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Survival of patients with de novo metastatic breast cancer

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ABSTRACT

Introduction: For the 2020-2022 trieniumm more than 2 million cases of breast cancer were estimated worldwide. De novo metastatic breast cancer is so called when metastasis is diagnosed at the same time as the primary tumor. It affects approximately 3.5 to 10% of breast cancer patients and only 25% of these will be alive after 5 years. **Methods:** We conducted a retrospective cohort study of women with de novo metastatic breast cancer treated at a single center from January 1, 2000 to December 31, 2012. Cases were identified in the Hospital Cancer Registry. Overall survival (OS) was estimated at 5 years with the Kaplan-Meier product limit, and the log-rank test was used to test differences between curves; Cox multiple regression and all tests were considered significant with p<0.05. **Results:** Of the 265 patients in the study, the estimated 5-year OS was 31.3%. There was a difference in survival according to the following: age group (p<0.046); having had breast surgery (p<0.001); having undergone chemotherapy simultaneously with radiotherapy, hormone therapy, targeted therapy or surgery (p<0.088); use of exclusive or multimodal hormone therapy (p<0.001); education (p<0.001); luminal tumors (p<0.003); and being treated between 2006 and 2012 (p=0.043). In the multiple model adjusted by age group and education, the following factors remained as predictors of a better prognosis: having undergone surgery (hazard ratio — HR=0.46, 95% confidence interval — 95%CI 0.32–0.66); luminal tumors (HR=0.34, 95%CI 0.23–0.50); and targeted therapy (HR=0.27, 95%CI 0.15–0.46). **Conclusion:** The risk of death in patients with de novo metastatic breast cancer was lower than in those undergoing local surgical treatment as part of multimodal treatment, as well as the luminal molecular subtype and the introduction of better systemic treatment strategies, such as target.

KEYWORDS: breast cancer; survival; metastasis.

INTRODUCTION

For the 2020-2022 triennium, more than 2 million cases of breast cancer were estimated worldwide, with just under 700,000 deaths, which represents a significant 15.5% of total cancer deaths in women[1,2]. In Brazil, the estimate was more than 73 thousand new cases and 18,068 deaths, with cancer being the first cause of death among women, which corresponds to 16.3% of all cancer deaths[3]. De novo metastatic breast cancer is so called when metastasis is diagnosed at the same time as the primary tumor. It affects approximately 3.5 to 10% of breast cancer patients and only 25% of these will be alive after 5 years[4-6]. It is a systemic disease that requires multimodal treatment and is classified, like the initial disease, into clinically relevant groups for treatment, according to the positivity or negativity of estrogen, progesterone and HER2 receptors[6-8]. The most frequent sites of metastases in these patients are bone, lung, liver and central nervous system[8,9]. The mutation profile is of greater complexity and heterogeneity than the initial stages[10-12]. Surgical treatment is considered in selected cases, with precise indication to control symptoms with the intention of hygienic surgery[12]. Some studies observed a positive impact on quality of life and others found an increase in overall survival (OS) when compared to patients who did not undergo surgery in the metastatic setting. A retrospective cohort analysis was conducted on the survival of de novo metastatic patients who underwent surgical treatment in relation to those who did not undergo surgery.

METHODS

This was a hospital-based retrospective cohort study with data extracted from the Hospital Cancer Registry (RHC); it

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was composed of women with de novo metastatic breast cancer treated in a single Brazilian center from January 1, 2000 to December 31, 2012. The sociodemographic variables analyzed were age group (≤50 years, 51–69 years and ≥70 years), education (complete and incomplete primary education, and complete secondary education and higher education), and health care (supplementary or public health care system). The molecular subtypes (luminal, HER2-positive luminal B, overexpressed HER2 and triple-negative), the histological grade (1, 2 and 3), the number of lines of chemotherapy and hormone therapy, and the topography of the metastases were analyzed. Treatment was stratified according to modality (yes and no), breast-conserving surgery (segmental resection and quadrantectomy), total mastectomy, axillary sentinel lymph node investigation, axillary dissection, chemotherapy, radiotherapy, hormone therapy and targeted therapy

The cases were staged according to the American Joint Commission of Cancer (AJCC), 8th edition, in 2018, which added histological grade, presence of estrogen/progesterone/HER2 receptors and multiple gene panel[13]. For qualitative variables, absolute (n) and relative frequency (%) were evaluated.

