

RESEARCH COMMUNICATION

Arm Symptoms and Overall Survival in Brazilian Patients with Advanced Breast Cancer

Anke Bergmann^{1*}, Nathalia Santos Bourrus¹, Cristiane Monteiro de Carvalho², Ricardo de Almeida Dias¹, Erica Alves Nogueira Fabro², Nria Silva Sales², Suzana Sales de Aguiar²

Abstract

Introduction: Advanced breast cancer is a very frequent serious public health problem. **Objective:** This study aimed to analyze the prevalence of arm symptoms and overall survival in affected patients. **Methodology:** A retrospective cohort study was accomplished in 196 women presenting with advanced breast cancer. A descriptive analysis was carried out by and overall survival probabilities were calculated according to Kaplan-Meier method and Cox regression. **Results:** These included 196 women had a medium age of 55.9 years, the majority being obese (71.3%) and having a IIIB clinical staging (52.3%). The most prevalent arm symptoms were pain (54.6%), paresthesia in upper limb (8.5%), lymphedema (> 200 ml) (6.6%), shoulder restriction (4.7%) and axillary web syndrome (0.6%). The median follow-up was 18.7 months (SD 7.33), 4.0% of the patients had metastasis and 31.6% were dead. The mean free disease survival was 20.4 months (95% CI 18.4-22.4), and the mean survival time was 26.3 months (95% CI 24.7-28.0). After adjusted the association with arm symptom and overall survival for clinical stage and presence of distant metastasis, the shoulder restriction was a predict variable, were represents the risk 2.59 for worse survival in compared with woman with no shoulder restriction (CI 95% 1.06-5.98). **Conclusion:** The population studied at this study presented high prevalence of complications earlier than neo adjuvant treatment. After controlling for effects of tumor variables, the shoulder restriction was statistically associated with poor overall survival after 2 years.

Keywords: Breast neoplasms - neoadjuvant therapy - arm symptoms - overall survival - advanced cancer

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Introduction

Breast cancer is the second most frequent cancer in the world and is the most common cancer in women. In Brazil, it has been estimated that for the year 2011, there will be 489,270 new cases of cancer, of which 49,240 will be breast cancer. Also, 60% of breast tumors are diagnosed as Stages III and IV. Hence, breast cancer is becoming a serious public health problem in our country (Ministrio da Sade, 2009).

Therapy of advanced breast cancer consists of multiple modalities that involve radical surgery, radiotherapy, chemotherapy, and hormonal therapy. Neoadjuvant therapy is indicated for locally advanced tumors, and the main goal is to improve surgical conditions and, consequently, minimize the complications generated by the disease. Furthermore, the therapeutic response achieved can help the prognosis, because tumors under complete remission show better survival figures (Smith, 2008; Straver et al., 2008). The success of locally advanced breast cancer treatment and the patient's survival depends on a number of prognostic factors, these including

clinical stage, involvement of the axillary lymph node, size of tumor, histological grade, hormonal status, and the presence of distant metastasis (Akhsan and Aryandono, 2010).

It is clear that neoadjuvant therapy is a standard treatment in patients with locally advanced breast cancer. However, women who have been diagnosed with advanced breast cancer can present with arm symptoms caused by tumoral compression, with the most frequent being pain, lymphedema, shoulder restriction, paresthesia, and brachial plexopathy (National Health and Medical Research Council, 2001). The presence of these symptoms before neoadjuvant therapy can predict the survival rate in patients with advanced breast cancer.

In this context, the knowledge of the prevalence of arm symptoms and its impact on survival can serve as a basis for implementing therapeutic programs in order to prevent and minimize complications, as well as contribute to the decision making regarding subsequent treatments.

The present study aimed to analyze the prevalence of arm symptoms and the overall survival in Brazilian patients with advanced breast cancer.

