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Original Article

Factors Associated with Time to Progression and Overall Survival in Patients with De Novo Metastatic Breast Cancer: A Colombian Cohort

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Abstract

Purpose: About 10% of breast cancer (BC) is diagnosed in stage IV. This study sought to identify factors associated with time to progression (TTP) and overall survival (OS) in a cohort of patients diagnosed with de novo metastatic breast cancer (MBC), from a single cancer center in Colombia, given that information on this aspect is limited.

Methodology: An observational, analytical, and retrospective cohort study was carried out. Time to progression and OS rates were estimated using the Kaplan–Meier survival functions. Cox models were developed to assess association between time to progression and time to death, using a group of fixed variables.

Results: Overall, 175 patients were included in the study; 33.7% of patients had luminal B HER2-negative tumors, 49.7% had bone involvement, and 83.4% had multiple metastatic sites. Tumor biology and primary tumor surgery were the variables associated with TTP and OS. Patients with luminal A tumors had the lowest progression and mortality rates (10 per 100 patients/year (95% CI: 5.0-20.0) and 12.6 per 100 patients/year (95% CI: 6.9-22.7), respectively), and patients with triple-negative tumors had the highest progression and mortality rates (40 per 100 patients/year (95% CI: 23.2-68.8) and 44.1 per 100 patients/year (95% CI: 28.1-69.1), respectively). Across the cohort, the median TTP was 2.1 years (95% CI: 1.6; the upper limit cannot be reached) and the median OS was 2.4 years (95% CI: 2-4.3).

Conclusions: In this cohort, patients with luminal A tumors and those who underwent tumor surgery given that they presented clinical benefit (CB) after initial systemic treatment, had the lowest progression and mortality rates. Overall, OS was inferior to other series due to high tumor burden and difficulties in accessing and continuing oncological treatments.

Key words: breast neoplasm, neoplasm metastasis, biological tumor markers, time to progression, overall survival.

Implications for Practice

In low- and middle-income countries, higher percentages of breast cancers (BC) are diagnosed at stage IV. This article identifies factors associated with time to progression and overall survival in a cohort of patients diagnosed with de novo metastatic BC from a single cancer center in Colombia.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women worldwide. For Colombia, incidence and mortality rates are estimated at 48.3 and 13.1 per 100 000 women, respectively.[1] In Western countries, between 5% and 10% of BC is diagnosed in stage IV,[2,3] while in low- and middle-income countries (LMIC) this figure can reach 25%.[4] In Colombia, there are no official statistics on the incidence of de novo metastatic breast cancer (MBC).

Metastatic breast cancer is regarded as an incurable clinical entity[5]; the mainstay of treatment is systemic therapy that aims to prolong patient survival. The prognosis of this disease has improved considerably thanks to the introduction of multiple cytotoxic drugs and targeted therapies. Today, nearly

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44% of patients will survive 3 years and about 20% at least 5 years.[2,6,7]

Metastatic breast cancer outcomes are related to clinical, histopathological, and therapeutic factors such as age, menopausal and functional status, comorbidities, number and location of metastases, disease-free period, and tumor biology.[7,8] For patients with hormone receptor-positive and HER2-positive (HER2+) tumors, the median overall survival (OS) is 4 to 5 years; for those with pure HER2-enriched tumors, it is 5 years, and for patients with triple-negative tumors, 10 to 13 months.[7] Based on current evidence, primary tumor surgery is not a standard treatment,[9,10] although there is scientific literature suggesting that some patients diagnosed de novo may benefit from locoregional control.[11-13]

Greater certainty in the identification of variables associated with the survival of patients with de novo MBC can help better understand the natural history of this disease and improve its therapeutic treatment. The objective of this study was to identify factors associated with time to progression (TTP) and OS in a cohort of patients diagnosed with de novo MBC in one of the most important cancer centers in Colombia.

Discussing this issue in patients diagnosed and treated in low- and middle-income countries (LMIC) is important because information in this regard is limited, and it is unknown whether these countries' political, socioeconomic, and cultural characteristics, among others, affect the oncological prognosis of patients with de novo MBC.

The Colombian population receives medical care through two major insurance plans: a contributory regime for workers and their families, and a subsidiary system for low-income families. Each plan is managed by insurance companies that define their own health services.[14] The employed and their families receive the health care services through a contributory model that has its own health benefits, and is funded by the employer's taxes and the employee's payroll. The unemployed, with no purchasing power, do not have access to these benefits, therefore, many of their health needs remain unattended because they are part of a subsidy-based model. But, at the top, there are people with a very high purchasing power who have more benefits than the average population, with a better form of medical care and an easier access to it.[15]

Methodology

An observational, analytical, and retrospective cohort study was conducted, approved by the Institutional Review Board of the National Cancer Institute (NCI). The NCI of Colombia is the most important cancer center in the country. It is a reference center for patients with cancer pathologies, most of them with low economic resources; this is the main reason why patients with BC are admitted in advanced stages of the disease.