Survival time was calculated by subtracting the date of last information (alive or dead) by the date of diagnosis. The Kaplan-Meier product limit estimator was used to compare survival curves, and the log-rank test was applied. The semiparametric Cox proportional hazards model was used to evaluate the prognostic potential, and the hazard ratio (HR) and 95% confidence interval (95%CI) were calculated for all variables. For the multiple model, variables were selected using the log-rank test, from the highest to lowest level of statistical significance. The survival analysis was divided into two periods (2000–2005 and 2006–2012) because of the importance of the introduction of taxane drugs and targeted therapy in treating patients more effectively from 2006 onwards. The proportional hazards assumption was based on Schoenfeld residuals. The significance level for all tests was set at 0.05. All statistical analyses were performed in STATA 15 (College Station, Texas, 2017).

This study was approved by the Research Ethics Council (CEP) under No. 2660/19.

RESULTS

Between 2000 and 2012, 265 patients with de novo metastatic breast cancer were identified. Of these, 42.5% (n=90) were aged 61 or over and 78.5% (n=208) received care through the supplementary health care system. Regarding clinical staging, 51.4% (n=136) of patients were T4; 34.3% (n=91), N1; histological grade 2 was the most common, present in 47.5% (n=126) of patients (Table 1).

The molecular subtypes of the cases evaluated were: luminal (58%; n=153), HER2-positive luminal B (21%; n=56),

Table 1. Sociodemographic characteristics, clinical staging and molecular subtype of 265 patients with de novo metastatic breast cancer treated at the A. C. Camargo Cancer Center, from 2000 to 2012.

Variable	n=265	%
Age group (years)		
≤50	90	33.8
51–60	63	23.7
≥61	112	42.5
Education		
Primary, complete and incomplete	47	18.1
Secondary, complete, and Higher Education	77	28.9
Unknown	141	53.0
Health care		
Public health care system	50	18.8
Supplementary care health system	208	78.5
Not reported	7	2.6
Year of diagnosis		
2000–2005	90	33.8
2006–2012	175	66.2
T – Clinical tumor size		
Tx	4	1.5
T1	12	4.5
T2	68	25.7
T3	43	16.2
T4A/C/D	28	10.6
T4B	108	40.8
Not reported	2	0.8
N – Lymph node status		
N0	61	23.0
N1	91	34.3
N2	83	31.3
N3	28	10.5
Not reported	2	0.7
Molecular subtype		
Luminal	153	58.0
Luminal B HER2-positive	56	21.0
HER2-overexpressing	25	9.4
Triple-negative	19	7.1
No information	12	4.5
HER2*		
Negative	171	64.5
Positive	82	31.0
Not reported	12	4.3

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Table 1. Continuation.

Variable	n=265	%
Estrogen receptor		
Negative	56	21.0
Positive	202	76.0
No information	7	3.0
Progesterone receptor		
Negative	85	32.0
Positive	170	64.0
No information	10	4.0
Histological grade		
1	15	5.6
2	126	47.5
3	106	40.0
Not reported	18	6.8
Metastases (n=324)		
Bone	199	99.4
Lung	97	64.0
Liver	86	56.1
Central nervous system	40	28.5
Others	76	66.1

*HER2 + (IHC 3+ or 2+ with ISH amplified).

HER2-overexpressing (9.4%; n=25) and triple-negative (7.1 %; n=19) (Table 1).