¹Centro Universitrio Augusto Motta and Instituto Nacional de Cancer, BR, ²Instituto Nacional de Cancer, Brazil *For correspondence: bergmann@inca.gov.br

Materials and Methods

A retrospective cohort study with women presenting with advanced breast cancer recommended for neoadjuvant therapy, from May 1, 2006 to April 30, 2007, who have been enrolled in a public hospital of breast cancer (Hospital of Cancer III/National Cancer Institute/Brazil), has been accomplished. Patients who underwent previous oncologic treatment out of the institution were excluded.

Recruitment was accomplished in accordance with the institutional routine that requires physiotherapeutic assessment prior to oncologic treatment as well as continuous follow-ups during all the phases of treatment. In this study, data (both clinical and socio-demographic) were collected up to two years after initial assessment, using proper instrument, and including physiotherapist evaluation and oncologic response to therapy.

In order to assess the arm symptoms, the following criteria were used: lymphedema caused by tumoral obstruction (range of difference of up to 200 ml in the upper limbs, obtained through indirect volumetry); shoulder restriction (limited movement on flexion or abduction of shoulder which was testified through active range of motion of the limb); paresthesia (perception related to tactile stimulus at the upper limb tested by means of superficial touch); axillary web syndrome (presence of fibrosis of lymphatic collector diagnosed by touching the limb); arm pain (measured using the visual analogue scale).

All the 220 eligible patients were submitted to physiotherapeutic assessment prior to the neoadjuvant or palliative treatment. For this study, 4 patients were excluded because treatment has been accomplished in another institution and 20 were considered ineligible due to their difficulty in accessing the medical handbook. The total population was composed, therefore, of 196 women. Twenty-two (11.2%) of them were reclassified as Stage IV, however, their previous stage was retained in the analysis once they had had an initial indication for neoadjuvant therapy.

A descriptive analysis of the studied population was accomplished through the central tendencies measures for the continuous variables, and for absolute and relative values for the categorical variables. Overall survival and survival free from the disease were analyzed, taking into consideration the evaluation of the physiotherapeutic date as the beginning of survival time. Data that were considered withheld were the ones referring to women who were still alive at the end of the follow-up period, or to whom it was not possible to prove vital condition (losses of follow-up). The probabilities of survival were calculated according to the Kaplan-Meier method. Comparison among strata in the same sample was performed by means of the log-rank test, admitting statistical levels of significance of 5%. To assess the association with arm symptom and overall survival, the variables were tested with the multivariate Cox regression. The statistical package used in these analyses was SPSS 13.0.

This project has been approved by the Research Ethics Committee of the Brazilian National Cancer Institute/Brazil.

Table 1. Clinical and Pathologic Characteristics of the 356 CRC Cases in this Study

Variable	Prevalence (%)	No.*	Survival Time (mean)	IC 95%	P valor
Pain					
No	89 (45,4%)	25	26,7	24,2 – 29,2	0,4873
Yes	107 (54,6%)	37	25,8	23,5 – 28,0	
Shoulder Restriction					
No	183 (95,3%)	55	26,8	25,2 – 28,5	0,0003
Yes	9 (4,7%)	6	14,6	9,6 – 19,5	
Lymphedema (Vol>200ml)					
No	183 (93,4%)	54	26,7	25,0 – 28,4	0,0145
Yes	13 (6,6%)	8	19,6	14,4 – 24,7	
Arm Paresthesia					
No	173 (91,5%)	53	26,6	24,8 – 28,3	0,4926
Yes	16 (8,5%)	06	22,5	17,9 – 27,1	
Axillary Web Syndrome					
No	158 (99,4%)	44	27,1	25,2 – 29,0	0,0001
Yes	1 (0,6%)	1	6,9	6,9 – 6,9	

*Number Deaths

Results

The average age of the women in the beginning of this study was 55.9 years (SD 13.3); most are overweight or obese (71.3%), with 46.4% reported living with their partner and 51.6% of women who declared, at least, to having completed grade school.

