original reports abstract

Low Overall Survival in Women With De Novo Metastatic Breast Cancer: Does This Reflect Tumor Biology or a Lack of Access to Health Care?

Leonardo R. Soares, MD, PhD[1]; Ruffo Freitas-Junior, MD, PhD[1,2]; Maria P. Curado, MD, PhD[3]; Regis R. Paulinelli, MD, PhD[1,2]; Edesio Martins, BSc, PhD[1]; and José C. Oliveira, MD, PhD[4]

PURPOSE As a result of its epidemiologic and therapeutic aspects, metastatic breast cancer (MBC) is a highly relevant clinical condition. This study aimed to estimate overall survival (OS) in women with de novo MBC in a Brazilian population.

PATIENTS AND METHODS Patients were identified in the Goiânia population-based cancer registry between 1995 and 2011. All women with metastatic disease at diagnosis were included in the study. OS was analyzed at 5 and 10 years of follow-up. We used the Kaplan-Meier estimator and Cox regression for statistical analysis.

RESULTS Over the 16-year period covered by the study, 5,289 women were diagnosed with breast cancer in Goiânia. Of these, 277 women (5.2%) had MBC. OS rates at 5 and 10 years were 19.9% and 7.3%, respectively. The mean OS time of women treated in the public health system was 7.5 months shorter than in women who had private health care (19.7 *v* 27.2 months, respectively). In the univariable analysis, the following factors were statistically significant for OS: T3/4 staging, histologic grade 3, progesterone receptor status, tumor phenotype, breast surgery, CNS metastasis at initial presentation, and surgery for resection of metastasis. In multivariable analysis, initial CNS metastasis (hazard ratio, 3.09; 95% CI, 1.16 to 8.19) and breast surgery (hazard ratio, 0.45; 95% CI, 0.25 to 0.78) remained independent prognostic factors.

CONCLUSION OS was lower than rates found in specialist centers in Brazil and in developed countries. Several intrinsic and extrinsic factors were significant in predicting OS. Despite the difference in the 5-year survival rate, the type of access to health care was not significant in the multivariable analysis of the entire period.

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INTRODUCTION

Breast cancer is a public health issue of global scale. Two million new patients were estimated to be diagnosed worldwide in 2018,[1] of whom 5% to 30% were expected to be diagnosed at metastatic stage.[2-4] Over recent decades, screening programs in the United States have unexpectedly failed to reduce the percentage of women diagnosed at metastatic stage.[5] Because breast cancer is a heterogeneous pathology with various patterns of tumor biology,[2,6] it translates into individualized types of clinical behavior and therapeutic response.[7,8]

Metastatic breast cancer (MBC) is also a heterogeneous condition with a diverse clinical course.[3,9,10] In recent years, increased knowledge on tumor biology, advances in the diagnosis of the disease, and access to new therapeutic agents have increased the overall survival (OS) of patients with MBC.[10,11] Nevertheless, these advances have also uncovered new challenges regarding the management of the metastatic disease itself and of the adverse events caused by systemic treatment.[12,13] Individuals with metastatic conditions are generally given a continuous regimen of palliative treatment, which results in a high demand on health care facilities as a result of the constant need for tests, prescription of medication, and hospitalization for clinical support.[12,14,15]

In low- and middle-income countries, there are additional problems, such as limited access to health care, with diagnosis often being made late and at more advanced stages, and the use of treatments below the already established standard.[16,17] For example, in the Brazilian public health care system, which provides care to approximately 70% of the country's population, trastuzumab became available for the treatment of metastatic HER2-positive breast cancer in 2017, almost 20 years after the US Food and Drug Administration approved the drug for use in the United States.[18,19] With the subsequent introduction of the CDK4/6 inhibitors and other anti-HER2 therapies in high-income countries,[10,20] this difference in oncologic outcomes may have increased even further.

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To estimate overall survival in women with de novo metastatic breast cancer in a Brazilian population.

