

## RESEARCH ARTICLE

# Impact of Treatment Type on Overall Survival in Elderly Brazilian Women with Breast Cancer

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### Abstract

**Objective:** To analyze the survival of elderly patients with breast cancer according to the type of treatment used. **Methods:** A cohort study of women aged 80 or over with breast cancer registered with the Brazilian National Cancer Institute (Instituto Nacional do Câncer - INCA) between 2008 and 2009 was conducted. Prognosis was analyzed according to the cancer treatment performed: surgery, radiotherapy, or hormone therapy. Analysis of the overall 5-year survival rate was performed using the Kaplan - Meier method, and comparisons of curves were undertaken using the log-rank test. For multiple regression analysis, Cox regression was used, adjusting for age and clinical stage, considering values of  $p < 0.05$  as significant. Data were all analyzed using the statistical package SPSS version 20. **Results:** 70 women with a mean age of  $84.0 \pm 3.7$  years at diagnosis participated in the study. The median follow-up time was 37.1 months (range 0.5–75.5), and 31 deaths (44.3%) occurred during this time. The median survival time was 51.2 months (95% CI, 44.9–57.4), higher in those who underwent surgery ( $p = 0.012$ ) and those who had hormone therapy ( $p=0.001$ ). Treatment with surgery reduced the risk of death by 61.7% (HR 0.3; 95% CI, 0.1–0.6;  $p = 0.001$ ) when adjusted for clinical stage and age at diagnosis. However, there was no significant benefit from radiotherapy (HR 1.2; 95% CI, 0.5–2.5;  $p = 0.694$ ). **Conclusion:** Treatment with surgery and hormone therapy increased the survival of our Brazilian patients with breast cancer aged 80 or over.

**Keywords:** Breast cancer- elderly- survival analysis- treatment

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### Introduction

Breast cancer represents 31.4% of the cancer cases in the world (Ferlay et al., 2013). In Brazil, the occurrence of 57,960 new cases of the disease has been estimated in 2016, breast cancer being the leading cause of death from cancer in women (Brazil, 2015).

Age has been identified as the main risk factor for the development of breast cancer. The pattern of the world's population growth and increases in the quality of life and lifespan have brought considerable and new challenges for the health sector, with a significant increase in the number of new cases and deaths from breast cancer in elderly women (Van de Water et al., 2012). Screening programs generally exclude women older than 70 years, making it difficult to access early diagnosis in this age group. This and other risk factors lead to a diagnosis of the disease at an advanced stage and consequently to a poor prognosis, with reduced chance of survival (Silva et al., 2013).

The treatment of breast cancer in elderly women must be individualized and as complete as possible. The same principles that guide treatment in younger patients must be considered as the under-treatment of these women has a negative impact on their survival. Moreover, the effectiveness and potential adverse effects of treatment must not be neglected (Silva et al., 2013). The choice of the best treatment for this age group must be preceded by a comprehensive geriatric assessment, including the physical condition of the patient, comorbidities, functional dependence, socio-economic, emotional and cognitive conditions, and life expectancy for the next five years (Parks et al., 2015).

Several authors have identified factors that have an effect on the prognosis amongst these patients. A study performed by Cappellani et al., (2013) deduced that breast cancer in elderly women is as aggressive as the same type of cancer in young women. However, there is an erroneous belief that the disease in this age group presents

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an indolent behavior, frequently resulting in the offer of fewer treatments than recommended in international guidelines (Naito et al., 2010). Under-treatment may lead to a worse prognosis (Bouchardy et al., 2003). In addition, many studies (Townsend et al., 2005) tend to exclude elderly women, making it necessary to undertake studies that include the elderly population affected by the disease. Thus, this study intends to analyze the survival of elderly patients with breast cancer according to the type of treatment used.

## Material and Methods

A cohort study was conducted including women aged 80.0 years or over, with a confirmed breast cancer diagnosis, registered with the National Cancer Institute (Instituto Nacional de Câncer - INCA, Rio de Janeiro, Brasil) from January 1, 2008, to December 31, 2009. Patients previously treated for cancer, those who did not present the results for estrogen receptors, progesterone receptors and over-expression of HER2, as well as those whose records were not found, were excluded from the study (n = 10). The patients were identified through the Hospital Cancer Registry (HCR), and the information was obtained through a review of electronic and physical records.

