

RESEARCH ARTICLE

Breast Cancer at Extreme Ages - a Comparative Analysis in Chile

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Abstract

Background: Young onset breast cancer (BC) has a worse outcome as compared to in the elderly. However, some studies have shown that BC in the elderly, despite indolent features, does also cause increase in mortality. In an attempt to compare clinic-pathological characteristics, BC subtypes and survival in patients with BC presenting at extremes of age, we performed a retrospective study. **Materials and Methods:** Patients were either ≤ 40 or ≥ 70 years old. Subtypes were defined using immunohistochemistry and histological grade. Chi-Square test was used for evaluation of categorical variables, and Kaplan-meier and log-rank for disease-specific survival (DSS) and disease free survival (DFS). **Results:** We analyzed 256 patients ≤ 40 and 366 patients ≥ 70 . Younger patients presented with more aggressive disease, with less luminal A but more luminal B and triple negative (TN) subtype. With a median follow-up of 57.5 months, DFS at 5 years in younger patients was 72.3% vs 84.6% in the elderly ($p=0.007$). Luminal A and B disease presented with worse DFS in younger patients. The opposite was seen in the TN subgroup. Although we found no significant differences in DSS, older patients with TN tumors died of BC more frequently. This group also received less chemotherapy. **Conclusions:** Young patients present with more aggressive disease, this translating into worse DFS. However, elderly patients with TN disease represent a particular subpopulation with worse DFS and DSS, suggesting that chemotherapy should not be withheld only because of age.

Keywords: Breast neoplasm - age of onset - aged - young onset - premenopause - chemotherapy

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Introduction

BC is the leading cause of cancer death in Chilean women (www.deis.cl). Early diagnosis and better treatment options have resulted in a systematic decline in mortality from this disease in the last decades (Berry et al., 2005). Unfortunately, many patients are not treated appropriately, with some being over treated and others undertreated. Many clinical and pathological prognostic factors have been described in BC, those factors allows us to identify tumors with the greatest risk to relapse (Cianfrocca and Goldstein, 2004).

Age is considered an important prognostic factor in BC patients (Adami et al., 1985; Kroman et al., 2000). Young onset BC has a more aggressive behavior, with a worse clinical outcome compared with older women (Vollmer, 1996; Anders et al., 2009). Based upon multiple retrospective analyses showing the unfavorable impact of young age over BC prognosis, some consensus guidelines have included age less than 35 years as the only risk factor to consider adjuvant systemic chemotherapy irrespective of other tumor characteristics (Goldhirsch et al., 2007). On the other side, there are multiple studies demonstrating that BC in elderly, in spite of having a biologically indolent disease (Morrison et al., 2012), may also have an increase

in mortality compared to younger patients (Morrow, 1994). The latter may be attributed to an advanced stage at diagnosis, higher comorbidity and the fact that elderly patients are treated less aggressively than the younger counterpart (Singh et al., 2004; Schonberg et al., 2010; Van Leeuwen et al., 2011).

In an attempt to evaluate the prognostic value of established clinical and pathological subtypes in young BC patients and its comparison with the same defined clinico-pathological subtypes in elderly women, we performed a retrospective study in our institution.

Materials and Methods

This is a retrospective study performed at the Cancer Center of Pontificia Universidad Catolica de Chile in Santiago, Chile, and approved by our local Ethics Committee.

We recruited all patients diagnosed with BC in our institution from 1997 to 2013. Inclusion criteria were: (i) age at time of diagnosis either less than 41 or more than 69 years old and (ii) invasive breast carcinoma.

Epidemiological and clinical data were extracted from the medical records. Vital status was obtained from the Civil Registry of Chile. Pathological reports were review

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regarding histological type, tumor size, HG (according to Elston and Ellis) (Elston and Ellis, 1991), and nodal compromise.

Status of estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor type 2 (HER2) were determined by immunohistochemistry (IHC). The cutoff value to determine if ER and PR were positive was $\geq 1\%$ of tumor cells with nuclear staining. Tumors with HER2 score of 3+ were considered positive. If the HER2 grading was reported as 2+, fluorescence in situ hybridization (FISH) study was done in the majority of cases (this study was not compulsory in our center until 2006). Since we don't routinely perform the Ki67 study, we decided not to include it in the analysis.