Knowledge Generated

The overall survival of women with metastatic breast cancer after 5 and 10 years of follow-up and the respective prognostic factors in this population.

Relevance

In this population-based study, the overall survival was lower than rates found in specialist centers in Brazil and in developed countries. Several intrinsic and extrinsic factors were significant in predicting overall survival.

Prognostic factors are ultimately associated with OS because they are indicators of various clinical outcomes involving the risk of recurrence or death. Identifying these factors is crucial for clinical follow-up and the specific treatment of patients with cancer. Currently, most of the data on MBC originate from retrospective, hospital-based studies or controlled trials involving specific populations and treatments.[10,11,21,22] However, population-based studies have the advantage of enabling an epidemiologic analysis to be made of different populations, which may help in the development of specific public policies.[4,23,24] Therefore, the objective of the current study was to estimate OS and identify the prognostic factors associated with MBC in a Brazilian population for the period from 1995 to 2011.

PATIENTS AND METHODS

An ecologic study of OS was conducted in patients with de novo MBC between January 1, 1995, and December 31, 2011. The patients were retrieved from a database at the Goiânia population-based cancer registry for the period from 1995 to 2011.

Goiânia Population-Based Cancer Registry

This cancer registry was created in 1986 and has registered all new patients with cancer diagnosed in the city of Goiânia uninterruptedly from its creation to the present day.[24,25]

Eligibility Criteria

Women whose records were found to include the description "metastatic" or "unknown" under the heading "Extent of the Disease" were considered potentially eligible.

Patients

All women previously classified as having MBC at diagnosis were included in the study.[26] This classification was determined by the patients' clinical records, imaging tests, and/or histology results showing the presence of metastatic cancer (ie, disease beyond the breast and axillae).[12,13]

We revised all the eligible patients by actively performing a search of the medical archives at the Goiás Association for the Combat of Cancer's Araújo Jorge Hospital and at the Teaching Hospital of the Federal University of Goiás. Both hospitals are referral centers for cancer treatment in the city of Goiânia and active data collection sources for the population-based cancer registry. Patients with breast carcinoma in situ and patients without histologic confirmation were excluded from the study, as were patients for whom the only record of diagnosis was on the death certificate.

Variables

A questionnaire based on previous studies conducted with populations with metastatic cancer[9] and the standardization used by the Goiânia population-based cancer registry[24] were used for data collection. The following demographic variables were analyzed: age at diagnosis, age at menarche, family history of breast or ovarian cancer, and whether care was provided within the public or private health care system.

The site of the tumors and their morphologic classification were coded in accordance with the International Classification of Diseases for Oncology, third edition, encompassing the morphologic codes 8500/3, 8520/3, and 8521/3.[27,28] Sarcomas (8800/3) and other morphologic types (anaplastic carcinoma and spindle cell types) were classified as other subtypes.

Histologic grade was classified as grade 1, 2, or 3 according to the Bloom-Richardson grading system.[29] Locoregional staging was classified according to the TNM staging system, as defined in the eighth edition of the American Joint Committee on Cancer staging manual.[30,31]

The immunohistochemical expression of estrogen and progesterone receptors was considered positive or negative according to the report from each laboratory. HER2 expression was considered positive when the degree of positivity was expressed as 3 plus symbols (+++) or when confirmed by immunofluorescence. Tumor phenotype classification was determined in accordance with the recommendations of the 15th St Gallen International Breast Cancer Conference.[32]

Data on the location of metastases were collected from the medical records at the 2 hospitals involved in the study. The site of metastatic lesions and the presence of associated clinical symptoms were evaluated, as well as whether

TABLE 1. Clinical Characteristics and Overall Survival at 60 Months of Follow-Up in Patients With De Novo Metastatic Breast Cancer in the City of Goiânia (1995-2011)