The study analyzed clinicopathological characteristics and clinical outcomes of women diagnosed with de novo MBC at the breast unit (BU) of the NCI between September 1, 2013 and August 31, 2017. Those patients who developed recurrent metastatic disease or who did not receive treatment at the NCI were excluded (Figure 1). The initial evaluation of the distant disease was carried out through a chest and abdominal tomography and bone scan. Only in selected cases were other extension studies requested (magnetic resonance imaging of the spine, brain, chest, etc.). Information

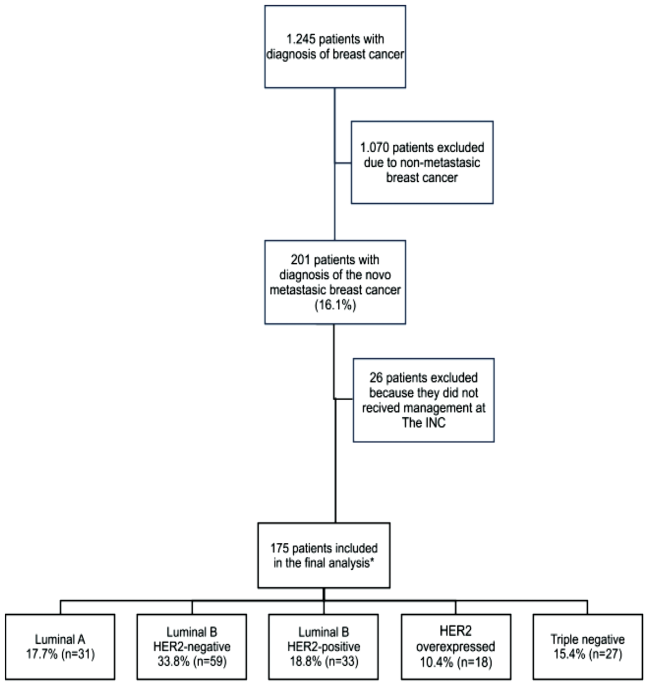

Figure 1. Selection of the patients. *No data were obtained on the biological subtype of BC in seven participants (4%).

on sociodemographic and clinicopathological characteristics was extracted from the BU database and the NCI's electronic medical history system (SAP). Data were retrospectively collected by two of the authors and then transferred to an electronic platform designed to store clinical study information (REDCap). Information quality and accuracy was evaluated by an assistant of the Research Division of the NCI.

The analyzed variables were age, menopausal status, clinicopathological characteristics of patients and tumors, first-line medical treatment and response to it, other medical or surgical treatments, the characteristics and treatment of disease progression, and death. Tumor biology was defined according to the classification proposed by the Clinical Practice Guidelines of the European Society of Medical Oncology (ESMO) in 2015[16]. Disease progression was defined as an increase of more than 20% in the size of the primary tumor or metastatic lesions, or the appearance of new tumor lesions.[17] Clinical benefit was defined as the presence of stable disease, or a partial or complete response to treatment.[18] New paraclinical exams such as tomography, bone scan, or magnetic resonance were only requested in cases of clinical suspicion of disease progression.

The descriptive analysis of categorical and nominal variables was carried out using absolute and relative frequency measurements; mean and standard deviations were used for continuous variables. The study incorporated an analytical component that considered TTP and OS as outcomes of interest. Time to progression was defined as the time between the confirmed diagnosis of de novo MBC and the first documented disease progression (local, locorregional, and distant progression); OS was defined as the time between the confirmed diagnosis of de novo MBC and death from any cause.

The frequency of these outcomes was calculated using incidence rates expressed as events per 100 patients-year. Rates were reported with confidence intervals (CI) at 95%. For

these two outcomes, Kaplan–Meier survival functions were estimated. Cox proportional risk models were used to analyze the association between outcomes and a group of variables considered as risk factors. For statistical analysis purposes, cases of loss of follow-up or termination of the study without reaching an outcome were taken as censoring to the right (right-censored). A minimum period of 24 months was established as the end of the follow-up, or any presentation of the outcomes. The assumption of risk proportionality was verified using Schoenfeld residuals to test the hypothesis of slope equal to zero. Hazard ratios (HR) were used to interpret the Cox model coefficients. Significance values of 5% were used in all hypothesis tests. The analyses were carried out with the statistical program Stata 16.

