 2 and 4). Anders et al. found similar trends in which tumours in young women have lower ER positivity and a trend towards inferior DFS [14]. All of these studies support the concept that tumours developing in VYWBC are biologically different from tumours in YWBC and tend to be more aggressive

Table 2
Differences in therapies between the VYWBC and YWBC groups.

	VYWBC Group, n (%)	YWBC Group, n (%)	P value
Chemotherapy			
Given	218 (73.5%)	201 (66.7%)	**0.049**[a]
Not given	76 (25.5%)	100 (33.3%)	
NA	3 (1%)	0 (0%)	
Radiotherapy			
Given	222 (74.8%)	236 (78.5%)	**0.402**[a]
Not given	72 (24.2%)	65 (21.5%)	
NA	3 (1%)	0 (0%)	
Endocrine therapy			
Given	169 (57%)	198 (65.7%)	**0.037**[a]
Not given	125 (42%)	103 (34.3%)	
NA	3 (1%)	0 (0%)	
Surgery			
BCS	144 (48.4%)	166 (55.1%)	**0.103**[a]
Mastectomy	153 (51.6%)	135 (44.9%)	

BCS: breast-conserving surgery.
NA: not available.
[a] Chi-square test.

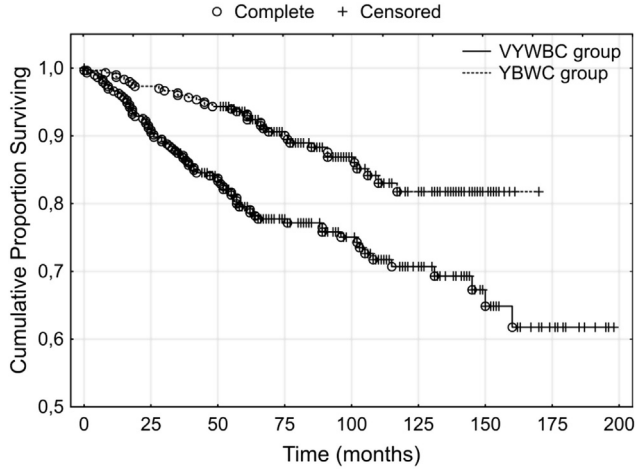

Fig. 2. *Kaplan-Meier curve for the OS of the VYWBC and YWBC groups* (P = 0.00005**; log-rank**).

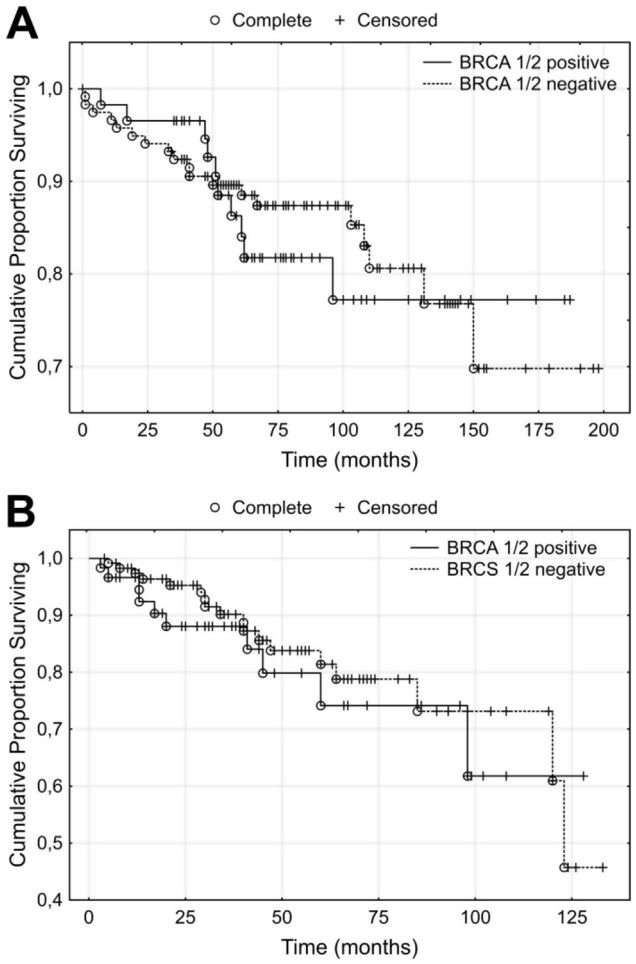

Fig. 3. Kaplan-Meier curve for the OS of the BRCA1/2 mutation positive and negative groups (**P = 0.749**; log-rank) Kaplan-Meier curve for the DFS of the BRCA1/2 mutation positive and negative groups (***P = 0.845****; log-rank)*..

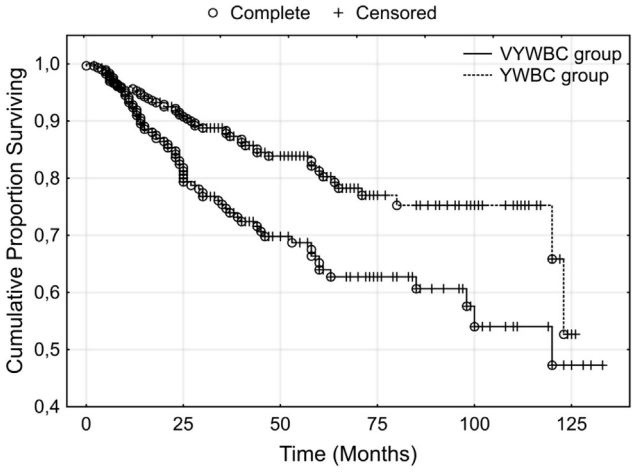

Fig. 4. Kaplan-Meier curve for the DFS of the VYWBC and YWBC groups.

with unfavourable biological markers, which portend a poor prognosis [27,41–43].

There are some limitations to our study, which are inherent to any retrospective cohort study. Although the VYWBC group received significantly more aggressive multimodality therapies, the survival rates were worse than those in the YWBC group. Another limitation is the low rate of genetic testing, such as *BRCA 1* or *BRCA 2* mutations, and the lack of data on behavioural risk factors (e.g., physical activity, smoking, alcohol consumption, and use of hormone replacement therapy).

Conclusions

In conclusion, we found that the VYWBC group was not diagnosed at a more advanced pT and pN category of disease compared with the YWBC group. The incidence of distant metastases was significantly higher in the VYWBC group. Tumours in the VYWBC group were characterized by more unfavourable biological parameters (more likely a higher grade, ER-negative, PR-negative and a higher Ki67 value). Despite the more frequent use of chemotherapy and endocrine therapy in the VYWBC group, the diagnosis of breast cancer at a younger age was associated with inferior OS and DFS rates. The VYWBC group presented a worse prognosis than the YWBC group. Our results support the concept that tumours developing in VYWBC are biologically different from tumours in YWBC and tend to be more aggressive with unfavourable biological markers, which portend a poorer prognosis. These results suggest that young women with breast cancer should be subgrouped into very young and young women populations. VYWBC should be regarded as higher-risk patients with a worse prognosis and decreased OS and DFS rates. VYWBC and YWBC, as different subgroups, should be targeted by specialized multicentre clinical trials and further investigations.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.007.

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