Characteristic[a]	No. of Patients	%	Survival Rate (%)	Mean Survival Time (months)	95% CI for Survival (months)	*P*[b]
Age at diagnosis, years (n = 277)						.4
≤ 49	103	37.2	16.6	25.4	21.2 to 29.6	
50-59	75	27.1	23.1	27.7	22.4 to 33.0	
≥ 60	99	35.7	16.1	23.4	18.5 to 28.4	
Presence of symptoms (n = 126)						.1
Yes	103	81.8	8.9	20.4	17.0 to 23.9	
No	23	18.2	19.7	27.2	18.4 to 36.0	
Histologic type (n = 136)						.02
Carcinoma, not otherwise specified	19	14.0	0.0	16.2	10.4 to 22.0	
Ductal carcinoma	107	78.6	22.2	27.7	23.5 to 31.9	
Lobular carcinoma	6	4.4	0.0	18.8	5.1 to 32.4	
Sarcoma and others	4	3.0	0.0	15.0	1.3 to 28.6	
Histologic grade (n = 89)						.03
1	11	12.3	51.9	37.3	22.2 to 52.5	
2	51	57.3	18.0	30.2	24.8 to 35.6	
3	27	30.4	8.0	21.8	15.1 to 28.4	
Estrogen receptor status (n = 79)						.02
Positive	53	67.1	26.4	33.5	28.2 to 38.9	
Negative	26	32.9	5.1	24.7	18.3 to 31.2	
Progesterone receptor status (n = 76)						< .01
Positive	42	55.3	35.1	38.9	33.2 to 44.6	
Negative	34	44.7	3.0	21.4	16.2 to 26.6	
c-erbB (n = 71)						.4
Positive	24	33.8	11.7	29.1	21.8 to 36.3	
Negative	47	66.2	24.1	31.8	26.1 to 37.5	
Tumor phenotype (n = 71)						.02
Luminal	34	47.9	33.0	36.9	30.5 to 43.3	
Luminal-HER2	16	22.5	15.7	28.4	17.6 to 39.2	
HER2	8	11.3	0.0	27.2	19.1 to 35.3	
Triple negative	13	18.3	7.7	20.2	11.2 to 29.1	

(Continued on following page)

TABLE 1. Clinical Characteristics and Overall Survival at 60 Months of Follow-Up in Patients With De Novo Metastatic Breast Cancer in the City of Goiânia (1995-2011) (Continued)

Characteristic[a]	No. of Patients	%	Survival Rate (%)	Mean Survival Time (months)	95% CI for Survival (months)	*P*[b]
T stage (n = 129)						.01
T0	3	2.3	0.0	18.7	4.5 to 32.9	
T1	12	9.3	41.7	38.1	26.0 to 50.2	
T2	22	17.1	36.9	36.4	27.6 to 45.2	
T3	25	19.4	12.0	21.1	13.6 to 28.7	
T4	67	51.9	11.4	21.1	16.4 to 25.9	
N stage (n = 123)						.5
N0	31	25.2	23.8	30.0	22.3 to 37.6	
N1	40	32.5	22.2	23.1	16.1 to 30.1	
N2	37	30.1	8.3	23.4	17.5 to 29.4	
N3	15	12.2	13.3	21.8	12.4 to 31.3	
Type of health care (n = 128)						.04
Public	90	70.3	6.9	19.7	16.2 to 23.3	
Private	38	29.7	22.4	27.2	20.2 to 34.1	
Site of metastases (n = 129)						.02
Bone	36	27.9	20.9	27.2	20.1 to 34.2	
Visceral	41	31.8	10.4	22.0	16.4 to 27.7	
Visceral and bone	24	18.6	9.2	20.4	13.1 to 27.7	
CNS	11	8.5	0.0	9.8	4.7 to 15.0	
Skin, subcutaneous cell tissue, or distant lymph nodes	17	13.2	5.9	20.7	12.9 to 28.4	
Surgery to resect breast tumor (n = 123)						< .01
Yes	50	40.6	21.0	31.7	25.9 to 37.4	
No	73	59.4	5.7	16.0	12.5 to 19.5	
Metastasis extirpation (n = 108)						.08
Yes	10	9.2	30.0	33.5	18.7 to 48.4	
No	98	90.8	9.8	20.9	17.7 to 24.2	

Abbreviation: HER2, human epidermal growth factor receptor 2.