When evaluating metastases, all patients had involvement in multiple organs, with bone being the most affected, followed by the lung and liver (Table 1).

In multimodal treatment, chemotherapy was performed in 81.9% (n=217) of patients, radiotherapy in 76.7% (n=204), hormone therapy in 66.8% (n=177); targeted therapy in 15.8% (n=42) and surgery in 32.5% (n=86) (Table 2).

The 5-year OS in patients with de novo metastatic breast cancer from 2000 to 2012 was 31.3%: 20.22% in the period of 2000 to 2005 and 34.95% in the period of 2006 to 2012. The highest survival rates were identified in women with age under 50 years (35.89%), higher education (42.2%), luminal molecular subtype (34.4%), surgical breast treatment (47.7%), axillary surgery (49.3%), radiotherapy (34.5%) and targeted therapy (54.2%) (Table 3 and Figure 1).

In the multiple regression model adjusted by age group and education, a reduction in the risk of death was observed in patients who underwent surgical treatment in the breast (HR=0.46, 95%CI 0.32–0.66), with luminal tumors (HR=0.34, 95%CI 0.23–0.50) and with HER2 tumors using targeted therapy (HR=0.27, 95%CI 0.15–0.46). An increased risk of death was also observed in patients with N2 and N3 axillary involvement (HR=1.71, 95%CI 1.12–2.62) (Table 4).

Table 2. Treatment modalities in 265 patients with de novo metastatic breast cancer at A. C. Camargo Cancer Center, from 2000 to 2012.

Treatment	n	%
Primary surgery – breast		
Yes	86	32.5
No	179	67.5
Type of breast surgery – primary		
Mastectomy (total)	71	82.5
Conservative surgery	15	17.4
Axillary surgery		
Yes	79	30.0
No	186	70.0
Type of axillary surgery		
Axillary dissection	76	96.2
Sentinal lymph node	3	3.8
Chemotherapy		
Yes	217	81.9
No	48	18.1
Hormonne therapy		
Yes	177	66.8
No	88	33.2
Targeted therapy		
Yes	42	15.8
No	223	84.2
Radiotherapy of primary lesion – breast		
Yes	68	25.6
No	244	78.2
Radiotherapy of metastases		
Yes	136	51.1
No	108	40.7
Bone	76	28.6
Central nervous system	40	15.1
Others*	20	7.4

*plastron, neuroaxis, ocular, lymph nodes.

DISCUSSION

In this study, it was possible to verify a 31.3% probability of survival of *de novo* metastatic patients within 5 years in the period from 2000 to 2012. It was observed that, among these, patients who underwent surgical treatment of the primary tumor had an increase in survival, but it was found that the most common tumor profile was luminal, which are usually tumors with a better prognosis and great possibility of drug treatment.

Table 3. Probability of survival according to sociodemographic and clinical characteristics of 265 patients with de novo metastatic breast cancer.