Tumors were classified into 4 subtypes according to IHC markers (Table 1): Luminal A (ER positive and / or PR positive, HG 1-2, HER2 negative), luminal B (ER positive and/or PR positive, HG 3 and/or HER2 positive), TN (ER, PR and HER negative), HER2-enriched (ER and

Table 1. Tumors were Classified into 4 Subtypes According to ER, PR, HER2 and HG

Molecular Subtype	Definition
Luminal A	ER and/or PR (+); HER-2(-); HG 1-2
Luminal B	ER and/or PR (+); HER-2 (-) plus HG3 or HER-2 (+) independent of HG
HER-2	ER and PR (-); HER-2 (+) independent of HG
Triple negative	ER, PR and HER-2 (-), independent of HG

*ER: estrogen receptor; PR: progesterone receptor; HER-2: Human epidermal growth factor receptor type 2; HG: histological grade; HR: hormonal receptor

Table 2. Comparison of Pathological and Clinical Characteristics between Patients ≤ 40 and ≥ 70 Years Old

	≤ 40 years (n=256)		≥ 70 years (n=366)		p
AGE median (range)	36.0 (19-40)		75.5 (70-101)		
HISTOLOGY					<0.0001*
Ductal	220/252	87.30%	259/356	72.80%	
Lobulillar	8/252	3.20%	42/356	11.80%	
Other	24/252	9.50%	55/356	15.40%	
TUMOR SIZE (cm)					0.03*
Median (Range)	2.2 (0.1-12.6)		2.5 (0.1-14.0)		
LYMPHNODE METASTASIS					
YES	146/235	62.10%	135/316	42.70%	<0.0001*
RATIO compromised/resected	0.13		0.23		0.005*
TNM STAGE					0.001*
I	45/240	18.80%	107/332	32.20%	
II	108/240	45.00%	133/332	40.10%	
III	75/240	31.30%	66/332	19.90%	
IV	12/240	5.00%	26/332	7.80%	
HISTOLOGICAL GRADE					<0.0001*
1	14/221	6.30%	48/304	15.80%	
2	78/221	35.30%	121/304	39.80%	
3	129/221	58.40%	135/304	44.40%	
IMMUNOHISTOCHEMISTRY					
Hormonal Receptor Positive	187/241	77.60%	289/347	83.30%	0.05*
HER-2 overexpression	46/210	21.60%	37/294	12.60%	0.007*
TREATMENT					
Total Mastectomy	110/239	46.00%	119/325	36.60%	0.03*
Axillary Dissection	176/235	74.90%	193/311	62.10%	0.002*
Radiation Therapy	166/192	86.50%	201/254	79.10%	0.02*
Chemotherapy	197/225	87.60%	57/270	21.10%	<0.0001*

*Difference is statistically significant

PR negative, HER2 positive).

Statistical analysis and outcomes

Categorical variables were analyzed using Chi-Square or Fisher exact test. Wilcoxon test was used to compare medians. Multivariate analysis was performed through a COX logistic regression. Overall survival (OS) was defined as the time since diagnosis (first biopsy) to death of any cause. In order to better visualize the impact of age in mortality due to BC, we calculated the Age-Cause-Specific Death (ACSD) Ratio. DSS was defined as the time since first biopsy to death due to BC. We also calculated DFS and metastasis free survival (MFS) defined as the time since diagnosis to either any first recurrence or a systemic recurrence, respectively. Survival was calculated according to Kaplan-Meier curves, and compared using log-rank test. In case the hazards turned out to be non-proportional (crossed survival curves), Breslow test was used.

In the survival analysis we decided to exclude patients with stage IV disease at diagnosis.

Statistically significant difference was considered with p value < 0.05. All data were analyzed using IBM® SPSS® version 21 program.

Results

From January 1997 to December 2013, 2023 patients with BC were diagnosed at our institution. 256 patients (12.6%) were younger than 40 and 366 (18.0%) older than 70 years old. The median age at diagnosis was 54, 9 (19-95).

The characteristics and distribution of the clinico-pathological subtypes of these 622 patients included in the analysis are reported in Table 2. The median age of the younger and the older group was 36.0 (19-40) and 75.5 (70-101), respectively.