[a]Numbers of individuals with data for each variable are in parentheses.

[b]Log-rank test.

aspiration and/or biopsy of the lesions had been performed. With respect to treatment, data were collected on the type of surgery performed for the primary tumor and/or metastasis and the use of systemic treatments.

Survival

For the survival analysis, the cutoff date for the duration of follow-up or active search for the women was December 31, 2018. Initially, the data available in the registry database and/or medical records were retrieved. To complete the data set with information on patients' vital status, a search was made of the Goiás mortality database, the electoral roll, and the Municipal Social Services Department.

Data Analysis

OS was divided into analyses conducted at 5 and 10 years of follow-up and over the entire period. Time of follow-up was calculated from the date of diagnosis until the occurrence of the event of interest (death) or until censure (ie, women who remained alive at the end of the follow-up time were censored).

The database was constructed and the statistical analysis conducted using the SPSS software package for Windows, version 22.0 (IBM Corporation, Armonk, NY) and MedCalc for Windows, version 18.11 (MedCalc Software, Ostend, Belgium). The qualitative variables were described using frequency distributions and percentages. The distribution of survival was calculated using the Kaplan-Meier estimator and compared between the groups using the log-rank test, with 95% CIs. Cox regression analysis was used for the univariable and multivariable analysis. First, all the potential prognostic variables were tested, each by using the univariable Cox regression model. The prognostic variables with a significance level of $P < .2$ were considered as candidates for the multivariable analysis. In addition, interaction between the variables was tested, and none returned significant values. $P < .05$ was considered statistically significant.

Ethical Issues

The internal review board of the Association for the Combat of Cancer's Araújo Jorge Hospital approved the study protocol under reference No. CAAE 61987716.0.0000.0031. All the recommendations of good clinical practice outlined in the Brazilian National Health Council's resolution 466/2012 and in the Declaration of Helsinki were followed.

RESULTS

Over the 16-year period analyzed, 5,289 breast cancers were diagnosed in residents of the city of Goiânia, Brazil. Of these, 277 cancers (5.2%) were identified as de novo MBC. Access to the patient's medical records was obtained in 156 of these patients, the majority of whom (70.3%) were treated in the public health care system.

The mean age of the women with MBC included in this study was 54.7 years (standard deviation, 14.5 years).

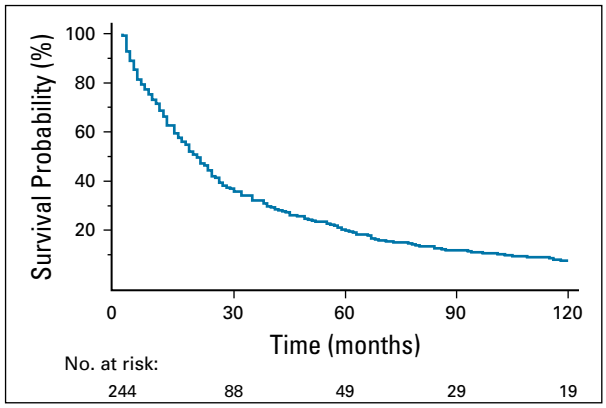

FIG 1. Overall survival of women with de novo metastatic breast cancer in the city of Goiânia (1995-2011).