Results

Between September 1, 2013 and August 31, 2017, 1245 women were diagnosed and treated as first-time patients with BC, 201 (16.14%) of them were in stage IV; 26 patients were excluded due to lack of treatment at the NCI and 175 were included in the final data analysis. The mean age at diagnosis was 58.8 years (SD = 14.5 years); 62.9% (n = 110) of patients were postmenopausal. The most common histological subtype was ductal (81.1%; n = 142) and most of the tumors (48%; n = 84) were grade II; T4 tumors were present in 90.8% (n = 159) of the cases, and the main biological subtype was luminal B HER2-negative (33.8%; n = 59). Multiple metastatic sites were identified in 83.4% (n = 146) of patients, and 65.7% (n = 115) had four or more metastatic lesions. The most common metastatic site was bone (49.7%; n = 87), and 56.6% (n = 99) of patients had visceral disease. In luminal tumors, the most common metastatic site was bone (42.9%; n = 75); in triple-negative tumors, lung (6.2%; n = 11), and in pure HER2-enriched tumors, skin (4%; n = 7). Metastatic involvement of the skin was defined as a tumor invasion to the skin beyond the limits of the breast (Table 1).

All but one patient (99.4%; n = 174) received systemic therapy as an initial treatment; this one patient (0.6%; n = 1) presented with medullary compression syndrome secondary to a metastatic polyostotic lumbosacral spine disease and required emergency laminectomy and palliative radiation therapy (Table 2). Of 175 patients, 38.8% (n = 68) presented clinical benefit (CB) with first-line systemic therapy, while 42.9% (n = 75) had disease progression. Progression was more frequent at the locoregional level (17.1%; n = 30). Distant progression occurred mainly in bone (16%; n = 28) and lung (11.4%; n = 20). Patients with luminal A tumors had the lowest rates of progression and mortality, and patients with triple-negative tumors had the highest rates of progression and mortality rates (Table 3). Only 39 patients (22.3%) received surgical treatment, most of them primary tumor surgery (20%; n = 35). Table 2 presents in detail the types of treatment received by the patients of the cohort.

Time to Progression

The included 175 patients provided a total of 290.1 years of follow-up for TTP. The median follow-up was 1.2 years (95% CI: 0.9-1.5). During this period, 75 events of disease progression occurred. The median TTP was 2.1 years (the lower bound of the 95% CI was 1.6; the upper limit cannot be reliably estimated). Disease progression rate was 25.8 progression events per 100 patients/year (95% CI: 20.6-32.4).

Table 1. Clinicopathological characteristics of the patients.

Characteristics	Number	Percentage
Age		
<35 years	9	5.2
35-50 years old	45	25.7
>50 years	121	69.1
Menopausal status		
Premenopausal	53	30.3
Postmenopausal	110	62.9
No data	12	6.8
T (tumor size)		
T1	2	1.2
T2	13	7.4
T3	1	0.6
T4	159	90.8
N (nodes)		
N0	4	2.3
N1	35	20
N2	62	35.4
N3	74	42.3
Histological type		
Ductal	142	81.1
Lobular	14	8
Other special subtypes[a]	15	8.6
No data	4	2.3
Histological grade		
I	15	8.5
II	84	48
III	74	42.3
No data	2	1.2
Biological subtype[b]		
Luminal B/HER2-negative	59	33.8
Luminal B/HER2+	33	18.8
Luminal A	31	17.7
Triple-negative	27	15.4
Pure HER2+ enriched	18	10.3
No data	7	4
Type of metastatic disease		
Visceral	99	56.6
Non-visceral	76	43.4
Number of metastatic sites		
1	29	16.6
2-3	31	17.7
≥4	115	65.7
Location of metastatic disease[c]		
Bone	87	49.7
Lung	73	41.7
Skin[d]	42	24
Distant lymph nodes	43	24.6
Contralateral axillary nodes	38	21.7
Liver	33	18.6
Pleura	21	12
Contralateral breast	15	8.6

Table 1. Continued.

Characteristics	Number	Percentage
Central nervous system (CNS)	2	1.2
Other	25	14.3

[a]Including some rare subtypes such apocrine carcinoma and signet-ring cell carcinoma.
[b]According to the classification proposed by the Clinical Practice Guidelines of the European Society of Medical Oncology (ESMO), 2015[14].
[c]More than 50% of the patients with visceral metastasis, had concomitant metastatic disease in two or more visceral organs (i.e., lung and liver); and 71 of the 99 patients with visceral disease had concomitant non-visceral involvement.
[d]Metastatic involvement to the skin was defined when there was tumor invasion to the skin beyond the limits of the breast.

Two variables were associated with an increased risk of disease progression: the biological subtype of BC and primary tumor surgery. Taking patients with luminal A tumors as reference, the probability of progression was higher in those with HER2+ or triple-negative tumors. Compared with patients who underwent primary tumor surgery because they presented CB with the first-line systemic treatment, the risk of disease progression was higher in patients who did not undergo primary tumor surgery and in those who received this procedure as a palliative care (Table 4; Figure 2A and C).