When cancer was diagnosed, the prevalence of arm symptoms was: pain (54.6%), paresthesia in the upper limb (8.5%), lymphedema (>200 ml) (6.6%), shoulder restriction (4.7%), and axillary web syndrome (0.6%) (Table 1).

The clinical staging of cancer was IIA in 1.5%, IIB in 5.1%, IIIA in 13.3%, and IIIB in 80.1%. In relation to the neoadjuvant therapy, 60.0% of the patients underwent chemotherapy and 51.8% had FAC (fluorouracil, adriamycin, and cyclofostamid) as the first option of treatment. Radiotherapy was performed in 18.4% and it was with application over the breast and axillary lymph nodes in 61.3% of all women. In 15.8%, hormone therapy was the eligible treatment. All patients were recommended for neoadjuvant treatment, as a criterion for this study, however, 57 patients (29.08%) were not submitted to neoadjuvant treatment or surgery, and were considered, therefore, as palliative cases.

Mastectomy was carried out in all the women who underwent surgical treatment for breast cancer (34.2%). A mean of 14.8 lymph nodes were removed (SD 6.03), with 3.17 showing malignancy (SD 4.41). Immediate breast reconstruction was performed in 2 patients (2.3%). Mean time of follow-up between the beginning of the study and the surgery was 8.2 months (SD 3.07). Adjuvant treatment was performed in 74.7% of the patients, where 47 (54.02%) underwent radiotherapy, 41 (47.12%) hormone therapy (47.12%), and 9 (10.35%) chemotherapy.

During the follow-up, 94 (48.0%) patients had metastasis, the most frequent of which occurred in the bone (21.9%), lung (15.3%), and liver (10.2%) (Table 2). The mean free disease survival was 20.4 months (95% CI 18.4–22.4).

The median follow-up was 18.69 months (SD 7.33) and

Table 2. Patients Characteristics and Overall Survival

Variable	Prevalence (%)	No.*	Survival Time (mean)	IC 95%	P value
Age					
< 59	122 (62,2%)	39	26,7	24,8 – 28,6	0,4073
≥ 60	74 (37,8%)	23	25,9	22,9 – 28,9	
Nutritional Status					
Obese	139 (71,3%)	39	27,3	25,4 – 29,2	0,0294
Not	56 (28,7%)	23	23,2	20,0 – 26,3	
Clinical Staging					
≥ III B	157 (80,1%)	57	25,2	23,3 – 27,1	0,0064
< III A	39 (19,9%)	5	30,5	27,8 – 33,3	
Breast Surgical					
Yes	67 (34,2%)	7	31,0	29,1 – 32,9	0,0001
No	129 (65,8%)	55	23,6	21,5 – 25,8	
Metastatic Lymph Nodes					
Yes	158 (80,6%)	60	25,0	23,1 – 26,8	0,0008
No	38 (19,4%)	2	30,2	28,7 – 31,7	
Metastasis					
Yes	94 (48,0%)	49	22,0	19,7 – 24,2	0,0001
No	102 (52,0%)	13	30,3	28,5 – 32,1	
Lung Metastasis					
No	166 (84,7%)	44	27,0	25,3 – 28,7	0,0018
Yes	30 (15,3%)	18	21,5	17,7 – 25,2	
Bone Metastasis					
No	153 (78,1%)	37	28,3	26,5 – 30,0	0,0001
Yes	43 (21,9%)	25	18,9	15,7 – 22,0	
Liver Metastasis					
No	176 (89,8%)	53	26,7	24,9 – 28,4	0,2918
Yes	20 (10,2%)	9	23,6	18,6 – 28,7	

*Number Deaths

62 (31.6%) patients were dead at the date of evaluation, all of them due to advanced disease. The mean survival time was 26.3 months (95% CI 24.7–28.0).

