

Breast Cancer in Argentine Women Aged 80 Years and Older

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Abstract

Introduction: The frequency of breast cancer in women older than 80 years is nearly 400 cases per 100,000 women. Even though this age group has usually been excluded from research protocols, evidence suggests that elderly women could have less aggressive tumors with better prognosis than younger women. The goal of the current study was to describe the pathological features, the treatments performed and the survival rates in patients over 80 years surgically treated at Hospital Italiano de Buenos Aires.

Methods: All consecutive patients older than 80 years with breast cancer who received surgical treatment between January, 2000 and December, 2010 at Hospital Italiano de Buenos Aires in Argentina were retrospectively reviewed.

Results: Our analysis included 150 patients with breast cancer aged 80 and older who underwent surgical treatment. Breast conservative surgery was performed in 78% of the patients, while 22% underwent mastectomy. Any form of axillary surgery was performed in 56.7% of the cases. The proportion of patients treated with breast conservative surgery who received radiotherapy was 55.5% whereas 15% of patients underwent radiotherapy in the mastectomy group. After a median follow-up of 48 months, we estimated an overall survival rate of 79.3%, with an overall mortality rate of 20.7% and a disease-specific survival rate of 92.6%.

Conclusion: The decision about what type of breast surgery to perform in older women is probably more influenced by tumor: breast volume ratio than by age. In fact, our ratio of breast conservative surgery is near 78%, similar to that obtained in younger patients. The situation is different for axillary staging and radiotherapy, where therapeutic decisions are probably more influenced by the presence of clinically suspicious nodes in the axilla and by patient life expectancy.

Keywords: Breast cancer; Older women; Treatment; Survival

Introduction

Over the last decade the elderly population has increased in absolute terms and the population pyramid has witnessed a change as a result of these demographic variations. The base of the pyramid has narrowed due to a lower fertility rate and the peak of the pyramid has widened because of an increase in life expectancy.

In many developed countries, it took a century for the older population to rise from 8% to 12%; in Argentina, similar changes have taken place only in 40 years. Projections to 2015 predict that more than 1 million people will be aged 80 and older [1].

The frequency of breast cancer in women older than 80 years is nearly 400 cases per 100,000 women [2]. Even though this age group has usually been excluded from research protocols, evidence suggests that elderly women could have less aggressive tumors with better prognosis than younger women. This assumption could account for the fact that physicians do not follow standard practices recommended in clinical practice guidelines, with the potential risk of under or overtreatment [3].

Physicians encounter several difficulties when facing the challenge of having to find the right balance between decreases in the number of surgical interventions.

(Which may affect quality of life in the short term) and the relief of local and systemic effects of cancer. The goal of the current study was to describe the pathological features, the treatments performed and the survival rates in patients over 80 years surgically treated at Hospital Italiano de Buenos Aires, Argentina.

Methods

All consecutive patients older than 80 years with breast cancer who

received surgical treatment between January, 2000 and December, 2010 at Hospital Italiano de Buenos Aires in Argentina were retrospectively reviewed. Clinical and pathologic characteristics (age at diagnosis, histological subtype, tumor size, lymph node metastasis, hormone receptor status and HER2 over-expression), treatment delivery (type of surgery, radiotherapy, chemotherapy and hormonal therapy), recurrence and mortality rates were gathered from electronic medical records.

Those patients with non-operable breast cancer, with distant metastasis at diagnosis and those who had undergone surgery outside the institution were excluded from the study.

In order to assess the specificity of estrogen receptor (ER) and progesterone receptor (PR) immunoreaction, cases with nuclear staining reaction in more than 1% of neoplastic cells were considered positive. Determination of HER2 over-expression was carried out in a semiquantitative way and the score was classified according to Hercep Test guidelines proposed by DAKO and accepted by the FDA [4].

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Results

Our analysis included 150 patients with breast cancer aged 80 and older who underwent surgical treatment. The median age at diagnosis was 82 (range 80-91) (Table 1). Sixty-two percent of the patients had pathologic T1 tumors (pT1), 28% pT2, 5% pTis, and 4% had pT3-4 tumors (According to Breast Cancer Staging, American Joint Committee on Cancer, 7th edn). Invasive ductal carcinoma was the most frequent histologic subtype (65.3%), followed by invasive lobular carcinoma (14%). The percentage of patients with ductal in situ carcinoma was 5.4%. Hormone receptor (HR) status was determined in all cases, and approximately 76% of the cases expressed ER-positive/PgR-positive, 12.7% ER-negative/PgR-negative, and 11.3% were discordant (ER-positive/PgR-negative or ER-negative/PgR-positive). Her2-neu status was available in 135 cases; 122 of these were negative (90.4%), and 13 were positive (9.6%). Taking into account tumor phenotype, 82.3% (111/135) were HR+/Her-, 5.2% (7/135) were HR+/Her+, 4.5% (6/135) HR-/Her+ and 8% (11/135) were triple negative.