Eighty-eight patients (68.2%) had only one metastatic site at diagnosis, regardless of disease volume. Patients' clinical data and data on diagnosis and treatment of the disease are listed in Table 1. Most patients (100 [91.7%] of 109 patients) received chemotherapy as first-line systemic treatment irrespective of the tumor phenotype. In the group of patients with hormone receptor–positive cancer, endocrine therapy was prescribed in 14.0% of patients (6 of 43 patients) as first-line treatment of MBC and in 48.5% of patients (17 of 35 patients) as second-line treatment. Of the 23 women with HER2-positive breast cancer for whom data were available on the treatment received, 3 patients had received trastuzumab as first-line treatment and 2 as second-line treatment.

OS rates at 60 and 120 months were 19.9% and 7.3%, respectively (Fig 1). The mean survival time was 37.2 months (95% CI, 31.5 to 42.2 months), and the median survival time was 20.0 months (95% CI, 16.3 to 23.7 months). The mean OS of women treated in the public health system was 7.5 months shorter than in private health care users (19.7 *v* 27.2 months, respectively; Table 1).

The univariable hazard ratios and 95% CIs of risk factors for mortality are listed in Table 2. In the group of patients with hormone receptor–positive tumors, there was no difference in survival as a function of the type of first-line treatment received (chemotherapy *v* endocrine therapy). In the multivariable analysis, CNS metastasis at initial presentation and having undergone surgery to remove the breast tumor were factors found to be statistically significant in predicting OS (Table 3).

DISCUSSION

To our knowledge, this is the first population-based study dealing with MBC to be conducted in Brazil. In the United States, approximately 6% of women are diagnosed with MBC,[5] a figure that is similar to the percentage of 5.2% found in this series. In the current study, the OS rate was 19.9% at 5 years and 7.3% at 10 years in a population of women with MBC in the city of Goiânia. In women with

TABLE 2. Univariable HR and 95% CIs of Risk Factors for Mortality in Women With De Novo Metastatic Breast Cancer in the City of Goiânia, Brazil (1995-2011)

Factor	HR	95% CI	No. of Patients (%)	Wald	P[a]
Age, years					
< 50	1	—	103 (37.18)	—	—
50-59	0.94	0.69 to 1.29	75 (27.08)	0.15	.70
≥ 60	1.24	0.92 to 1.67	99 (35.74)	2.02	.15
Age > 60 years	1.27	0.98 to 1.66	99 (35.74)	3.16	.07
Menarche > 12 years old	1.04	0.53 to 2.03	32 (69.57)	0.011	.91
First-degree family history (breast or ovary)	1.62	0.85 to 3.09	12 (18.18)	2.11	.14
Ductal histology	0.60	0.31 to 1.14	126 (92.65)	2.42	.12
Grade					
1	1	—	11 (12.36)	—	—
2	1.43	0.72 to 2.85	51 (57.30)	1.06	.30
3	2.29	1.08 to 4.89	27 (30.34)	4.61	.03
Grade 3	1.70	1.05 to 2.73	27 (30.34)	4.74	.02
T3/4	1.80	1.21 to 2.67	92 (71.32)	8.58	< .01
Node positive	1.39	0.92 to 2.11	89 (74.80)	2.38	.12
ER positive	0.64	0.40 to 1.04	53 (37.09)	3.23	.07
PR positive	0.43	0.26 to 0.68	42 (55.26)	12.51	< .01
HER2 positive	1.31	0.79 to 2.17	24 (33.80)	1.11	.29
Subtype					
Luminal	1	—	34 (47.89)	—	—
Luminal/HER	1.42	0.78 to 2.60	16 (22.54)	1.28	.25
HER positive	1.86	0.84 to 4.12	8 (11.27)	2.33	.12
TN	2.04	1.06 to 3.92	13 (18.31)	4.58	.03
Luminal	0.60	0.40 to 1.00	50 (70.42)	3.82	.05
Multiple metastatic sites	1.36	0.92 to 1.99	41 (31.78)	2.41	.12
Primary metastatic site					
Bone only	1	—	36 (27.91)	—	—
Visceral only	1.24	0.78 to1.97	41 (31.78)	0.87	.35
Visceral and bone	1.45	0.85 to2.46	24 (18.60)	1.89	.16
Skin, subcutaneous tissue, or lymph nodes	1.36	0.76 to2.46	17 (13.18)	1.07	.30
CNS	2.75	1.32 to5.69	11 (8.53)	7.40	< .01
Initial CNS metastasis	2.24	1.16 to 4.35	11 (8.53)	5.69	.01
Public funding	1.30	0.88 to 1.92	90 (70.31)	1.78	.18
No breast surgery	2.22	1.51 to 3.27	73 (59.35)	16.26	< .01
Surgery of the metastasis					
Excisional biopsy	1	—	10 (7.81)	—	—
Incisional biopsy	1.69	0.78 to 3.66	20 (15.63)	1.77	.18
No Surgery	2.02	1.03 to 3.97	98 (76.56)	4.21	.04
Metastasis extirpation	0.51	0.26 to 1.00	10 (7.81)	3.86	.05
Symptomatic metastasis	1.45	0.90 to 2.34	103 (81.75)	2.37	.12