Younger patients presented with smaller tumor size (2.2 vs 2.5 cms, $p=0.032$), but with more lymph node compromise rates (62.1% vs 42.7%, $p<0.0001$) and more advanced stage at presentation (stage I: 18.8% vs 32.2%; stage III 31.3% vs 19.9%, $p=0.001$). Considering only patients with nodal compromise, the median number of positive nodes was 2 and 3 in the younger and older group respectively, although this difference was not statistically different ($p=0.23$). Also, the younger group presented with a lower ratio between the compromise and resected lymph nodes (13 vs 23%, $p=0.005$).

As shown in Table 2, older patients underwent to total mastectomy and axillary dissection less frequently than younger patients (36.6% vs 46.0%, $p=0.03$ and 62.1% vs 74.9%, $p=0.002$). Most young patients received chemotherapy: 87, 6% compared to 21, 1% in the older group ($p<0.0001$). Nearly all of the cytotoxic treatment in the former group was based on anthracyclines (93.2%) compared to 72, 2% in the elderly patients ($p=0.001$). In the latter population, the CMF (cyclophosphamide, methotrexate, fluorouracil) scheme was more frequently used (22.2 vs 2.7%, $p=0.001$). Older patients with BC also received less frequently radiation therapy 40 (79.1% vs 86.5%, $p=0.02$).

The most common histological type was ductal invasive carcinoma: 87.3% and 72.8% in the younger and older group, respectively. The lobulillar subtype was more frequent in the latter ($p<0.0001$).

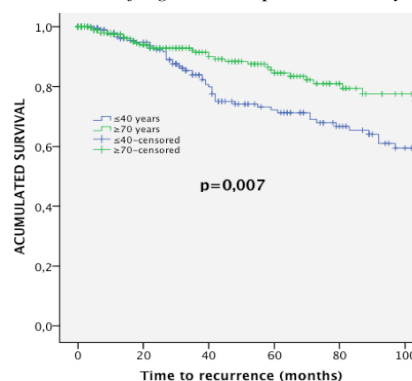


Figure 1. Disease Free Survival Comparison in Breast Cancer Patients ≤ 40 vs ≥ 70 Years Old

Younger patients presented with higher frequency of high-grade tumors (grade 1, 6.3% vs 15.8%; grade 3, 58.4% vs 44.4%, $p<0.0001$), higher HER-2 over-expression (21,6% vs 12,6%, $p=0.007$) and less ER expression (77.6% vs 83.3%, $p=0.05$).

Regarding subtype (Table 3), less luminal A (33.2% vs 49.0%) but more luminal B (43.0% vs 33.3%) and TN (17.8% vs 11.7%) were observed in the younger group ($p=0.003$) compared to the older counterpart. There was no difference in the HER-2 enriched population.

Survival data are shown in Table 4. With a median follow up of 56.0 months (1-210), recurrences occurred more frequently in the younger group (25.8% vs 11.7%, $p=0.0001$). The DFS at 5 years in this group was 72.3% (± 3.9), compared to 84,6% (± 3.0) in the older population ($p=0.007$) (Figure 1). The magnitude of this difference was wider in luminal A disease but still significant in luminal B population (Figure 2A-B). Conversely, when