Table 2 describes the type of treatment established. Breast conservative surgery was performed in 78% of the patients, while 22% underwent mastectomy. Any form of axillary surgery was performed in 56.7% of the cases (85/150); namely 50 sentinel lymph node biopsies, 3 sentinel lymph node biopsies plus axillary node dissection, and 32 axillary node dissections alone. Thirty-five percent of the patients had node-positive breast cancer. Postoperative complications were reported

Variable	No. of patients (%)
Age	
Mean	83
Median (range)	82 (80-91)
Pathologic tumor size*	
pTis	8 (5.4%)
pT1	94 (62.6%)
pT2	42 (28%)
pT3-4	6 (4%)
Tumor Grade	
G1	38 (25.3%)
G2	79 (52.7%)
G3	33 (22%)
Pathologic Nodal status	
pNX	65 (43%)
pN-	55 (37%)
pN+	30 (20%)
Histologic type	
Infiltrating ductal carcinoma	98 (65.3%)
Infiltrating lobular carcinoma	21 (14%)
In situ ductal carcinoma	8 (5.3%)
Other infiltrating carcinomas	23 (15.4%)
Receptor status	
ER+/PgR ⁺	114 (76%)
ER-/PgR ⁻	19 (12.7%)
Discordant (ER+/PgR ⁻ or ER-/PgR ⁺)	17 (11.3%)
Her-2 status (available in 135)	
Negative	122 (90.4%)
Positive	13 (9.6%)

*pT- according Breast Cancer Staging AJCC 7th ed
 pNX- lymph node not removed for pathologic study
 pN- no lymph node metastasis identified histologically
 pN+ lymph node metastasis identified histologically
 ER- Estrogens receptor
 PgR- Progesterone receptor

Table 1: Clinical and pathologic characteristics.

Variable	No. of patients (%)
Breast Surgery	
Conservative	117 (78%)
Mastectomy	33 (22%)
Axillary surgery	
No	65 (43%)
Yes	85 (57%)
SLND	50
SLND + ALND	3
ALND	32
Aduvant radiotherapy	
No	80 (53%)
Yes	70 (47%)
BCS	65
Mastectomy	5
Aduvant hormonal therapy	
No	22 (15%)
Yes	128 (85%)
Tam	104
AI	17
Sequential	7 Chemotherapy
No	135 (90%)
Yes	15 (10%)

SLND- Sentinel Lymph Node Dissection
 ALND- Axillary Lymph Node Dissection
 BCS- Breast Conservative Surgery
 Tam- Tamoxifen
 AI- Aromatase Inhibitor

Table 2: Therapeutic options.

in 16.7% of the patients, with 8 surgical wound infections, 11 seromas with repeated needle aspiration, 2 seromas with wound infection and 4 hematomas with nonsurgical resolution. Hormonal therapy was indicated in 128 patients (85.3%). Five years of tamoxifen was the most common hormone treatment (81.2%), followed by aromatase inhibitors (13.3%) and sequential therapy (5.4%). Six patients abandoned the treatment because of adverse effects or intolerance, whereas five reported abnormal vaginal bleeding but continued medication. Regardless of the type of surgery, radiotherapy was performed in 46.7% of all cases. The proportion of patients treated with breast conservative surgery who received radiotherapy was 55.5% whereas 15% of patients underwent radiotherapy in the mastectomy group. Chemotherapy was indicated in 10% of the patients; half of them experienced adverse effects, namely there were 4 cases of myelosuppression, 1 case of dehydration, 1 case of deep vein thrombosis and 1 case of fever of unknown origin. Sixty-four percent (7/11) of patients with triple negative breast cancer received chemotherapy, three of whom experienced undesirable effects.

