

Adjuvant treatment delay in breast cancer patients

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SUMMARY

Background: to evaluate if time between surgery and the first adjuvant treatment (chemotherapy, radiotherapy or hormone therapy) in patients with breast cancer is a risk factor for lower overall survival (OS).

Method: data from a five-year retrospective cohort study of all women diagnosed with invasive breast cancer at an academic oncology service were collected and analyzed.

Results: three hundred forty-eight consecutive women were included. Time between surgery and the first adjuvant treatment was a risk factor for shorter overall survival (HR=1.3, 95CI 1.06-1.71, p=0.015), along with negative estrogen receptor, the presence of lymphovascular invasion and greater tumor size. A delay longer than 4 months between surgery and the first adjuvant treatment was also associated with shorter overall survival (cumulative survival of 80.9% for delays ≤ 4 months *vs.* 72.6% for delays > 4 months; p=0.041, log rank test).

Conclusion: each month of delay between surgery and the first adjuvant treatment in women with invasive breast cancer increases the risk of death in 1.3-fold, and this effect is independent of all other well-established risk factors. Based on these results, we recommend further public strategies to decrease this interval.

Keywords: breast neoplasms, time-to-treatment, prognosis, survival, health care quality assurance.

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INTRODUCTION

Breast cancer is the most prevalent neoplasm in women in Brazil and around the world.¹ In less-developed countries, breast cancer is frequently diagnosed in advanced stages, which leads to a decrease in overall survival rates.² There are other variables that also influence the prognosis of these patients, including age, lymph node status, hormone receptor status, histologic grade and tumor size.³⁻⁵ In addition to these variables, some studies have shown that delays in the initiation of breast cancer treatment can also lead to a worse prognosis.^{2,6}

However, this remains a controversial issue in the literature; while some studies define that a three-month or longer delay between diagnosis and treatment can decrease survival in up to 12%,⁷⁻⁹ others argue that time until treatment does not influence the survival rates of women with breast cancer.^{10,11} This conflict cannot be easily resolved, because a prospective study to evaluate this variable and its possible confounding factors would be unethical.¹²

Therefore, we conducted a retrospective cohort study to determine if an increased delay between surgery and the first adjuvant treatment is a risk factor for lower overall survival among women with invasive breast cancer.

METHODS

This was a retrospective cohort review. After ethics committee approval, we obtained from the digital program used to attend patients in the ambulatories a list with all cases registered in medical records coded as C50, according to the “International Code of Diseases”. These women presented consecutively at the Oncology Service of a public academic hospital (Hospital Estadual Mário Covas – Santo André – Brazil) between January 2005 and December 2010. Data were, then, extracted from the medical records of all female patients with epithelial line invasive breast cancer already submitted to curative surgery. Since the authors were granted a waiver of consent by the ethics committee, these women were not contacted at all.

Women with metastatic breast cancer at diagnosis, those who received neoadjuvant treatment, and those who did not undergo curative surgery or adjuvant treatment for any reason were excluded from the analysis. Patients who were missing any important medical record data (regarding their surgery or first adjuvant treatment) were also excluded.

For each case, the time between the date of definitive surgery and the date of the first adjuvant treatment was calculated. A cutoff for delay until treatment of 4 months or 120 days was established according to the guideline proposed by the American Society of Clinical Oncology (ASCO).¹³ The overall survival was calculated as the time from diagnosis until death. Cases with follow-up loss were censored on the last date of contact.

Clinical and pathological data were also collected from original medical records, including age at diagnosis, histologic type (ductal *vs.* non-ductal), pathological stage according to the American Joint Committee on Cancer¹⁴ (I / II *vs.* III), number of positive axillary lymph nodes, tumor size, angiolymphatic invasion, perineural invasion, histologic grade (I / II *vs.* III), estrogen receptor status, HER2 status and type of adjuvant treatment (chemotherapy *vs.* radiotherapy *vs.* hormone therapy).

For statistical analysis, the categorical data were expressed as absolute numbers and relative rates, and the continuous data were expressed as the means and standard deviation (SD) or median and range. A Cox regression model was used for the univariate and multivariate analyses (backward likelihood ratio method) to calculate the hazard ratio (HR) with a 95% confidence interval (95CI). For the multivariate analysis, only the variables with $p < 0.20$ on univariate analysis were included. The Kaplan-Meier method was used to estimate the overall survival, and the log rank test was used to compare the survival curves. All analyses were performed using SPSS® 17.0 (SPSS® Inc.; Illinois, USA). A *p*-value of less than 5% was considered significant.