The socio-demographic variables verified were: age (in years), reported race/skin color (white versus nonwhite), education (< 7 years versus ≥ 8 years of study), marital status (living with a partner versus without a partner), smoking (yes and former smoker versus no), and alcoholism (yes and former alcoholic versus no), nutritional status (body mass index [BMI] < 23 low weight; 23.0–27.9 normal; 28.0–29.9 overweight; ≥ 30.0 obese). For the variables related to cancer, we observed: the size of the tumor (Tis, T1, T2, T3, T4), lymph node status (N0, N1, N2), distant metastasis after diagnosis (yes or no), clinical staging (0, I, IIA, IIB, IIIA, IIIB, IIIC, IV), histological type (invasive ductal carcinoma, invasive lobular carcinoma, other), histological grade (1, 2, 3), estrogen receptor (positive or negative), progesterone receptor (positive or negative), HER2 expression (positive or negative). The molecular subtype was classified as triple negative (estrogen receptor, progesterone receptor, and HER2 negative), HER2 neu (negative estrogen and progesterone receptor, positive HER2), and luminal (other combinations). In terms of the treatments, surgery, radiotherapy, and hormone therapy were considered. Data on chemotherapy were not analyzed because there were only few cases undergoing this treatment (n = 4). The presence of comorbidities was verified using the Charlson Index (Charlson et al., 1987), current breast cancer not being computed. The final score was categorized into no comorbidities (score = 0), medium degree of comorbidity (score = 1), and a high level of comorbidity (score ≥ 2).

Death was considered as the outcome of interest (yes or no). For the participants with loss of follow-up, the Brazilian Mortality Information System was also consulted. Data were censored at the date of the last follow-up or December 31, 2013, for those who remained alive. The follow-up time was calculated from the

date of the diagnosis until the date of the last available information.

The database was analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, Inc., USA) version 20.0, using measures of central tendency and dispersion (mean and standard deviation, median and interquartile range) for the continuous variables and frequency distribution (absolute and relative numbers) for the categorical variables (valid percentages presented).

For the categorical variables, with the purpose of analyzing the factors linked to the cancer treatment, the distributions of variables were compared using the chi-square test or Fisher's exact test, when appropriate. The overall 5-year survival rate was calculated using the Kaplan–Meier method and the comparisons of the curves with the log-rank test. For the multiple regression analysis, a Cox regression model adjusted by age and by clinical staging was used, considering  $p < 0.05$  as significant.

This study was approved by the INCA Ethics Research Committee (n° 128/2011), which respects the ethical principles established by the National Health Council, Resolution 466/12.

## Results

Seventy women with a mean age of 84.0 years ( $\pm 3.7$ ) at diagnosis participated in the study. They were mainly white (72.5%), living without a partner (88.6%), with 0 to 7.0 years of study (76.9%), non-smokers (84.3%) and non-alcoholic (85.5%). In relation to the nutritional status, 36.1% had low body weight, 27.9% normal weight and 36.1% was overweight or obese .

About the presence of comorbidity 40% had Charlson index equal to 1.0 and 35.7% had high levels of comorbidity ( $\geq 2$ ). . The tumor size was Tis or T1 in 16.9%, T2 in 47.7%, T3 in 13.8% and T4 in 21.5%. Most of them had negative lymph nodes (58.6%). In terms of the clinical staging, it was observed 15.4% at stage 0 or 1.0, 47.7% at stage II (30.8% IIA and 16.9% II B), 33.8% stage III and 3.1% at stage IV. . The most common histological type was invasive ductal carcinoma (74.3%) and the most frequent histological type was grade II (46.9%) and III (36.7%). Estrogen receptor was positive in 76.9%, progesterone in 65.2% and HER-2 overexpression in 13.0%. The most frequently molecular

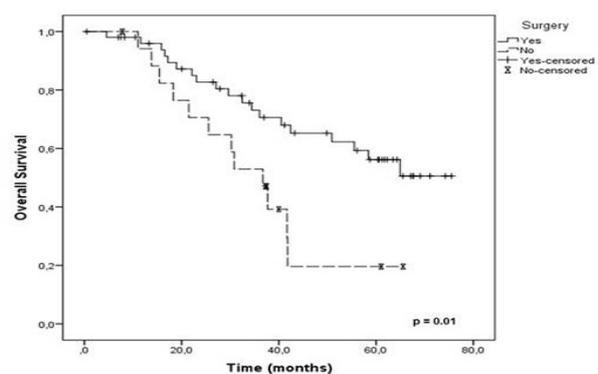


Figure 1. Overall Survival in Elderly Women with Breast Cancer as Performing Surgery