Median follow-up time was 48 months (range 1-112). During this period, 31 (20.6%) patients died, 11 (7.3%) due to disease progression and 20 (13.3%) from other causes not related to breast cancer. We estimated an overall survival rate of 79.3%, with an overall mortality rate of 20.7% and a disease-specific survival rate of 92.6% (Figure 1). Figure 2 illustrates Kaplan Meier curves for global mortality considering tumor phenotypes. The fact that triple negative tumors present a steeper slope in comparison with the other type of tumors is not statistically significant. This is probably due to the small sample size. In addition, Cox multivariate analysis was performed to identify factors impacting on global mortality. Both type of surgery and tumor phenotype were not statistically significant. Eight (5.3%) loco-regional recurrences were observed, with a median time to recurrence of 23.5 months (range 12-33); six of them after a breast conservative surgery

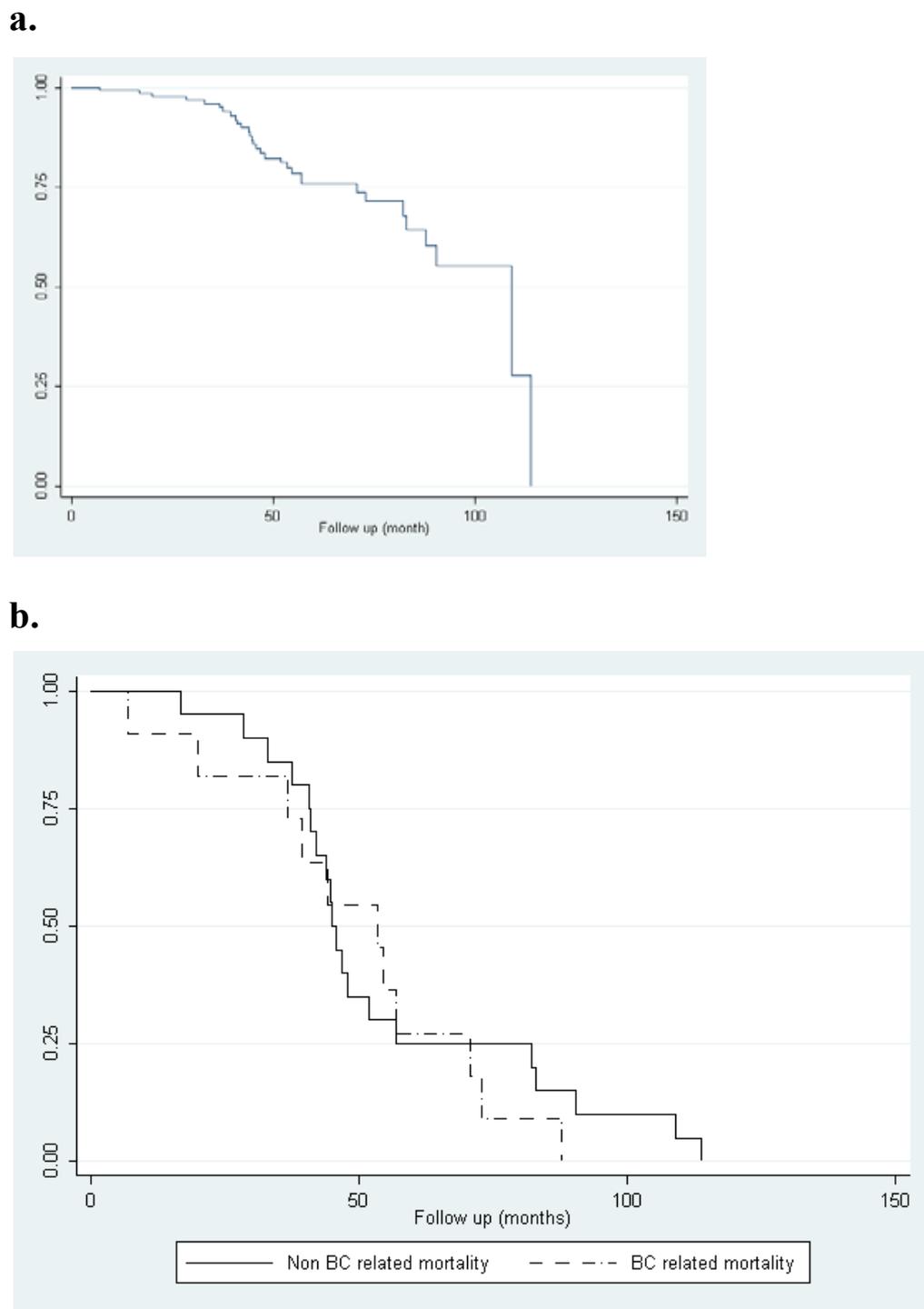


Figure 1: Mortality. Kaplan Meier curves for a) all cause mortality b) breast cancer (BC) mortality and non breast cancer (Non BC) mortality.