Overall Survival

The 175 patients provided a total of 384.5 years of follow-up for OS. The median follow-up was 1.9 years (95% CI: 1.6-2.2). During this period, 88 deaths were registered. The median OS was 2.4 years (95% CI: 2-4.3). The mortality rate was 22.9 deaths per 100 patients/year (95% CI: 18.6-28.2). The biological subtype different from luminal A was associated with an increased risk of death, except in patients with luminal B HER2+ tumors. Compared with patients who were taken to primary tumor surgery because they obtained CB with first-line systemic treatment, the risk of death was higher only in patients who did not undergo primary tumor surgery (Table 4, Figure 2B and D).

Characteristics of Patients Who Underwent Primary Tumor Surgery

Thirty-five patients were taken to primary tumor surgery; 24 of them presented CB with initial systemic treatment; 19 had partial or complete response. Of the 24 patients with CB, 21 had mono-metastatic or oligometastatic disease (≤3 organs). The univariate analysis did not show that primary tumor surgery offered additional survival (OS) gain in those patients who presented CB with first-line systemic treatment (38.8%; n = 68): HR 0.32 (95% CI: 0.09-1.10). Regarding tumor biology, no significant association was found between the biological classification of BC and primary tumor surgery (Fisher's exact test: $P > 0.05$).

Discussion

At the NCI, about 17% of BC is diagnosed in stage IV. Variables such as age, race, tumor size, number and location of metastases, and histological and biological subtype have been extensively studied as prognostic factors for recurrent MBC; however, their validity is questioned in cases of de novo MBC.[19,20]

This cohort is similar to other cohorts where the clinical-pathological characteristics of patients with de novo MBC were analyzed.[19,21,22] The mean age at diagnosis was 58.8 years, slightly lower than the mean age reported at diagnosis of BC in the general population, between 62 and 64 years.[21,23] The main histological subtype was ductal (>80%); however, high-grade tumors accounted for nearly 50% of cases, a much higher figure than 35% reported for early or locally advanced BC.[19] A higher percentage of tumors showed HER2 overexpression (between 25% and 30%), while it is 1%5 to 20% for the general population.[12,24] The predominant location of metastatic disease was consistent with what has been reported in the literature for luminal and triple-negative tumors: bone and lung, respectively.[25] In 83.4% of the patients, there were multiple metastatic involvement, well above the 33% reported by a similar study of more than 18 000 patients of the Surveillance, Epidemiology, and End Results database.[23] This explains why chemotherapy was the first line of treatment in more than 50% of the patients.

In this study, patients with hormone receptor-positive tumors had better outcomes than those with HER2+ or triple-negative tumors. Neuman et al.[26] noted that the status of hormone and HER2 receptors were the variables that best predicted survival in de novo MBC; but, unlike the present work, they observed that patients with HER2+ tumors had better survival, something they attributed to the availability of effective targeted therapy. He et al.[27] also studied the value of some biological factors in de novo MBC, finding that patients with high-grade, HER2-negative, single hormone receptor-positive, or triple-negative tumors had lower BC-specific survival. These biomarkers showed a good prognostic performance so the authors consider it worthwhile to incorporate them into a new staging system for patients diagnosed in stage IV, as occurs in the 8th edition of the American Joint Committee on Cancer staging system for non-metastatic BC. Lin et al.[28] suggested a subdivision system for de novo MBC based on the number and location of metastases, since brain and liver involvement, in addition to the number of metastatic sites, appear to be independent factors of poor prognosis.

According to world literature, patients with HER2+ tumors have better outcomes in the metastatic setting than those with HER2-negative or triple-negative tumors.[12,21,27,29] However, in this study, although the highest mortality rate was observed in patients with triple-negative tumors, those with HER2+ BC had the highest progression rate. This is probably because Colombia's health system structure promotes a differentiated and unequal health care for its citizens, based mainly on their financial capacity. Those who contribute with part of their salary to the health system, or have a private health insurance, are more likely to have access to antineoplastic drugs; while patients with state-subsidized health care have to face multiple administrative barriers to initiate or continue different cancer treatment schemes.[30,31]

In this cohort, none of the patients with luminal tumor received a CDK4/6 inhibitor as initial treatment, which are drugs that form part of the standard first-line treatment of patients with hormone receptor-positive and HER2-negative tumors.[12] Of the 51 (29.1%) patients with HER2+ tumors, only 27 (15.4%) received CLEOPATRA scheme (trastuzumab, pertuzumab, and docetaxel) as initial treatment, and in many cases pertuzumab was added late. As second-line treatment, T-DM1 was administered to 11 (6.2%) of the 27 patients (15.4%) who progressed with the CLEOPATRA scheme. This

Table 2. Treatment received by the patients.