In the Kaplan-Meier analyses, overall survival was not statistically associated with pain and paresthesia in the arm. Woman with shoulder restriction had a mean survival of 15 months compared with 27 months for those with no restriction (p=0.0003). The mean survival for lymphedema was 20 months and for those without lymphedema was 17 months (p=0.0145) (Table 1, Figure 1).

Taking clinical variables into consideration, overweight or obese women had a better survival time (27 months) in relation to those with appropriate nutritional status (23 months) (p=0.0294). Women with advanced clinical staging (>IIIB) had a mean survival time of 25 months and those with early staging had a 30.5 months survival (p=0.0064). Breast surgery proved to be a predictive factor related with better survival time (p=0.0001). The presence of positive axillary lymph nodes, distant metastasis, and secondary cancer in the lung and bone was associated with worse survival time (Table 2).

After adjusting for the association of arm symptoms with overall survival, clinical stage, and the presence of distant metastasis, shoulder restriction was classified as a predictor variable, which represents a 2.59 risk for worse survival compared with woman without shoulder restriction (95% CI 1.06-5.98) (Table 3).

Discussion

The population included in this study was composed of

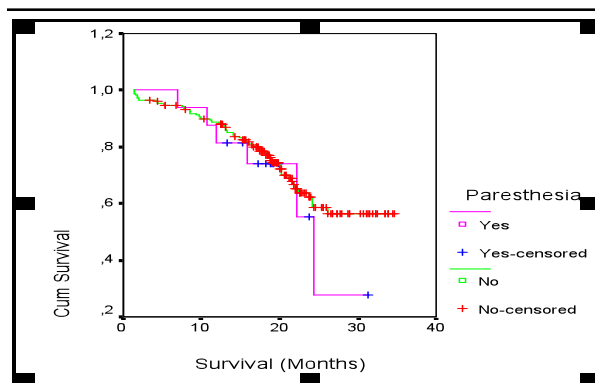


Figure 1. Kaplan Meier Curve for Overall Survival and Arm Symptoms

Table 3. Crude Adjusted Hazard Ratios for Arm Symptoms and Overall Survival

Symptom	Arm	Crude			Adjusted*		
		HR	CI 95%	P value	HR	CI 95%	P value
Pain	Yes	1,20	0,72 – 1,99	0,488	1,11	0,66 – 1,87	0,679
	No						
Shoulder restriction	Yes	4,29	1,82 – 10,09	0,001	2,59	1,06 – 5,98	0,035
	No						
Lymphedema	Yes	2,45	1,16 – 5,16	0,018	1,56	0,73 – 3,31	0,247
	No						
Arm paresthesia	Yes	0,74	0,32 – 1,73	0,494	1,07	0,46 – 2,52	0,867
	No						

*HR adjusted for clinical stage and distant metastasis

women with a median age of 55 years. Other studies with advanced breast cancer have included younger women (Hung et al., 2000; Akhsan and Aryandono, 2010; Iqbal et al., 2010; Khokher, 2010; Chong et al., 2010; Raina et al., 2011). In terms of tumor characteristic, the most frequent clinical staging was IIIB, which is similar to Akhsan and Aryandono (2010), who found 42% under Stage IIIB, and Chong et al (2010), who reported 61% in the same stage.

In our study of advanced breast cancer, we have encountered several methodological difficulties, one of them is the measurement of response. Pathological complete response of the neoadjuvant therapy is considered a surrogate marker for survival and is associated with best long-term outcome. However, because breast cancer is a heterogeneous disease from clinical, biological, genetic, and molecular points of view with disparities across racial and ethnic groups, the response rates vary from different populations (Khokher, 2010).

The frequency of operable patients can be one of the response criteria, occurring in 34%. Mastectomy was performed in all the participants, with a mean of 14.8 lymph nodes removed and 3.17 showing malignancy. However, these numbers have been underestimated due to prior chemotherapy. Raina et al (2011) reported that surgery with mastectomy was performed in 91.4% after neoadjuvant therapy, with a mean of 11 lymph nodes identified and 2 positives. Other studies reported 80% and 98% of surgery after neoadjuvant therapy and include breast conservative treatment (El-Sayed et al, 2010). However, tumoral characteristics of the population under study are distinct, making it impossible to draw comparisons from the results of the neoadjuvant therapy.