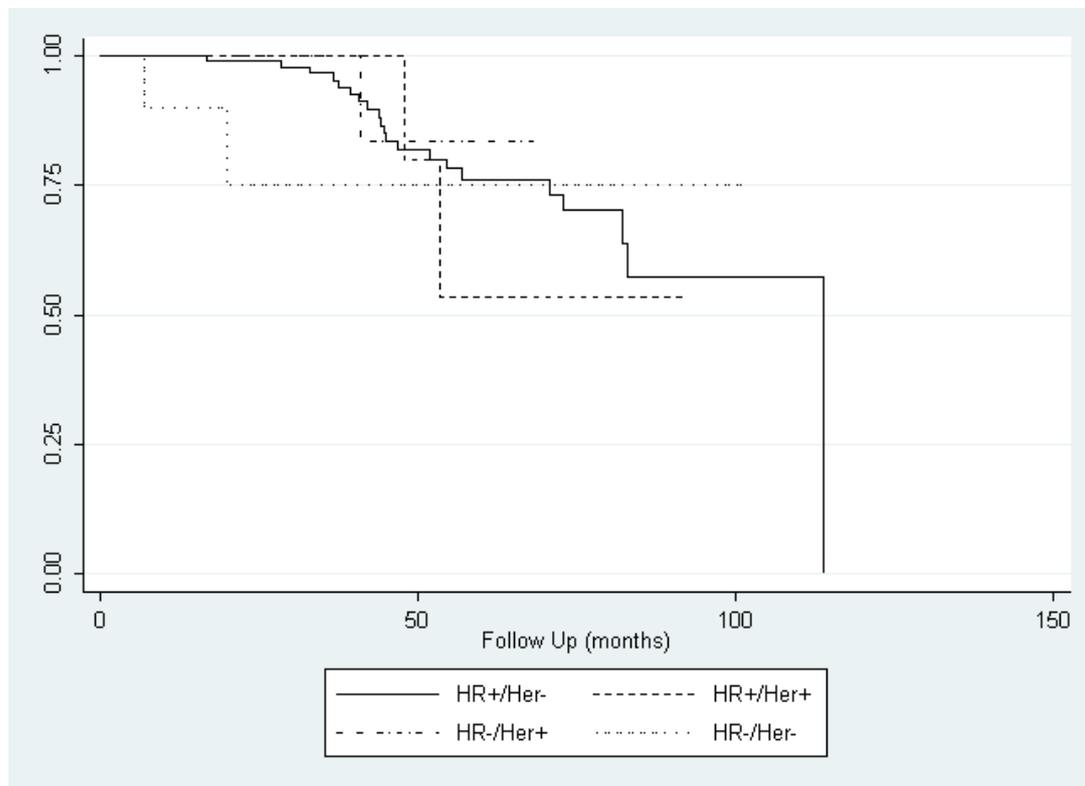
and 2 after a radical surgical procedure (Table 3). Progression to stage IV disease was observed in 18 patients (12%), with the first metastasis site being in bones in 7 cases, in liver in 2, in lungs in 4, in the brain in 1, and in multiple organs in 4 cases.

Discussion

Age is an important risk factor for breast cancer. In fact, the

incidence in women older than 80 years is around 400 cases per 100,000 [2]. In addition, controversy exists around the natural history and the optimal management of the disease in this population.

Some researchers suggest that women older than 70 years old could have tumors with less aggressive biological behavior, high levels of hormonal receptor expression, and thereby could benefit from less aggressive treatments. However, other authors suggest that, when



HR: hormonal receptor
Her: Her2neu

Figure 2: Kaplan Meier curves for all cause mortality by tumor phenotype.

Variables	No. of patients (%)
Recurrence	
All (local, regional, distant)	26 (17.3%)
Loco-regional	8 (5.3%)
Distant	18 (12%)
Death	
All causes	31 (20.6%)
BC-Related	11 (7.3%)
Not BC-related	20 (13.3%)

BC-Related- Breast Cancer Related;
Not BC-related- Not Breast Cancer Related.

Table 3: Recurrence and death.

considering the stage of the disease, survival and recurrence rates are similar to those observed in younger women [5,6].