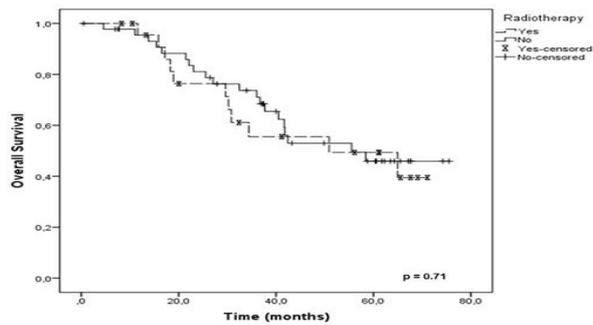


Figure 2. Overall Survival in Elderly Women with Breast Cancer as Performing Radiotherapy

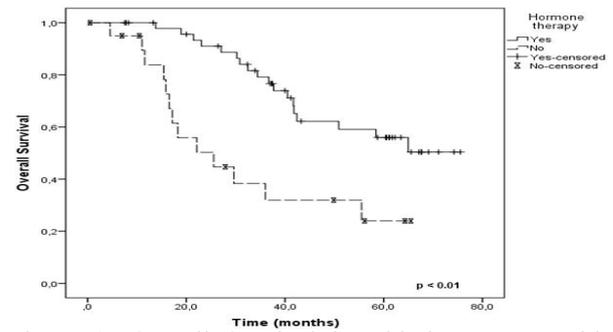


Figure 3. Overall Survival in Elderly Women with Breast Cancer as Performing Hormone Therapy

Table 1. Distribution of the Frequency of Demographic and Clinical Variables, According to the Treatment Modalities

Characteristics	Surgery			Radio therapy			Hormone therapy		
	Yes (n=52)	No (n=18)	p value	Yes (n=24)	No (n=46)	p value	Yes (n=49)	No (n=21)	p value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
<b>Race/skin color</b>									
White	41 (78.8)	9 (52.9)	0.04	15 (62.5)	35 (77.8)	0.18	35 (72.9)	15 (71.4)	0.90
Non-white	11 (21.2)	8 (47.1)		9 (37.5)	10 (22.2)		13 (27.1)	6 (28.6)	
<b>Side of tumor</b>									
Unilateral	50 (96.2)	18 (100.0)	1.0	22 (91.7)	46 (100.0)	0.11	47 (95.9)	21 (100.0)	1.00
Bilateral	2 (3.8)	0 (0.0)		2 (8.3)	0 (0.0)		2 (4.1)	0 (0.0)	
<b>Size of tumor</b>									
Tis / T1	10 (20.8)	1 (5.9)	0.03	2 (9.5)	9 (20.4)	0.64	8 (18.2)	3 (14.3)	0.42
T2	26 (54.2)	5 (29.4)		10 (47.6)	21 (47.7)		20 (45.5)	11 (52.4)	
T3	5 (10.4)	4 (23.5)		4 (19.0)	5 (11.4)		8 (18.2)	1 (4.8)	
T4	7 (14.6)	7 (41.2)		5 (23.8)	9 (20.5)		8 (18.2)	6 (28.6)	
<b>Clinical Lymph Node Status</b>									
Positive	18 (34.6)	11 (61.1)	0.05	12 (50.0)	17 (37.0)	0.29	19 (38.8)	10 (47.6)	0.49
Negative	34 (65.4)	7 (38.9)		12 (50.0)	29 (63.0)		30 (61.2)	11 (52.4)	
<b>Clinical Staging</b>									
≤ IIA	27 (56.2)	3 (17.6)	<0.01	7 (33.3)	23 (52.3)	0.15	20 (45.5)	10 (47.6)	0.87
≥ IIB	21 (43.8)	14 (82.4)		14 (66.7)	21 (47.7)		24 (54.5)	11 (52.4)	
<b>Histological type</b>									
Ductal invasive	36 (69.2)	16 (88.9)	0.21	17 (70.8)	35 (76.1)	0.52	35 (71.4)	17 (81.0)	0.31
Lobular invasive	5 (9.6)	0 (0.0)		1 (4.2)	4 (8.7)		5 (10.2)	0 (0.0)	
Other	11 (21.2)	2 (11.1)		6 (25.0)	7 (15.2)		9 (18.4)	4 (19.0)	
<b>Histological grade</b>									
Grade 1	6 (15.8)	2 (18.2)	0.08	4 (22.2)	4 (12.9)	0.69	7 (21.2)	1 (6.2)	0.11
Grade 2	15 (39.5)	8 (72.7)		8 (44.4)	15 (48.4)		17 (51.5)	6 (37.5)	
Grade 3	17 (44.7)	1 (9.1)		6 (33.3)	12 (38.7)		9 (27.3)	9 (56.2)	
<b>Molecular subtypes</b>									
Luminal	39 (76.5)	14 (77.8)	0.69	16 (66.7)	37 (82.2)	0.34	47 (95.9)	6 (30.0)	<0.01
Triple negative	10 (19.6)	4 (22.2)		7 (29.2)	7 (15.6)		2 (4.1)	12 (60.0)	
Her2-neu	2 (3.9)	0 (0.0)		1 (4.2)	1 (2.2)		0 (0.0)	2 (10.0)	
<b>Charlson Index</b>									
0	13 (25.0)	4 (22.2)	0.10	6 (25.0)	11 (23.9)	0.35	13 (26.5)	4 (19.0)	0.67
1	24 (46.2)	4 (22.2)		12 (50.0)	16 (34.8)		20 (40.8)	8 (38.1)	
≥ 2	15 (28.8)	10 (55.6)		6 (25.0)	19 (41.3)		16 (32.7)	10 (42.9)	