RESULTS

We included 348 consecutive women, with a median age of 57 years and a median time between surgery and first adjuvant treatment of 2 months (range: 0-11 months). The majority had invasive ductal carcinoma (75%) and was classified as having early stage breast cancer (77%). The mean tumor size was 2.6 cm, and the mean number of positive axillary lymph nodes was 2.6. Estrogen receptor was positive in 78% of the patients, and only 10% of the patients were Her2-positive. The first adjuvant treatment was chemotherapy in 59%, radiotherapy in 28% and

hormone therapy in 13% of the women. Nearly 10% of the women experienced delay in treatment longer than 4 months. A total of 23 deaths (6.6%) occurred, including 18 out of 312 patients (5.8%) in the group with delay between surgery and the first adjuvant treatment shorter than or equal to 4 months, and 5 out of 36 patients (13.9%) in the group with delay longer than 4 months. Other relevant characteristics and the corresponding percentages of cases are listed in Table 1.

TABLE 1 Distribution of included patients according to the studied characteristics.

Characteristic	Cases	
	n	%
Age*	57 years (27-92)	
Time from surgery until 1 st adjuvant treatment*	2 months (0-11)	
Delay to treatment		
≤ 4 months	312	89.6%
> 4 months	36	10.4%
Adjuvant treatment (1st)		
Chemotherapy	205	58.9%
Radiotherapy	98	28.2%
Hormone therapy	45	12.9%
Histologic type		
Ductal carcinoma	262	75.3%
Non-ductal carcinoma	86	27.7%
Pathological stage		
I / II	268	77.0%
III	80	23.0%
Tumor size**	2.6 cm ± 1.7	
Positive lymph nodes**	2.6 ± 4.2	
Angiolymphatic invasion		
No	168	70.0%
Yes	72	30.0%
Perineural invasion		
No	181	75.4%
Yes	59	24.6%
Histologic grade		
Grade I/II	258	74.1%
Grade III	90	25.9%
Estrogen receptor		
Positive	269	78.2%
Negative	75	21.8%
HER2 status		
Negative	290	89.5%
Positive	34	10.5%

N = number of patients; * Median (range); ** Mean ± standard deviation.

The characteristics associated with worse overall survival in the univariate analysis were younger age, pathological stage, tumor size, number of positive axillary lymph nodes, angiolymphatic invasion, perineural invasion, histologic grade, estrogen receptor status, type of adjuvant treatment and time between surgery and the first adjuvant treatment (Table 2).

The multivariate analysis then indicated that time between surgery and the first adjuvant treatment (continuous variable) is an independent risk factor (HR=1.35, 95CI 1.06 – 1.71, $p=0.015$, Cox regression) for worse overall survival, along with negative estrogen receptor, the presence of angiolymphatic invasion and larger tumor size (Table 2). When the delay to adjuvant treatment was categorized

using the 4-month cutoff and multivariate analysis was once again performed, the results were similar (HR=5.34, 95CI 1.22 – 23.26, $p=0.026$, Cox regression).

The overall survival curves using ASCO's suggested cutoff also demonstrated that women with a delay between surgery and the first adjuvant treatment longer than 4 months had worse overall survival (72.6 *vs.* 80.9%; $p=0.041$, log rank test, Figure 1).

DISCUSSION

In the present study, delay longer than 4 months between surgery and the first adjuvant treatment was found to be related to worse overall survival in patients with invasive breast cancer. Moreover, when considering time interval

TABLE 2 Univariate and multivariate analysis with delay as a continuous variable.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95CI	p*	HR	95CI	p*
Time from surgery until first adjuvant treatment	1.13	0.96 – 1.33	0.146	1.35	1.06 – 1.71	0.015
1st adjuvant treatment						
Chemotherapy	1.00			1.00		
Radiotherapy	0.35	0.12 – 1.04	0.059	0.39	0.04 – 4.10	0.369
Hormone therapy	0.19	0.03 – 1.44	0.108	1.43	0.13 – 15.6	0.927
Age	0.96	0.93 – 0.99	0.039	1.01	0.96 – 1.06	0.637
Histologic type						
Ductal carcinoma	1.00				N/A	
Non-ductal carcinoma	1.22	0.50 – 3.00	0.669			
Pathological stage						
I/II	1.00			1.00		
III	5.69	1.83 – 17.7	0.030	1.76	0.27 – 11.3	0.552
Tumor size	1.34	1.13 – 1.59	0.001	1.36	1.06 – 1.75	0.016
Positive lymph nodes	1.09	1.01 – 1.18	0.022	0.91	0.78 – 1.05	0.208
Angiovascular invasion						
No	1.00			1.00		
Yes	5.37	1.96 – 14.7	0.001	4.85	1.21 – 19.4	0.025
Perineural invasion						
No	1.00			1.00		
Yes	1.96	0.74 – 5.17	0.172	0.83	1.17 – 4.13	0.818
Histologic grade						
Grade I/II	1.00			1.00		
Grade III	5.27	0.67 – 41.3	0.114	0.71	0.17 – 2.94	0.635
Estrogen receptor						
Positive	1.00			1.00		
Negative	3.20	1.38 – 7.40	0.007	3.58	1.01 – 12.7	0.049
HER2 status						
Negative	1.00				N/A	
Positive	1.53	0.45 – 5.18	0.493			