Variable	Death (total)	OS – 5y	p-value
Age group (years)			
≤50	68 (89)	35.89	0.046
51–69	103 (124)	28.79	
≥70	41 (51)	21.65	
Education			
Primary incomplete/complete	41 (47)	12.77	<0.001
Secondary	23 (32)	28.13	
Higher education	25 (45)	42.20	
Unknown	141		
Year of diagnosis			
2000–2005	71 (89)	20.22	0.004
2006–2012	111 (176)	34.95	
Health care			
Public health care system	41 (50)	26.18	0.897
Supplementaryl health care system	164 (208)	31.82	
Not determined	7		
Clincal staging – cT			
T0/1	9 (16)	43.75	0.016
T2	40 (68)	39.93	
T3	25 (43)	38.03	
T4 A/C/D	21 (28)	25.00	
T4B	85 (108)	20.01	
Not determined	2		
Clincal staging – cN			
N0	34 (63)	44.18	<0.001
N1	56 (91)	36.44	
N2	69 (82)	15.85	
N3	21 (27)	22.22	
Not determined	2		
Topography of metastases			
Bone	101 (152)	31.92	0.466
Lung	30 (45)	32.15	
Liver/central nervous system	51 (69)	23.92	
Luminal			
Yes	136 (212)	34.44	<0.001
No	46 (52)	11.92	
Not determined	1		
HER2			
Yes	54 (82)	33.84	0.496
No	116 (171)	30.09	
Not determined	12		
Triple-negative			
Yes	17 (19)	5.92	<0.001
No	156 (237)	32.87	
Not determined	9		
Histological grade			
1	11 (15)	25.28	0.223
2	95 (126)	35.62	
3	88 (106)	28.62	
Not determined	18		
Breast surgery			
Yes	57 (86)	47.67	<0.001
No	137 (179)	21.05	
Type of breast surgery			
Mastectomy	36 (71)	49.3	0.586
Conservative surgery	9 (15)	40.00	
Axillary surgery			
Yes	51 (79)	49.37	<0.001
No	142 (186)	21.33	
Type of axillary surgery			
Axillary dissection	38 (76)	50.00	0.801
Sentinel lymph node	2 (3)	33.33	
Chemotherapy			
Yes	173 (217)	30.77	0.088
No	35 (48)	25.89	
Radiotherapy			
Yes	124 (157)	34.53	0.008
No	101 (108)	23.12	
Targeted therapy			
Yes	26 (42)	54.19	<0.001
No	163 (223)	25.23	
Hormone therapy			
Yes	135 (177)	39.11	<0.001
No	76 (88)	11.41	
Not determined	1		
Hormone therapy lines			
0	74 (74)	10.60	<0.001
1	43 (59)	39.07	
2	43 (54)	32.67	
3	40 (56)	52.80	
Not determined	12		
Chemotherapy lines			
0	42 (44)	24.31	0.016
1	50 (69)	36.79	
2	36 (46)	30.09	
3	60 (74)	35.91	
Not determined	25		

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The significance level for all tests was set at 0.05.