Table 2. Overall Survival and Cox Regression Analysis (Crude and Adjusted)

Treatment	Time of Survival (months)			Univariate Analysis		Multiple Analysis*		
	Mean	95%CI	HR	95%CI	p value	HR	95%CI	p value
<b>Surgery</b>								
Yes	55.8	48.7 - 62.8	0.4	0.2 – 0.8	0.01	0.4	0.2 – 0.9	0.02
No	35.9	27.0 – 44.9	Reference			Reference		
<b>Radiotherapy</b>								
Yes	48.0	37.9 – 58.2	1.1	0.5 – 2.4	0.71	1.2	0.5 – 2.5	0.69
No	52.1	44.5 – 59.7	Reference			Reference		
<b>Hormone therapy</b>								
Yes	57.3	50.8 – 63.9	0.3	0.1 – 0.6	<0.01	0.3	0.1 – 0.6	<0.01
No	33.1	22.9 – 43.3	Reference			Reference		

\*Adjusted by clinical stage and age at diagnosis; HR, Hazard Ratio; CI, Confidence interval

subtype was luminal (75.7%), followed by the triple negative (20.3%). The cancer treatment was performed in 95.7 of the patients; being the first treatment was surgical in 74.6%, hormone therapy in 20.9%, radiotherapy in 3.0% and chemotherapy in 1.5%. Distant metastases were rare, occurring in 15.7%. At the end of the follow-up period, most of the patients were alive, with 31.0 (44.3%) deaths registered during the period.

The factors associated with the surgical treatment are shown in Table 1. The women who underwent surgery were predominantly white (p = 0.04), did not have clinically positive nodes on physical examination (p = 0.05), and clinical staging of IIA or less (p = <0.01). There were no differences between the women who did or did not undergo radiotherapy and hormone therapy, except for those patients using hormone therapy, who more often had the luminal tumor subtype (p < 0.01).

The median follow-up time was 37.1 (0.5–75.5 months), within which period the patients survived an average of 51.2 months (95% CI, 44.9–57.4). Surgical treatment was statistically associated with better overall survival (p = 0.01), as was the use of hormone therapy (p < 0.01). Radiotherapy did not show an association with overall survival (p = 0.71) (Table 2). Figure 1, Figure 2, and Figure 3 show the survival curves according to the treatment modalities.

The multiple regression analysis showed that the patients who did not undergo surgery or receive hormone therapy had an increased risk of death when compared to those who received these treatments. Surgery reduced the risk of death in 62.0% (HR 0.4; 95% CI, 0.2–0.9; p = 0.0), and the hormone therapy reduced this risk in 71.0% (HR 0.3; 95% CI, 0.1–0.6; p < 0.01), when adjusted for clinical staging and for age at diagnosis. However, there was no benefit from radiotherapy (HR 1.2; 95% CI, 0.5–2.5; p = 0.7) (Table 2).

## Discussion

This study included 70.0 women aged 80 years or older in a single reference institution for breast cancer treatment in Brazil. After adjustments for clinical staging and age, the women who underwent surgery and/

or hormone therapy revealed a better overall survival rate. This is a low-education population, mainly white and not living with a partner at the time of the breast cancer diagnosis. The nutritional status was considered appropriate or low for most of the evaluations, based on BMI. The presence of comorbidities was observed in 75.7% of the patients. Concerning the characteristics of the tumor, most of the population was diagnosed with infiltrating ductal carcinoma grade 2, with positive estrogen and progesterone receptors and absence of HER2 overexpression. Most of the patients were diagnosed in advanced stages of cancer. A study undertaken by Miguelez et al., (2012) showed similar results, with 76.3% of the cases revealing infiltrating ductal carcinoma, 88.0% positive estrogen receptors, and 92.0% positive receptors; but the majority of patients (73.0%) were at stage II.