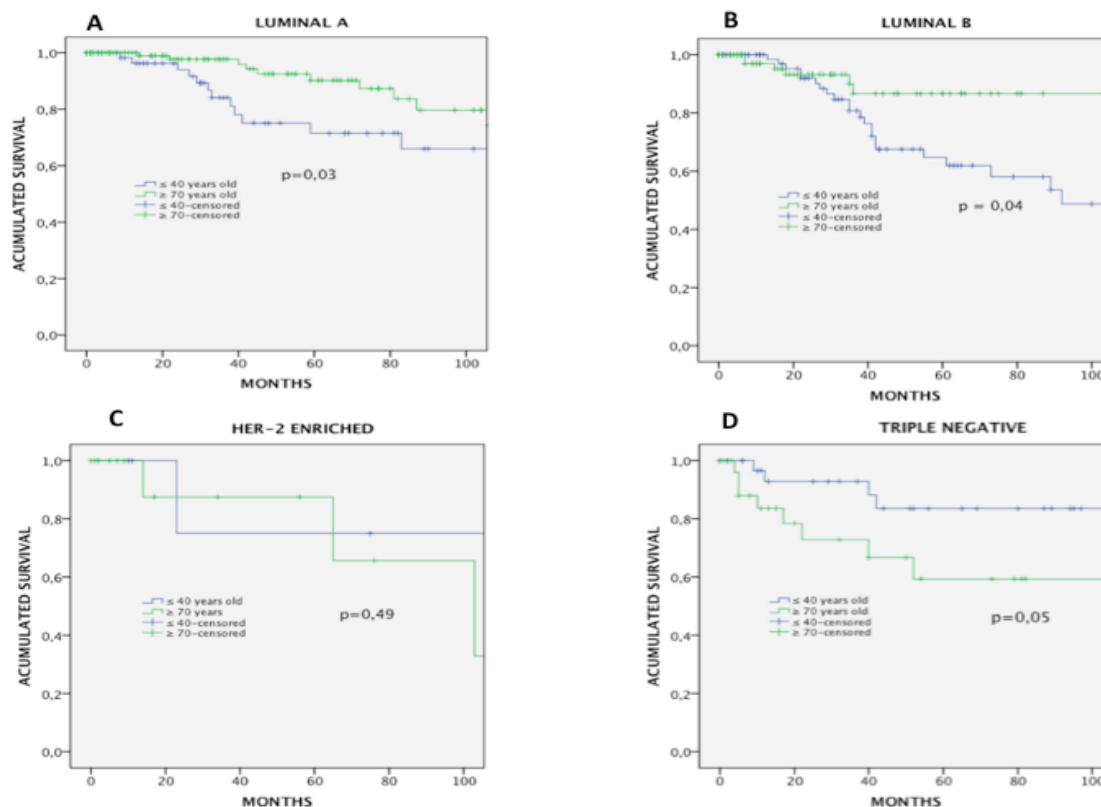


Figure 2. Disease Free Survival Curves in Patients with Breast Cancer ≤ 40 Vs ≥ 70 Years Old According to Subtype. (A) Luminal A; (B) Luminal B; (C) HER-2 enriched; (D) Triple negative

Table 3. Comparison of Molecular Subtypes between Patients ≤ 40 and ≥ 70 Years Old.

	≤ 40 years (n=214)		≥ 70 years (n=300)		p
Luminal A	71/214	33.20%	147/300	49.00%	0.003*
Luminal B	92/214	43.00%	100/300	33.30%	
Triple Negative	38/214	17.80%	35/300	11.70%	
HER2-enriched	13/214	6.10%	18/300	6.00%	

*Difference is statistically significant

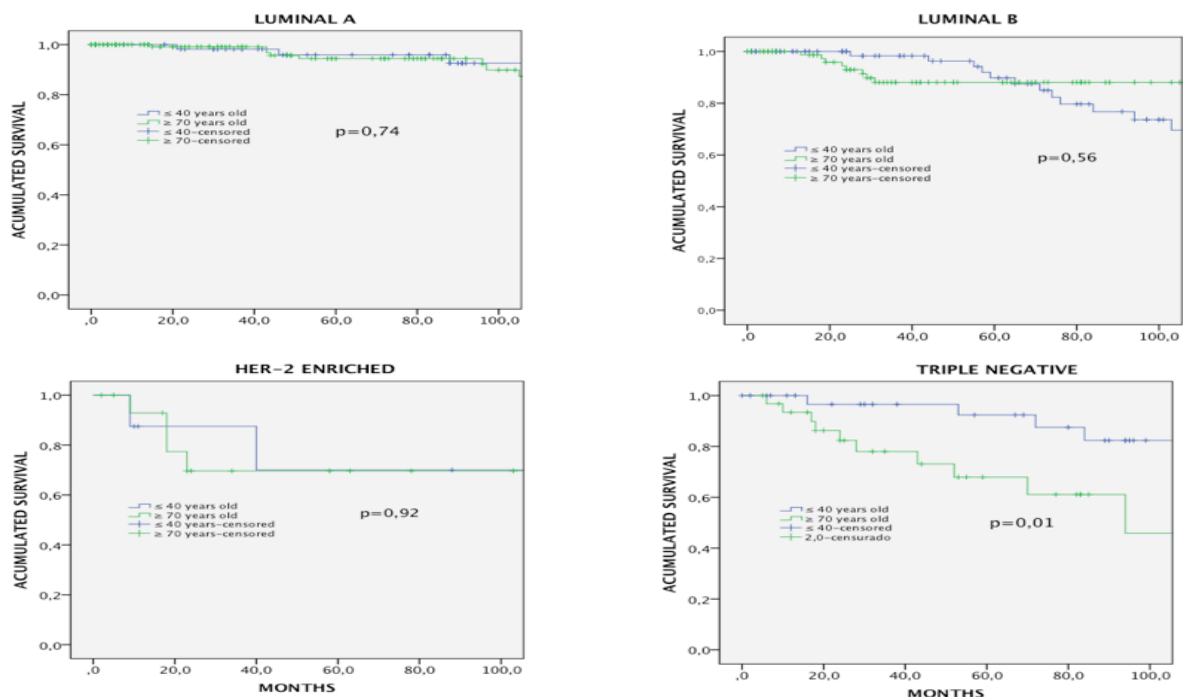
we analyzed the TN subgroup, DFS was significantly worse in the patients older than 70 years old compared to patients younger than 40 ($p=0.05$) (Figure 2D). Same effect was seen when analyzing MFS (Table 4), however the difference was no longer significant.