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor; RT, radiotherapy; TN, triple negative.

[a]Cox regression.

TABLE 3. Multivariable HRs and 95% CIs of Risk Factors for Mortality in Women With De Novo Metastatic Breast Cancer in the City of Goiânia, Brazil (1995-2011)

Factor	HR	95% CI	Wald	*P*[a]
Age > 60 years	1.32	0.70 to 2.50	0.74	.39
Grade 3	1.15	0.70 to 1.92	0.30	.58
T3/4	1.05	0.60 to 1.83	0.03	.87
Initial CNS metastasis	3.09	1.16 to 8.19	5.13	.02
Metastasis extirpation	0.63	0.28 to 1.45	1.16	.28
Breast surgery	0.45	0.25 to 0.78	7.86	< .01

Abbreviation: HR, hazard ratio.
[a]Cox regression.

early-stage breast cancer, prognostic factors such as histologic grade, tumor size, and axillary status have already been well established[24]; however, in women with metastatic breast cancer, controversies remain regarding the factors that affect OS.

In the present series, several factors proved significantly prognostic of OS. Factors related to the primary tumor such as histologic grade, as well as factors related to metastatic progression such as the initial site of metastases, significantly predicted OS. Other studies conducted around the world have reported several possible prognostic factors in MBC, such as, for example, patient age and the number of organs involved.[9,23,26,33] However, the majority of those studies analyzed patients who had metastases at diagnosis and patients who went on to develop metastasis after a disease-free interval as a single mixed sample.[26] However, these are groups of patients in whom biologic behavior is different. The findings of this population-based study, which included only women with MBC detected at diagnosis, contribute to a better characterization of the prognostic factors involved in patients with advanced disease at diagnosis.

Performing breast surgery in women with metastatic disease remains controversial and is usually reserved for selected patients.[12,23,34,35] At the time this study was conducted, scientific evidence was limited to retrospective, noncontrolled studies that showed greater OS rates in patients who underwent breast surgery.[34] Therefore, the finding of better survival rates in the women who underwent local treatment should be interpreted with caution, bearing in mind that a selection bias could have led the patients with a better prognosis to receive breast surgery and the patients with more extensive disease to receive systemic treatment alone. However, the poor survival in the population with CNS metastasis is probably a result of therapeutic limitations in these patients, whose blood-brain barrier limits the efficacy of systemic treatment.[36]

In recent years, increased knowledge regarding tumor biology has led to the development of new therapeutic agents that have contributed to increasing survival in patients with MBC.[10,11] For example, women with MBC and hormone receptor–positive or HER2-positive tumors seem to have similar oncologic outcomes when treated appropriately. However, OS and progression-free survival are poorer in women with triple-negative tumors.[3,23,37] Regretfully, the small number of patients in the present series who received anti-HER2 treatment (n = 3; 18.7%) points to socioeconomic constraints that restrict access to treatment. Conversely, the underutilization of endocrine therapy as first-line treatment of MBC may reflect inappropriate therapeutic conduct according to current recommendations and the standards in force during the period analyzed.[12,13,20]