Type of treatment	Number	Percentage
First-line systemic treatment	174	99.4
Chemotherapy	91	52
Chemotherapy plus targeted therapy	45	25.7
Hormonal therapy	35	20
Hormonal therapy plus targeted therapy	3	1.7
First-line non-systemic treatment		
Radiation therapy	1	0.6
Second-line systemic treatment (due to disease progression)	75	42.9
Chemotherapy with or without targeted therapy	43	24.6
Hormonal therapy with or without targeted therapy	16	9
Other	6	3.5
None	10	5.8
Palliative radiation therapy	63	35.9
Bone	32	18.3
CNS	16	9
Locoregional	14	8
Another location	1	0.6
Surgical treatment		
Intent of surgery of the primary tumor	35	20
Palliative[a]	11	6.3
Clinical benefit with first-line systemic treatment[b]	24	13.7
Stable disease with first-line systemic treatment	5	2.9
Partial response with first-line systemic treatment	14	7.9
Complete response with first-line systemic treatment	5	2.9
Type of surgery of the primary tumor	35	20
Modified radical mastectomy	31	17.8
Simple mastectomy	2	1.1
Quadrantectomy and sentinel node biopsy	2	1.1
Radiation therapy to the breast area after primary tumor surgery		
Yes	22	12.6
No	13	7.4
Metastatic disease surgery	(10)	5.8
Contralateral axillary lymph node dissection	5	2.9
CNS metastasectomy	2	1.1
Bone metastasectomy	1	0.6
Liver metastasectomy	1	0.6
Pulmonary metastasectomy	1	0.6

[a]Patients who underwent mastectomy with only palliative intent due to tumors with bleeding and fetid ulcers involving the mammary gland, or because locorregional progression, which caused pain, anemia, and social and family difficulties. The purpose of this procedure was to improve the quality of life of the patients
[b]Clinical benefit was defined as the presence of stable disease, or a partial or complete response to treatment[18]

indicates a suboptimal treatment of metastatic disease. On the one hand, it took almost 3 years for CDK4/6 inhibitors to be approved by the Colombian regulatory entities and they only became available after August 2017, which explains why none of the patients in this cohort received these drugs. On the other hand, although pertuzumab and T-DM1 have had sanitary registration in Colombia since 2014, their high costs make it difficult for all patients to access them.

The role of primary tumor surgery in patients with de novo MBC remains controversial. Although numerous retrospective studies suggest a possible association between surgery and better survival,[8,32-38] clinical trials have not been able to confirm this.[39-44] Retrospective studies (like this one) have multiple biases and confounding factors. First, patients who underwent surgery consistently had better prognostic characteristics.[5,10,28] Second, in most of these studies, patients who underwent primary tumor surgery had previously presented a good response to initial systemic treatment, which justified surgical intervention. Thus, not only patients with better clinical prognosis were selected but also those with better response to systemic therapy rather than surgery. This was pointed out by King et al.,[42] who observed that in patients with good response to systemic therapy, primary tumor surgery offered no advantage in survival. In this study, the

Table 3. Progression and mortality rates by biological subtype (univariate analysis).

Biological subtype	Progression		Mortality	
	Rate 100 patients/year	CI 95%	Rate 100 patients/year	CI 95%
Luminal A	10	5.0-20.0	12.6	6.9-22.7
Luminal B HER2-negative	23.3	15.1-35.6	23.5	16.3-33.8
Luminal B HER2+	36.2	23.6-55.5	18.4	11.2-30.1
Pure HER2+ enriched	34.5	17.2-69.0	28.1	14.6-54.0
Triple-negative	40	23.2-68.8	44.1	28.1-69.1

Table 4. Cox proportional risk model for time to progression and overall survival.

Variable	Time to progression		Overall survival	
	HR; CI 95%	*P*	HR; CI 95%	*P*
Age >50 years	1.17 (0.65-2.10)	.59	1.37 (0.80-2.34)	.25
Visceral metastatic disease	1.08 (0.58-2.03)	.79	1.03 (0.59-1.77)	.93
Number of metastatic sites				
1	1		1	
2 or 3	0.98 (0.36-2.63)	.97	0.54 (0.21-1.39)	.20
4 or more	1.20 (0.51-2.84)	.66	1.10 (0.49-2.47)	.82
Primary tumor surgery				
Clinical benefit[a]	1		1	
Palliative[b]	19.45 (3.50-108.06)	.001	3.38 (0.82-13.92)	.09
No primary tumor surgery	11.59 (2.58-52.06)	.001	4.20 (1.34-13.16)	.01
Metastatic disease surgery	0.96 (0.32-2.85)	.94	0.83 (0.24-2.83)	.77
Postmenopausal condition	1.00 (0.99-1.01)	.46	1.00 (1.00-1.01)	.28
Biological classification of BC				
Luminal A	1		1	
Luminal B HER2-negative	2.58 (1.12-5.94)	.026	1.98 (0.97-4.03)	.06
Luminal B HER2-positive	4.97 (2.12-11.60)	<.001	1.75 (0.79-3.85)	.17
Pure HER2+ enriched	6.89 (2.45-19.38)	<.001	3.10 (1.24-7.75)	.02
Triple- negative	3.66 (1.47-9.07)	.005	3.81 (1.76-8.24)	<.001

[a]Clinical benefit was defined as the presence of stable disease, or a partial or complete response to treatment.[18]
[b]Patients who underwent mastectomy with only palliative intent due to tumors with bleeding and fetid ulcers involving the mammary gland, or because locorregional progression, which caused pain, anemia, and social and family difficulties. The purpose of this procedure was to improve the quality of life of the patients.

univariate analysis of the impact of surgery on patients with BC with first-line systemic treatment (HR 0.32; $P = 0.072$) supports the above claim.