Surgery

Numerous research trials show equivalence, in terms of survival and mortality, between breast conservative surgery and mastectomy [7,8]. In fact, 70% of the cases may be treated in a conservative way. Mastectomy rate increases as age increases. Besides, the indication of radiotherapy after breast conservative surgery decreases. Mastectomy rate in older women may be close to 60% in different series [9,10]. Nevertheless, the impact of this fact on local recurrence rate and on mortality is still unknown.

Surgical staging of the axilla in older women, either with sentinel node biopsy or axillary dissection, is questionable. Probably, a

combination of tumor resection with adequate surgical margins plus hormonal therapy may be an optimal choice for treatment, especially if we consider the fact that most patients die from causes unrelated to the disease [11]. Martelli et al. [12] reported a cumulative incidence of 4.2% of axillary metastasis in a cohort of older women without axillary staging or postoperative radiotherapy after a 15-year follow-up [12]. They concluded that elderly patients with early breast cancer and no palpable axillary lymph nodes may be safely treated by conservative surgery without axillary dissection and without postoperative radiotherapy.

In our study, the percentage of elderly patients who received breast conservative surgery was 78%, 55% of whom underwent radiotherapy as well (breast volume and boost). Consistent with the literature, the percentage of axillary metastases in our population was 35%.

Radiotherapy

Application of radiotherapy after breast conservative surgery not only decreases the risk of recurrence, but also improves survival rates [13]. However, the value of this practice in elderly women is still unknown, since the vast majority of trials which investigate the benefits of adjuvant radiotherapy do not include this population. Hughes et al., who investigated the potential benefits of radiotherapy in patients older than 70 years with stage 1 hormone-receptor positive breast cancer, concluded that the addition of this therapy did not significantly decrease the rate of mastectomy for local recurrence, of distant metastasis, and overall survival [14]. They concluded that lumpectomy followed by hormonal therapy is an appropriate treatment for women older than 70 years.

We observed 8 cases of loco-regional recurrence, 2 of them in patients who had undergone mastectomy plus radiotherapy and 5 after lumpectomy without radiotherapy.

Probably, the best answer to the question about the advantage of radiotherapy in elderly population arises from a balance between the presence of comorbidities, life expectancy and tumor aggressiveness.

Hormonal therapy

Although the benefits of adjuvant hormonal therapy in patients with hormone-receptor positive breast cancer have been demonstrated, there is still some controversy regarding the first choice scheme in postmenopausal women [15].

In our study, nearly 81% of the patients received adjuvant therapy with Tamoxifen for 5 years, while only 18.7% received Aromatase Inhibitors as primary monotherapy or sequential treatment. The perception of a more indolent disease in elderly women and some considerations about the differences in the adverse effect profiles between these two drugs could explain our preference for Tamoxifen.

Chemotherapy

Existing evidence suggests that chemotherapy efficacy is not modified by age. Nevertheless, since elderly women are not included in clinical trials, this data is still limited [16,17]. It has been postulated that the use of chemotherapy in node-positive breast cancer improves overall survival and disease-free survival regardless of age [18]. Even so, the fact that elderly women have higher risk of toxicity and mortality associated with the administration of chemotherapy should be borne in mind [19]. Fifteen of our patients (10%) received chemotherapy, half of whom presented complications.

Our findings should be interpreted in the context of some limitations. First of all, we only analyzed patients who underwent some type of surgery, probably omitting patients with operable breast cancer and co-morbidities that contraindicated the intervention. Besides, we did not include patients with metastatic and non-operable breast cancer.

In addition, as our analysis was retrospective, we could not analyze the performance status of the patients enrolled in the present study. It is also important to point out that the follow-up time was short.

Conclusions

The decision about what type of breast surgery to perform in older women is probably more influenced by tumor: breast volume ratio than by age. In fact, our ratio of breast conservative surgery is near 78%, similar to that obtained in younger patients. The situation is different

for axillary staging and radiotherapy, where therapeutic decisions are probably more influenced by the presence of clinically suspicious nodes in the axilla and by patient life expectancy.

Older women with breast cancer have usually been excluded from research protocols and prospective data available to guide therapeutic decisions is limited.

We should not forget that they represent a heterogeneous group. Differences in health status and therefore in treatment tolerance may pose a risk of under or overtreatment.

As genomics knowledge advance, new biomarkers of prognosis and treatment response are developed. Future studies should focus on identifying which subgroup of patients may benefit from more aggressive treatments. Meanwhile, therapeutic decisions should be based on biological age rather than on chronological age.

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