The majority of the women included in the current study were patients in the public health care system, with limited access to early diagnosis and to the most effective forms of treatment.[13,19] Therefore, 5- and 10-year OS rates were low. A study conducted by the Brazilian Breast Cancer Research Group found that the type of health care system affected OS, with rates being lower for patients in the public health care system compared with those receiving care in the private sector, particularly in patients with stage III or IV disease at diagnosis.[38] In São Paulo, Brazil, a hospital-based study included 205 patients with MBC who had received similar oncologic treatment irrespective of their access to either public or private health care. In that series, 5-year OS was 20.7% between 2000 and 2004, 33.3% between 2005 and 2009, and 40.8% between 2010 and 2012.[39]

OS rates in women with MBC vary in the literature. A collaborative study conducted in 18 comprehensive cancer centers in France reported an OS of 37.2 months. After 5 years of follow-up, OS was practically twice that found in the current study.[26] In randomized clinical trials conducted in specific populations, this difference is even greater. For example, in the Clinical Evaluation of Pertuzumab and Trastuzumab Trial (CLEOPATRA), the median OS time was 56.5 months in women with HER2-positive tumors who received pertuzumab in addition to the standard first-line treatment of MBC.[40] Nevertheless, the majority of those studies failed to describe specific results for the women with de novo MBC and also do not reflect what is practiced in the public health care systems of most low- and middle-income countries.

The current study has some limitations that are inherent to retrospective studies, such as missing data in the medical records and even in the cancer registry database. Tumor phenotypes were established by immunohistochemistry, and no central review was conducted of the pathology reports, which could have affected the interpretation of these data.[41] However, the fact that the medical records identified were verified manually added greater robustness to the study and provided data on variables that are not systematically collected by the cancer registry. Finally, the

relevance of population-based registries in the context of MBC should be emphasized, considering that it is a heterogeneous population and with several particularities. Thus, collaborative records for patients with metastatic disease should be advocated, allowing the collection of de novo and recurrent case information.

OS was low in this population and lower than rates found in specialist centers in Brazil and in developed countries. Several intrinsic and extrinsic factors were significant in predicting OS. Despite the difference in the 5-year survival rate, the type of access to health care was not significant in the multivariable analysis of the entire period.

AFFILIATIONS

[1]Breast Program, Teaching Hospital, Federal University of Goiás, Goiânia, Goiás, Brazil
[2]Hospital Araújo Jorge, Association for the Combat of Cancer in Goiás, Goiânia, Goiás, Brazil
[3]A.C. Camargo Cancer Center, Fundação Antônio Prudente, São Paulo, São Paulo, Brazil
[4]Goiânia Population-Based Cancer Registry, Association for the Combat of Cancer in Goiás, Goiânia, Goiás, Brazil

CORRESPONDING AUTHOR

Ruffo Freitas-Junior, MD, PhD, Centro Avançado de Diagnóstico da Mama, 1ª Avenida, s/n, Setor Universitário, 74605-050, Goiânia, Goiás, Brazil; e-mail: ruffojr@terra.com.br.

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AUTHOR CONTRIBUTIONS

Conception and design: Leonardo R. Soares, Ruffo Freitas-Junior, Maria P. Curado, José C. Oliveira
Administrative support: Ruffo Freitas-Junior, Edesio Martins
Provision of study material or patients: Ruffo Freitas-Junior, José C. Oliveira
Collection and assembly of data: Ruffo Freitas-Junior, Regis R. Paulinelli
Data analysis and interpretation: Leonardo R. Soares, Ruffo Freitas-Junior, Regis R. Paulinelli, Edesio Martins
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Leonardo R. Soares
Speakers' Bureau: Libbs

Ruffo Freitas-Junior
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