Some authors suggest that the biological subtype influences the outcomes of patients with de novo MBC undergoing surgery.[28,41,45] In the study of Neuman et al.,[26] patients with hormone receptor or HER2+ tumors had better outcomes when the primary tumor was operated, considering that 89% and 90% of patients had previously received hormonal therapy and trastuzumab, respectively. Recent studies show the same survival benefit in patients with hormone-positive or HER2+ tumors[3]; even those with HER2+ tumors with three or more metastatic sites could benefit from surgical treatment.[25] In contrast, trials of Co et al.,[20] Soran et al.,[41] and Lane et al.[45] found that only patients with hormone-positive and HER2-negative tumors benefited from surgery. The described evidence is discordant, but it indicates a subgroup of patients who are not only more likely to benefit from surgery, but also from efficient targeted therapy.[28,46] Although in this study patients with HER2+ tumors would appear to have a greater benefit from primary tumor surgery, statistical power is lacking to confirm this association (data not shown).

The results of controlled clinical trials are contradictory. Badwe et al.[39] found that primary tumor surgery did not improve OS (HR 1.04; CI 95%: 0.81-1.34); in fact, patients who underwent surgery had a significant detriment in distant progression free-survival (HR 1.42, CI 95%: 1.08-1.85). Soran et al.[40,41] reported that surgical treatment increased OS to 5 years ($P = 0.005$). The POSYTIVE trial found no benefit in OS with primary tumor surgery (HR 0.69; CI 95%: 0.36-1.33).[43] Finally, based on preliminary results from the clinical trial E2108, which showed no benefit for survival with primary tumor surgery, Khan et al.[44] suggest that surgical treatment should not be offered to patients with de novo BMC with the expectation of improving survival or quality of life.

In this cohort, patients who underwent primary tumor surgery had better outcomes than those who only received