During a median of 19 months of follow-up, 48% were observed with metastasis and 31.6% of the subjects were deceased, with a mean free disease survival of 20.4 months and an overall survival of 26 months. Alvarado-Miranda et al (2009) have reported, after neoadjuvant chemotherapy in patients presenting with advanced breast cancer, 76.9% (95% CI 68.2–84.7%) of disease-free survival in 5 years and an overall survival of 84.2% (95% CI 75–93.2%).

The age at diagnosis was not associated with overall survival and these results are similar to the report of Akhsan et al (2010), who studied 52 patients with locally advanced breast cancer. Considering the clinical characteristics, the overall survival was associated with nutritional status, clinical staging, breast surgery, metastatic lymph node, distant metastasis, and the presence of metastasis in lung and bone. Akhsan et al (2010), found significant correlation (p value of 0.000) on survival analysis of the effect of clinical stage on survival.

The efficiency of neoadjuvant therapy in advanced breast cancer is clear (Straver et al, 2010), however, the prevalence of complications associated with advanced breast cancer prior to neoadjuvant therapy is rarely described. Symptoms in women with advanced breast cancer are multifactorial, and may be caused directly or indirectly by the underlying tumor (National Health and Medical Research Council, 2001).

The World Health Organization (WHO) Cancer and Palliative Care Unit evaluated the prevalence of symptoms in patients attending palliative care centers across the world, and the most commonly reported symptom in women with advanced breast cancer was pain (60%). In this study, a high prevalence of pain on the upper limb and breast before neoadjuvant treatment was observed and a similar frequency was observed by another study (Ramirez et al, 1998), but this was not associated with overall survival. Arm paresthesia and axillary web syndrome were less frequently cited in the literature.

Lymphedema due to the obstruction of lymphatic drainage was observed, but after controlling for the effects of metastasis and clinical stage, this variable was not statistically associated with overall survival. We have not found published studies on the prevalence of lymphedema prior to neoadjuvant treatment.

In advanced disease, the possible causes of shoulder restriction can be the neurological deficits, muscle weakness or wasting, and pain (National Health and Medical Research Council, 2001). In this study, shoulder restriction was not frequently cited as a symptom (4.7%) but was statistically associated with overall survival at the bivariate and multivariate analyses, representing 2.59 more risk of poor survival compared with patients who had a normal shoulder range of motion. We did not find studies that analyzed this complication in advanced breast cancer.

In addition, due to the high prevalence of complications as observed before the neoadjuvant treatment, it is evident that there is a need for an interdisciplinary therapy approach in order to minimize and control these symptoms, which tend to get worse after the institution of neoadjuvant, adjuvant, and surgical therapy. Further study that involves more patients should be conducted, and a longer duration of follow-up is required in order

to further evaluate the survival of patients with locally advanced breast cancer.

In conclusion, the sample profile was composed of women with a mean age of 56 years old, had a stable union (46.4%), had low scholarship (48.4%), were overweight or obese (71.3%), and presented with staging of the disease that is more prevalent in IIIB (52.3%). A high prevalence of complications prior to neoadjuvant treatment was noted, where pain (64.8%), lymphedema (6.6%), paresthesia (8.5%), and shoulder restriction (4.7%) prevailed. During follow-up, 48.0% of the patients had metastasis. The mean free disease survival was 20.4 months (95% CI 18.4–22.4). In the end of the follow-up, we have observed 62 deaths (31.6%), all of them due to advanced disease, with a mean survival time of 26.3 months (95% CI 24.7–28.0). After controlling for the effects of tumor variables, shoulder restriction was statistically associated with poor overall survival after 2 years.

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