HR = hazard ratio; 95CI = 95% confidence interval; * = Cox regression; N/A: not applied.

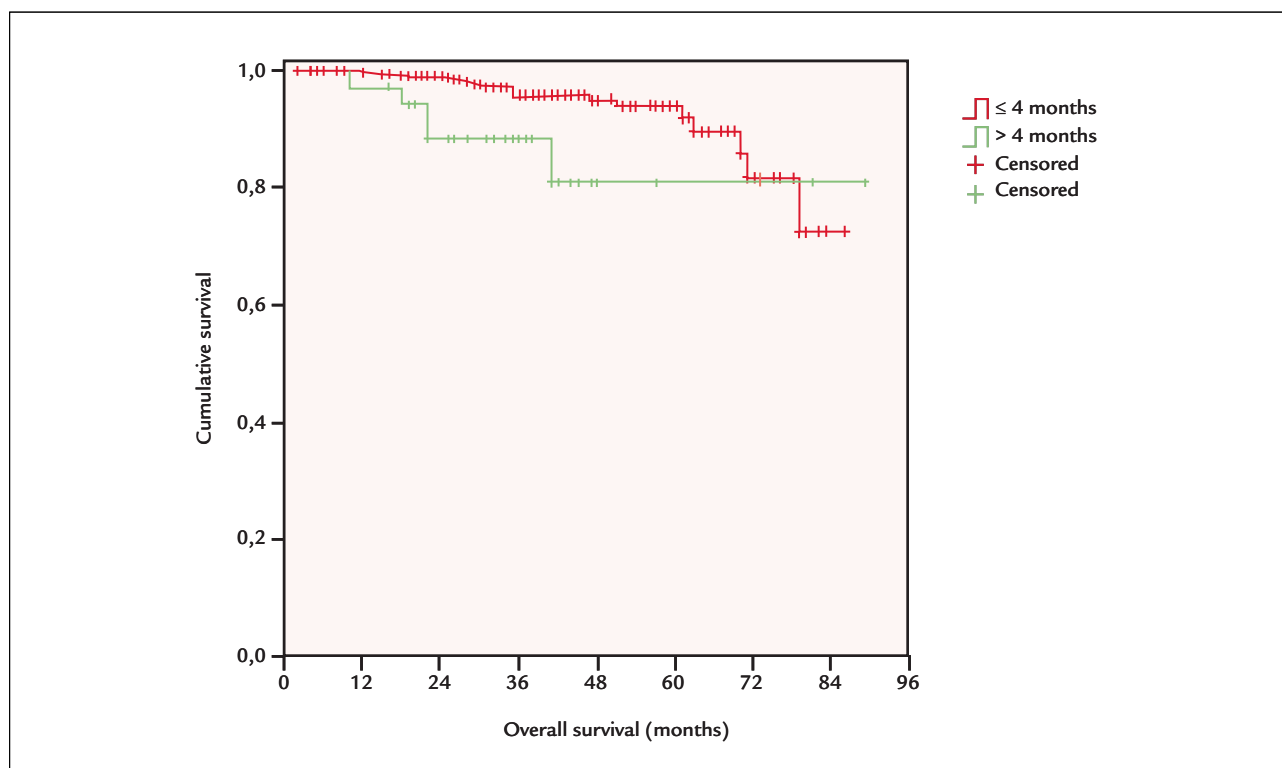


FIGURE 1 Kaplan-Meier curves showing that women with delay between surgery and the first adjuvant treatment longer than 4 months had a worse overall survival than those with this interval shorter than or equal to 4 months (72.6 vs. 80.9%; $p=0.041$, log rank test).

as a continuous variable, the risk of death was increased 1.3-fold for each month of delay, independently of other well-established factors.