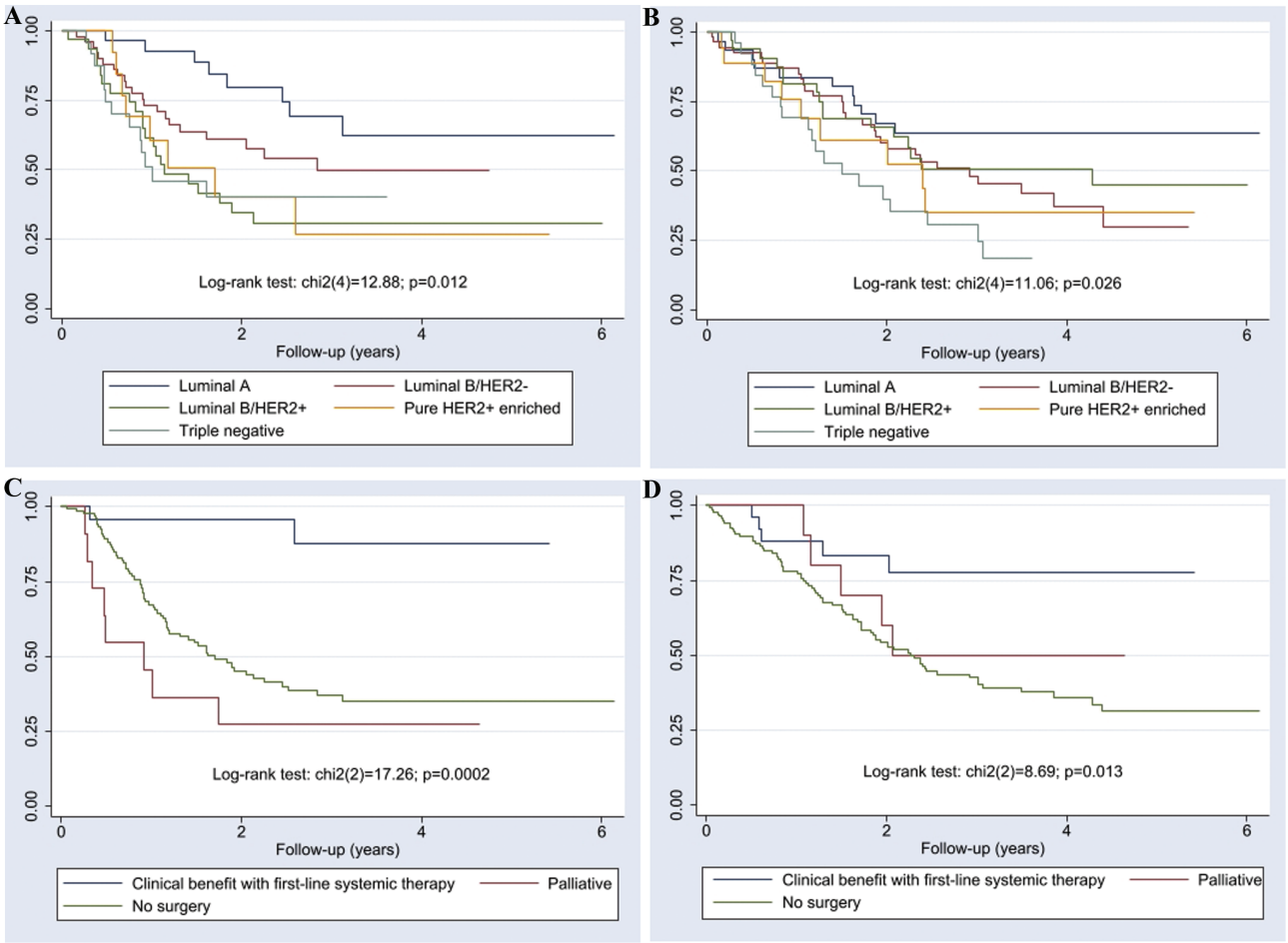

Figure 2. Time to progression (A) and overall survival (B) by biological subtype. Time to progression (C) and overall survival (D) in relation to primary tumor surgery. Median overall survival by biological subtype: Luminal A: The median was not reached (<50% of the patients presented the outcome of death). Luminal B/HER2-: 2.9 (IC 95%: 1.8-4.3). Luminal B/HER2+: 4.2 (IC 95%: 1.2-not reached). Pure HER2+ enriched: 2.3 (IC 95%: 0.8-not reached). Triple negative: 1.4 (IC 95%: 0.8-2.4).

systemic treatment, without a statistically significant association between tumor biology and surgery. Sample size could explain this lack of association. Similarly, the absence of statistical significance between luminal B HER2-negative tumors or primary tumor surgery with palliative intent, with a worse survival (P = 0.06 and P = 0.09, respectively), could be explained by the low power of the study to calculate this difference. Finally, the population size of the study could also explain why, in the univariate analysis, surgery of the primary tumor did not offer an additional gain in survival in those patients with BC after first-line systemic treatment.

The retrospective nature of this work does not allow drawing definitive conclusions on the role of surgery in de novo MBC, since as occurs in other retrospective series, most of the patients who underwent surgery were the ones who had initial systemic therapy, which constitutes an important selection bias and can explain the alleged benefit obtained from surgery. It is worth continuing to investigate which subgroups of patients may benefit from locoregional control, such as those with metastatic disease exclusively to skin or contralateral axillary metastases, who appear to have a similar clinical course than those with locally advanced BC.[47]

The proportion of patients diagnosed for the first time with stage IV cancer is much higher in this study (17%) than what is reported in the literature of developed countries (5%-10%).[2,3] In the same way, the median OS of patients in this study (2.4 years (95% CI: 2-4.3) or 28.8 months) is lower than the 39 to 48 months reported in recent publications.[20,27] This situation can be explained, on the one hand, by the high burden of disease at the time of diagnosis (90.8% had T4 tumors, 77.7% had N2/N3 tumors, and 83.4% had multiple metastatic sites), which indicates a low coverage of mammography screening, ranging between 32% and 50%,[48] and a late disease diagnosis, as a consequence of poor access to health services, either due to administrative barriers or the absence of specialized oncology services in a large part of the country. On the other hand, it can also be explained by a cancer treatment that is below the current standards, reflected in late start and lack of continuity in treatments, as well as in the absence of access to the newest available therapies. In LMIC like Colombia, this situation has already been clearly documented.[30,31,49]

Finally, it is necessary to point out that it is difficult to make direct comparisons between the results of this research and those of other studies carried out in Latin America, since there is a marked heterogeneity in the data that provide information on the proportion of patients diagnosed for the first time with stage IV cancer, with a range between 1% (Argentina) and 29% (Haiti).[50] It is essential to carry out transnational studies in Latin America to help improve the characterization of BC and other cancers in this region of the world.