The median OS was 191 months in the younger patients group and 138 months in the older population ($p=0.0001$). The OS at 5 years in the former were 88.2% compared to 76.8% in the latter ($p=0.0001$).

Table 4. Comparison of Survival (DFS, MFS, DSS and OS) at 5 Years between Patients ≤ 40 and ≥ 70 Years Old in Patients with Stage I to III

	≤ 40 years (n=244)		≥ 70 years (n=340)		p
NUMBER OF RECURRENCES	57/221	25.80%	34/291	11.70%	<0.0001*
DFS AT 5 YEARS	72.3% (± 3.9)		84.6% (± 3.0)		0.007*
Luminal A	71.5% (± 7.5)		90.2% (± 3.9)		0.03*
Luminal B	64.7% (± 6.9)		86.6% (± 5.4)		0.04*
Triple Negative	83.6% (± 7.6)		59.3% (± 11.7)		0.05*
Her2-enriched	75.0% (± 21.7)		87.5% (± 11.7)		0.49
NUMBER OF SYSTEMIC RECURRENCES	47/219	21.50%	27/290	9.30%	<0.0001*
MFS AT 5 YEARS	76.3% (± 3.8)		88.1% (± 2.7)		0.01*
Luminal A	79.5% (± 6.8)		91.9% (± 3.6)		0.07
Luminal B	69.2% (± 6.8)		87.2% (± 5.3)		0.21
Triple Negative	81.9% (± 8.5)		66.2% (± 12.9)		0.31
Her2-enriched	75.0% (± 21.7)		87.5% (± 11.7)		0.87
ACSD Ratio	39/42	92.80%	42/100	42.00%	<0.0001*
DSS AT 5 YEARS	89.1% (± 2.5)		86.4% (± 2.2)		0.75
Luminal A	95.9% (± 2.9)		94.4% (± 2.4)		0.74
Luminal B	89.8% (± 4.4)		88.1% (± 4.0)		0.56
Triple Negative	92.4% (± 5.2)		67.9% (± 9.7)		0.01*
Her2-enriched	70.0% (± 18.2)		69.6% (± 12.7)		0.92
NUMBER OF DEATHS	42/243	17.30%	100/340	29.40%	<0.002*
OS AT 5 YEARS	88.2% (± 2.5)		76.8% (± 2.7)		<0.0001*
Luminal A	95.9% (± 2.9)		86.1% (± 3.5)		0.003*
Luminal B	88.5% (± 4.5)		72.4% (± 5.9)		0.11
Triple Negative	92.6% (± 5.0)		58.5% (± 10.4)		<0.0001*
Her2-enriched	70.0% (± 18.2)		69.6% (± 12.7)		0.92

*Difference is statistically significant

**Figure 4. Disease Specific Survival Curves in Breast Cancer Patients ≤ 40 vs ≥ 70 Years Old According to Subtype. (A) Luminal A; (B) Luminal B; (C) HER-2 enriched; (D) Triple negative**