Since 2006, our group has been studying treatment delays in patients with breast cancer. In our first report, we analyzed the intervals between the first symptom and medical evaluation, biopsy and treatment, and found that the largest delay was that from the first abnormality noted by the patient and scheduling of the first medical appointment.¹⁵ Then, we conducted another study to identify potential delays in the management of patients with breast cancer, including medical suspicion, diagnosis and treatment. In this report, we found that the longest delay occurred between mammographic suspicion and biopsy, and that such delay was significantly longer in patients with advanced-stage breast cancer. We also found that the median time between surgery and the first adjuvant treatment was 1 month (varying between 0.5 to nearly 21 months).² In this paper, our aim was to evaluate the delay between surgery and the first adjuvant treatment, based on a larger and more homogeneous group of consecutive patients with non-metastatic invasive breast cancer attended within a six-year

period in a public hospital, and also to account for possible confounding factors.

The present study was conducted in a public hospital in a developing country where delays may be very long; we found a median interval of 2 months, a maximum delay of 11 months, and a rate of nearly 17% of patients who experienced an interval longer than 120 days (4 months). In an American study analyzing patients from the NCCN (National Comprehensive Cancer Network) database, Vandergrift et al.¹⁶ determined a median interval of approximately 6 weeks (1.5 months) between surgery and first adjuvant treatment; they also reported that 13% of the patients had a delay of more than 120 days.

The ideal interval between surgery and first adjuvant treatment is not yet well established in the literature. Richards et al.¹⁷ reported that delays longer than 12 weeks to first adjuvant treatment negatively affect survival of breast cancer patients. Lohrisch et al.¹⁸ also found lower overall survival in patients with intervals longer than 90 days. In contrast, there are several studies that indicate otherwise, i.e., that delays in adjuvant treatment do not influence survival.^{9,12,19,20} This controversy can be due to confounding factors, such as different patients selected and differ-

ent cutoffs to establish an interval as a delay. In a recent report, Gagliato et al.²¹ showed that overall survival was influenced by adjuvant treatment delays longer than 60 days only in patients with known factors for worse prognosis, such as triple negative breast cancer or trastuzumab-treated Her2-positive breast cancer. A guideline from ASCO suggests that the duration between diagnosis and treatment should not exceed 120 days; they consider this a “reasonable estimate of the time need to deliver the preceding components of therapy that would not jeopardize outcome”.¹³ Because this reasonable time estimate was given by a panel of specialists and was based on the current literature, this was the cutoff established to categorize the delay of treatment in the present study.

The limitations of this study were inherent to a retrospective design: missing data, loss of follow-up, different adjuvant treatments over time, as well as different treating physicians. Also, demographic data were lacking in medical records which can somehow bias our results, although this was a very homogeneous cohort once all patients were from underprivileged areas, with no medical insurance. Regarding its strengths, the most important aspect of this study was its use of delay as a continuous variable (it was the first study to do this, to our knowledge), which was adjusted for possible confounding factors; this method produced a more precise and clinically relevant result, i.e., that each month of delay progressively worsens overall survival.

CONCLUSION

This study showed that greater time intervals between surgery and the first adjuvant treatment lead to a worse prognosis among women with invasive breast cancer. These findings cannot be confirmed in a prospective trial, and observational studies are the most powerful evidence. Based on these results, we recommend further strategies to decrease the interval between surgery and the first adjuvant treatment.

RESUMO

Atraso no tratamento adjuvante em pacientes com câncer de mama

Objetivo: avaliar se o tempo da cirurgia até o primeiro tratamento adjuvante (quimioterapia, radioterapia ou hormonioterapia) em pacientes com câncer de mama é um fator de risco para pior sobrevivência global (SG).

Métodos: estudo retrospectivo em que foram coletados dados dos prontuários de todas as mulheres com câncer

de mama invasivo, diagnosticadas entre janeiro de 2005 e dezembro de 2010, atendidas consecutivamente em um serviço acadêmico de oncologia.

Resultados: foram incluídas 348 mulheres, com mediana de tempo entre a cirurgia e o primeiro tratamento adjuvante de 2 meses. A sobrevivência global foi pior entre as mulheres com maior tempo entre a cirurgia e o primeiro tratamento adjuvante. Após análise multivariada, essa variável permaneceu como fator de risco independente para SG, juntamente com receptor de estrogênio negativo, presença de invasão angiolinfática e maior tamanho tumoral.

Conclusão: o tempo entre a cirurgia e o primeiro tratamento adjuvante é um fator de risco independente para a sobrevivência global de mulheres com câncer de mama invasivo.

Palavras-chave: neoplasias da mama, tempo para o tratamento, prognóstico, sobrevivência, garantia da qualidade dos cuidados de saúde.

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