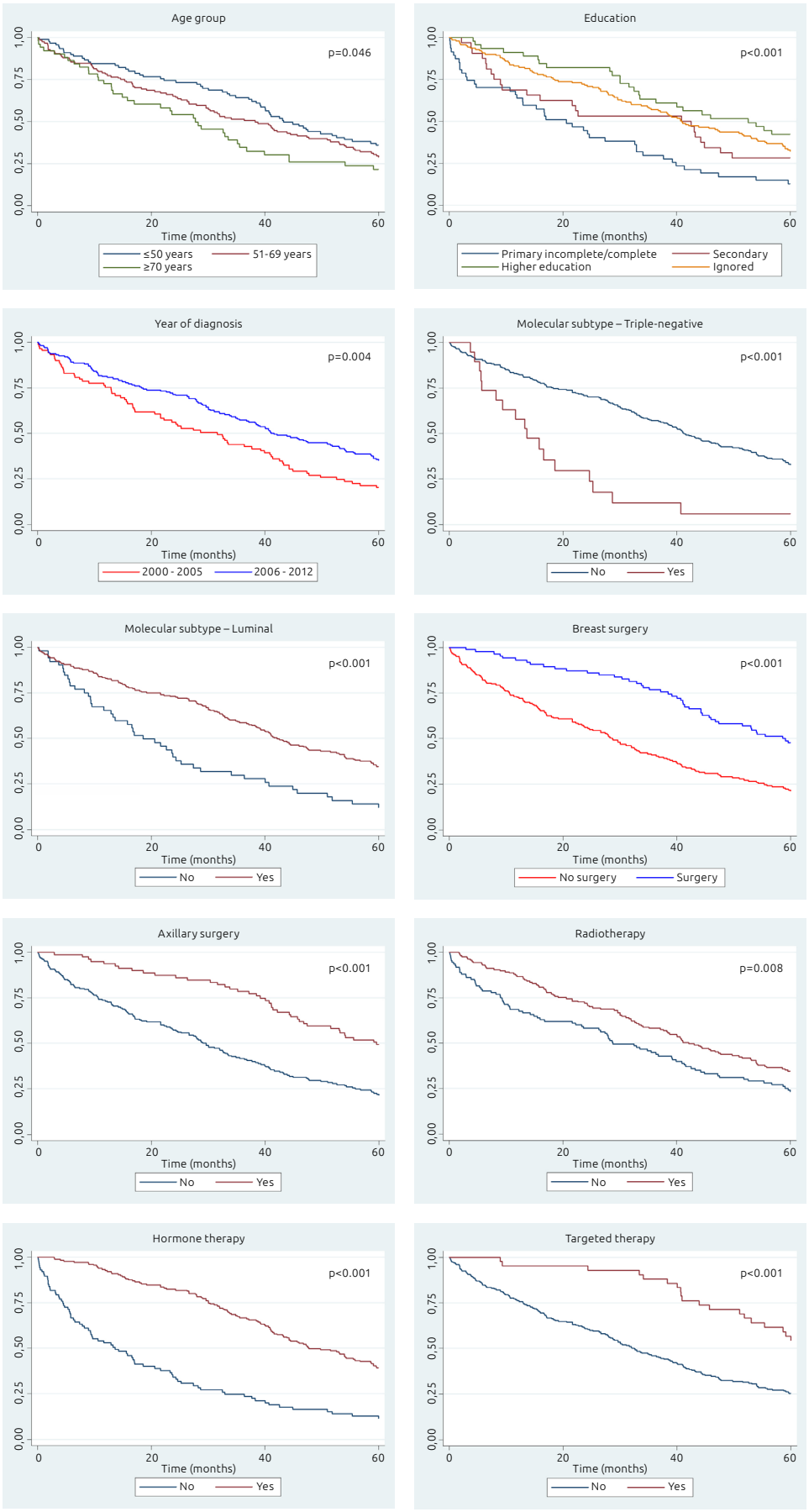

Figure 1. Estimated overall survival of 60 months for patients with de novo metastatic breast cancer.

Table 4. Prognostic factors associated with the survival of patients with metastatic breast cancer de novo at A. C. Camargo Cancer Center, from 2000 to 2012.

Variable	HR	HRa* (95%CI)
Breast surgery		
No	1.00	1.00
Yes	0.42 (0.29–0.59)	0.46 (0.32–0.66)
Luminal		
No	1.00	1.00
Yes	0.46 (0.33–0.65)	0.34 (0.23–0.50)
Targeted therapy		
No	1.00	1.00
Yes	0.38 (0.23–0.61)	0.27 (0.15–0.46)
cN		
N0	1.00	1.00
N1	1.25 (0.81–1.91)	1.21 (0.78–1.87)
N2	2.15 (1.42–3.25)	1.71 (1.12–2.62)
N3	1.80 (1.04–3.10)	1.87 (1.06–3.28)
Age group (years)		
≤50	1.00	1.00
51–69	1.25 (0.89–1.74)	0.90 (0.62–1.29)
≥70	1.67 (1.11–2.53)	0.98 (0.62–1.55)
Education		
Illiterate	1.00	1.00
Primary incomplete/ complete	0.59 (0.35–0.98)	0.72 (0.41–1.27)
Secondary	0.36 (0.22–0.60)	0.50 (0.29–0.85)
Higher education	0.48 (0.33–0.69)	0.73 (0.48–1.09)

HR: hazard ratio; 95%CI: 95% confidence interval. *Test of proportional--hazards assumption (p=0.218). Adjusted for schooling and age group.