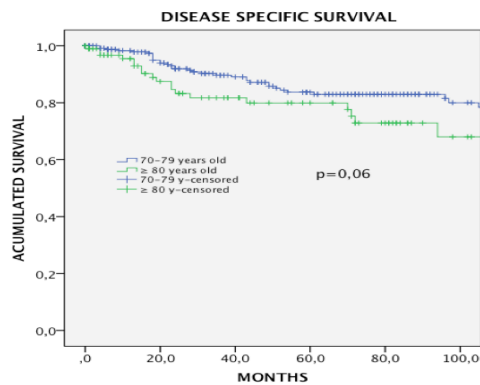


Figure 5. Disease Specific Survival Curves in Breast Cancer Patients Aged 70-79 vs ≥ 80 Years Old

The ACSO Ratio attributable to BC was 92.8% in the younger group compared to 42.0% in older patients ($p < 0.0001$). Although we didn't find any significant difference in the DSS curves in most subgroups, we did notice that older patients with TN disease die of BC more frequently than younger patients ($p = 0.01$) (Figure 4D).

On a multivariate analyses considering variables as age, stage, presence or absence of HR, presence or absence of HER2, lymph nodes compromise, HG and use of chemotherapy; only stage at diagnosis remain as predictor of DFS ($p < 0.002$).

Discussion

In the present retrospective study, we compare clinico-pathologic features, subtypes differences and outcomes variation presenting in BC patients at the extreme of ages. In the analysis, we found that patients aged 40 or less, compared to the elderly, presented with a more aggressive phenotype involving a greater chance of recurrence and, in fact, most deaths that occurred in this age group were attributable to BC.

The risk of BC increases with age. In United States, it has been estimated that the probability of a woman to be diagnosed with an invasive BC is 1.9% in patients aged 50 or less compared to 6.7% in those aged 70 or older (Siegel et al., 2014). Beside this close relation between ageing and BC, most of the studies and treatment suggestions for BC are focused mainly in patients between 40-70 years old and the information on patients in the extremes of life is sparse and segmented.

The definition of "young" patients to identify subjects at greater risk varies among studies, introducing bias in the study's reports. In a retrospective study, tumors in women younger than 40 were frequently ER negative, had higher Ki-67 index and higher p53 expression than patients over 50 years old (Morrison et al., 2012). A genomic analysis study showed that patients younger than 35 years old exhibit distinct deregulated signaling pathways, many of them associated with angiogenesis, tumor growth and metastasis (Colak et al., 2013). Nixon et al also demonstrated that BC presented in patients younger than 35 years showed features associated with bad prognosis and, even after adjusting for several variables, being young proved to be a powerful predictor of recurrence and survival (Nixon et al., 1994). Other studies had showed

that BC patients younger than 40 are more likely to die because BC, than older patients, especially in early-stage disease (Gnerlich et al., 2009). In order to verify whether patients < 35 have poorer prognosis than patients aged 35 to 40 years old, a Japanese retrospective study analyzed survival data on those groups. They didn't find differences regarding neither DFS nor OS (Yoshida et al., 2011). However, other study showed that patients aged 35 or less presented with worse outcome than patients older than 35 (Wei et al., 2013).

Although the St. Gallen Panel suggests to consider aged 35 or less as a sole indication to use cytotoxics (Goldhirsch et al., 2007), age as a threshold to categorize risk was discontinued in 2009 (Goldhirsch et al., 2009), and in the last meeting, the panel was equally divided as to whether age per se was an indication to add chemotherapy or not (Goldhirsch et al., 2013).

Defining the "elderly" population has the same difficulties than defining the young one. Despite their relatively high prevalence, this group has been excluded from most clinical trials. Most of the series have established 70 as the age to define "elderly", however even among these patients, several biologic and survival differences might be observed (Schonberg et al., 2010). Contrary to younger patients, BC in this age group presents with lower proliferation rate, more ER expression and less HER-2 overexpression (Diab et al., 2001). The same findings were observed in our study.