Surgery was the cancer treatment most frequently performed (71.4%), followed by hormone therapy (20.0%). Surgery has been described as the main breast cancer treatment in elderly women (Markopoulos and van de Water, 2012). A Cochrane review (Hind et al., 2007) showed that primary hormone therapy with tamoxifen is associated with the worst local control of the disease when compared to surgery, and that this therapy should be used exclusively in patients with positive receptors, when surgery is not recommended. Even though there seems to be a small increase in postoperative morbidity in this group of patients, there is no increased mortality (Wyld and Reed, 2007). In this study, 74.3% of the patients underwent surgery, similar to the results of Sierink et al. (2014) study, in which 67% of the patients underwent surgery.

In patients who underwent surgery, the overall survival was 56 months, whilst among others it was 36 months (p = 0.012). After adjustment for staging and age at diagnosis, the first group had 62.0% less risk of dying from breast cancer in relation to the latter (p = 0.025). A similar study showed a median overall survival of 50.0 and 44 months for women who did or did not undergo surgery respectively. However, women were mostly diagnosed with initial tumors (82.0%) (Miguelez et al., 2012), whereas in the present study only 52.9% of the surgical patients had the disease in its initial stage. This

may explain the poor overall survival in patients who did not undergo surgery, as diagnosis at a more advanced stage may be associated with less effectiveness of treatment.

Some authors have suggested that low life expectancy, the supposedly less aggressive nature of the disease, and the presence of multiple comorbidities leads to the under-treatment of elderly women (Holmes and Muss, 2013; Sanguinetti et al., 2014; Sierink et al., 2014). In this study, 25.7% of the patients did not undergo surgery, which may be explained by the advanced stage of the disease at diagnosis (82.4% of these patients were at a stage  $\geq$  IIB) ( $p = 0.006$ ). In addition, even though multiple comorbidities are frequently described as the main limiter for undertaking surgery in elderly patients (Louwman et al., 2005; Markopoulos and van de Water, 2012), in this study these conditions did not affect the recommendation concerning surgery.

Hormone therapy in elderly women aims to provide more effective local control of cancer, and is one alternative for those cases with positive hormonal receptors in which surgery is not recommended. Patients who underwent surgery benefited from the use of adjuvant tamoxifen with an improvement in disease-free survival (Hind et al., 2007). This study's results demonstrate that the patients who underwent hormone therapy had a 71.0% reduction in their chance of dying. In a cohort study performed with 1,837.0 women aged 65.0 years or more who underwent surgery, a decrease in mortality was observed in those patients who used tamoxifen for 5.0 years or longer (Yood et al., 2008).

According to a meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Gray et al., 1993), treatment with radiation reduces the risk of death and the chances of recurrence in patients who have undergone breast conservative surgery. When the radiation was omitted, the local recurrence rates increased. Other studies have also indicated a reduction in the risk of death and in local recurrence in patients undergoing adjuvant radiation therapy, with an increase in overall survival and in disease-free survival for women over 70.0 years of age (Antonini et al., 2007; Silva et al., 2013). In this study, there was no significant difference in the survival of patients who received or did not receive radiotherapy. These results were also observed by Omidvari et al (2015) who found that Iranian women aged 60 or over treated and followed-up between 1993 and 2014 showed no significant difference in survival.

However, this study has some limitations, the main one being the small number of women included. This number may not have been sufficient to analyze the association between radiotherapy and survival; moreover, although the associations between surgery and hormone therapy and overall survival were statistically significant, the magnitude of the association was not accurate as the confidence intervals were wide. Another limitation concerns the retrospective data collection, based on the description available from the hospital records. Some information was unknown, primarily that concerning the Ki-67 marker, which made the classification of luminal tumors as A or B difficult. Furthermore, to minimize the

bias of information related to the loss of follow-up, the Mortality Information System of the State of Rio de Janeiro was consulted for all cases with a lapse of more than one year since the last follow-up.

On the other hand, this study shows some strengths. It employs a population with homogeneous socio-demographic and clinical characteristics, treated in a reference institution for breast cancer treatment. As all the women included were diagnosed between 2008 and 2009 – a period of two years – it is believed that the incorporation of new technologies and treatments did not influence the outcome of these women. Finally, the results of this study fill in a blank of knowledge in the country, and they can be applied to populations with similar characteristics – women aged 80 or over seeking public health assistance services in Brazil.

Surgery and hormone therapy contributed to an increase in the survival rates of patients with breast cancer aged 80 or over. However, this was not observed for radiotherapy.

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#### Conflict of interest

No competing financial interests exist

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