Analyzing how these patients access care, there was no difference in survival between those treated in the public health care system and those treated in the supplementary health care system. Despite the treatment limitations imposed in the public system, access to chemotherapy and hormone therapy, at the time considered, was quite similar in our service, which was not the reality in Brazil as a whole. In the Amazona III study, a nationwide retrospective cohort that carried out an epidemiological analysis of breast cancer at all stages and evaluated the difference between patients treated by the public health care system and the supplementary health care system, it was observed that patients treated in the public system had tumors at more advanced stages and greater difficulty in accessing screening tests, which had a negative impact on their prognosis[14].

In our study, all patients were multimetastatic, with the main sites being bone, lung, liver and central nervous system, and no difference in survival was observed when evaluating the metastasis sites, which can be explained by the multiplicity of metastatic sites. In the work of Tian et al.[15], who evaluated mutations and possible biomarkers in patients with metastatic tumors and correlated them with impact on treatment and survival, liver metastases had a worse prognosis compared to other sites[15-17].

In this study, approximately 35.89% of patients were under 50 years of age, 80% belonged to the luminal subtype and regarding the combined treatment of chemotherapy, radiotherapy and surgery, 81.9% underwent chemotherapy and 32.5% surgery. This patient profile was similar to that studied in ECOG – ACRIN 2108, which evaluated surgical treatment in this group and observed no difference in OS or progression-free survival at 3 years[15]. In patients with de novo metastatic breast cancer, surgery is an option, but in the classic indication of controlling local complications, such as bleeding and infection[16]. Badwe et al.[17] found an improvement in survival in patients operated on with luminal profiles and single bone metastasis, while the ACRIN study did not observe an impact on survival[15,17].

It was observed in this study that the inclusion of surgery as part of the treatment showed an increase in survival. Our findings are consistent with those of Badwe et al.[17] and Soran et al. regarding the use of breast surgery in these patients[17,18]. It is important to note that the majority had the luminal molecular subtype, which has a better prognosis, a fact that may have influenced the results.

In clinical practice, however, the survival benefit of local treatments in de novo metastatic breast cancer is controversial. Retrospective studies have shown that local treatments increase survival, as shown in this study[17,18]. Recent randomized clinical trials[19,20] that investigated the survival benefit of primary site surgery revealed contradictory conclusions[14,15,21,22]. The reasons for this greater survival need to be studied by exploring possible mutations and genetic biomarkers, as identified in the study by Bertucci et al., from 2019, which determined the presence of mutations in nine controlling genes, such as TP53 and GATA3, among others, which impact the prognosis and survival of these patients[23]. The study concluded that metastatic disease has more mutations and greater complexity than the initial disease. Therefore, the identification of these mutations would help in conducting individualized and efficient treatment[15,23,24].

Analyzing the literature, it is possible to observe that the indication for surgery in de novo metastatic patients went through three phases: in the first, all patients underwent surgery; in the second, no patient underwent surgery; and in the third, at the moment, we individually evaluate each patient, each tumor type, disease control or progression and define cases that may benefit from surgery and those that, in fact, do not need surgery on the primary tumor[25-29].

Therefore, the study has limitations inherent to retrospective studies. However, it is a referral center specialized in cancer treatment in which data are systematically reviewed.

CONCLUSIONS

Greater survival was observed in de novo metastatic breast cancer patients whose multimodal treatment included breast surgery. However, factors such as luminal molecular subtype may have influenced these results. As the understanding of the biology of tumors evolves and treatments become more accessible to the population, our challenges will be greater in determining for whom and at what time each treatment should be carried out. What, in fact, is causing the best survival of our patients seems to us to be this quality multidisciplinary treatment.

AUTHORS' CONTRIBUTION

FPML: Investigation, Data curation, Writing – review & editing. GAF: Formal analysis, Methodology, Writing – review & editing. MPC: Formal analysis, Methodology, Writing – review & editing. SMS: Writing – review & editing, Supervision. LPF: Writing – review & editing. FBAM: Conceptualization, Project administration, Supervision, Writing – review & editing.

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