In spite of these indolent features, elderly patients are frequently diagnosed with larger tumor burden than younger patients (Gennari et al., 2004; E Bastiaannet et al., 2010; Schonberg et al., 2010; Oran et al., 2014). In our series, elderly BC patients presented with slightly higher tumor size. This may reflect reduced BC awareness among older women who are excluded from mammographic screening guidelines and also are less likely to self-examination among other factors (Champion, 1992; Kissal and Beser, 2011; U.S. Preventive Services Task Force, 2009; Memon et al., 2013). Although tumor size correlates with nodal metastasis in BC, we found that lymph node compromise was less frequent in elderly patients in spite of the larger size, phenomena that could be explained by a different biology between the age groups (Fisher et al., 1997). In addition, analyzing those patients who present with lymph node metastasis, the ratio between compromised and resected nodes was found to be larger in the elderly compared to younger patients. This information has been reported elsewhere and is associated with an increase in BC and overall mortality especially in patients older than 80 years old (Vinh-Hung et al., 2010).

Even among elderly patients, there are some clinical and pathological differences reported. As we mentioned, tumor size increases with age, but this increment is more dramatic after 80 years old and this subgroup are disproportionately more likely to have positive nodes than patients age 67 to 79 (Schonberg et al., 2010). Interestingly, although in our data patients aged 80 or older presented with similar biologic characteristics (HR, HG, subtype) they display a higher recurrence and a trend towards worst DSS than patients' aged 70 to 79 (Figure 5), data consistent with the published literature (Hanson

& Muss, 2010; Schonberg et al., 2010). We also found a significant difference regarding the use of chemotherapy (27.2% vs. 5.7%; $p < 0.0001$) and radiation therapy (89.1% vs 56.6%; $p < 0.0001$) in these two elderly groups.

Few data exists comparing BC characteristics and outcomes at the extreme of ages. In this study, we found that elderly patients presented with a lesser chance of local and systemic recurrence. Furthermore, luminal disease in this age group, despite having similar characteristics than patients younger than 40, presented with better outcome.

However, in the ER negative subpopulation (mainly TN disease), patients ≥ 70 years showed a higher risk of recurrence than their younger counterpart. Whether this difference may be related to biological differences or not is unknown. Some data suggests that elderly TN BC patients present with a slightly better outcome than their younger counterpart (Aapro and Wildiers, 2012), although this results have not been replicated in all studies. In a recent retrospective report, elderly (older than 80 years) patients are more likely to die of BC than younger women despite favorable tumor characteristics (Weiss et al., 2013). Moreover, BC as a cause of death exceeded cardiovascular death in the HR negative subpopulation, contrary to previous reports (Louwman et al., 2007) and their survival has not appear to be improving (Esther Bastiaannet et al., 2011), contrary to the trend observed in younger patients overtime (Berry et al., 2005).

Elderly patients in our study received less cytotoxic treatment than patients aged 40 or less (there are inequities in the delivery of this type of treatment even among the elderly, as we mentioned above). This finding may explain partially the increase in BC mortality (Bouchardy et al., 2003; E Bastiaannet et al., 2010; Schonberg et al., 2010; Weiss et al., 2013). A reported reason for under treatment are the common fear that elderly patients present related to higher risk of morbidity and mortality associated with treatment (Ring et al., 2013). Furthermore, personal preferences might play a role as we and others have been published before (Roder et al., 2012; Acevedo et al., 2014). In spite of this, the benefit of adjuvant chemotherapy persist in older women, especially in HR negative population (Elkin et al., 2006).

Our work has several important limitations. Because this is a single institution study, the number of patients evaluated is low. Also, since this is a retrospective study, there is a potential for information bias. We were not able to gather information on patient's comorbidities or performance status that may have impacted in the indication and use of cytotoxics, and hence the survival outcome. In addition, we have some imbalances in the collection of the data (e.g. information about the use of chemotherapy was collected in 90.9% of younger patients but only in 75.5% of elderly ones; $p < 0.0001$), which could have led us to overestimate the results or to have a positive/negative influence in the multivariate analysis.

In conclusions, BC patients aged 70 or more, are presented with a more indolent biology and lesser chance of recurrence than patients aged 40 or less. While HR negative BC in elderly patients represents a subgroup with higher relapse and mortality, they are frequently undertreated. In spite of the limitations mentioned, our data

suggest, consistently with guidelines recommendations (Biganzoli et al., 2012), that patients with BC should be treated according to evidence regardless of age. New tools are needed to help clinicians and patients to take better decision in these age groups.

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