Limitations and Strengths of the Study

This study has limitations due to its retrospective design and because data cannot be adjusted by unmeasured confounding factors. Diagnosis of de novo MBC was clinical and not histopathological. This study cannot provide definitive causality between the biological subtype of BC or primary tumor surgery, with a decreased risk of progression or death in patients with de novo MBC. Given the nature of this research, its results cannot be generalized to all patients with de novo MBC. In addition, there was a significant loss to follow-up in the general study population (22.3%; n = 39). However, as far as the authors know, this is one of the few studies conducted in a Latin American country with the aim of identifying factors associated with progression and survival in this specific group of patients, which could help define the special characteristics of de novo MBC in Latin American women. It is important to note that in Colombia there are previous publications that analyze the survival of BC diagnosed for the first time in all clinical stages, not only in stage IV.[51] This study contributes to better understanding the natural history of de novo MBC, which differs from recurrent metastatic breast tumors in its diagnostic and therapeutic treatment, as well as in its clinical prognosis.

Conclusions

De novo MBC is a clinical entity whose heterogeneity is primarily determined by tumor biology. Systemic treatment is the standard treatment for patients with stage IV cancer. In this cohort, patients with luminal A tumors had the best oncological outcomes, while patients with triple-negative tumors had the worst outcomes. The median OS of patients in this study was 2.4 years (95% CI: 2-4.3), which can be explained by the high tumor burden at the time of diagnosis (large tumor volumes due to T4 tumors in 90.8%, N3 lymph node involvement in 42.3%, and multiple metastatic sites in 83.4%), difficulties in accessing health care, as well as delay and lack of continuity in cancer treatment. The role of primary tumor surgery remains unestablished, and the association between tumor biology and primary tumor surgery with patient survival is also unclear.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: S.E.D.-C., X.B.-M. Provision of study material or patients: S.E. D.-C., C.L.-M., L.H.G.-A., J.A.-A., M.G.-M., C.A.D.-T., S.C.-B. Collection and/or assembly of data: S.E.D.-C., X.B.-M., L.J., P.-H., M.C.O.-O. Data analysis and interpretation: S.E.D.-C., X.B.-M., C.B.-M., R.S.-P.. Manuscript writing: S.E.D.-C., X.B.-M., C.B.-M., R.S.-P. Final approval of manuscript: all authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Global Cancer Observatory: Cancer Today: Data visualization tools for exploring the global cancer burden in 2020. [Internet]. Available from: https://gco.iarc.fr/today/online-analysis-multi-bars
2. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(Suppl 7):vii11-vii19. https://doi.org/10.1093/annonc/mds232
3. Lee JS, Toktas O, Soran A. Role of locoregional treatment in de novo stage IV breast cancer. *Clin Med Insights Oncol*. 2020;14:1179554920942440. https://doi.org/10.1177/1179554920942440
4. Yip CH. Palliation and breast cancer. *J Surg Oncol*. 2017;115(5):538-543. doi: 10.1002/jso.24560
5. Teshome M. Role of operative management in stage IV breast cancer. *Surg Clin North Am*. 2018;98(4):859-868. https://doi.org/10.1016/j.suc.2018.03.012
6. Bermas HR, Khan SA. Local therapy for the intact breast primary in the presence of metastasic disease. In: KI Bland, EM Copeland, III, eds. *The Breast: Comprehensive Management of Benign and Malignant Diseases*. 4th ed. Saunders/Elsevier; 2009:1211-1221.
7. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288-300. https://doi.org/10.1001/jama.2018.19323
8. Jagsi R, King TA, Lehman C, et al. Malignant tumors of the breast. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *Devita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 11th ed. New York, NY: Wolters Kluwer; 2018:1259-1268.
9. Dominici L, Najita J, Hughes M, et al. Surgery of the primary tumor does not improve survival in stage IV breast cancer. *Breast Cancer Res Treat*. 2011;129(2):459-465. https://doi.org/10.1007/s10549-011-1648-2
10. Cady B, Nathan NR, Michaelson JS, Golshan M, Smith BL. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. *Ann Surg Oncol*. 2008;15(12):3384-3395. https://doi.org/10.1245/s10434-008-0085-x
11. Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol*. 2006;24(18):2743-2749. https://doi.org/10.1200/JCO.2005.04.2226
12. Pagani O, Senkus E, Wood W, et al.; ESO-MBC Task Force. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? *J Natl Cancer Inst*. 2010;102(7):456-463. https://doi.org/10.1093/jnci/djq029
13. Singletary SE, Walsh G, Vauthey JN, et al. A role for curative surgery in the treatment of selected patients with metastatic breast cancer. *Oncologist*. 2003;8(3):241-251. https://doi.org/10.1634/theoncologist.8-3-241
14. Murillo R, Díaz S, Perry F, et al. Increased breast cancer screening and downstaging in Colombian women: a randomized trial of opportunistic breast-screening. *Int J Cancer*. 2016;138(3):705-713. https://doi.org/10.1002/ijc.29801
15. Briceño Morales X, Enciso Chaves LV, Yepes Delgado CE. Neither medicine nor health care staff members are violent by nature: obstetric violence from an interactionist perspective. *Qual Health Res*. 2018;28(8):1308-1319. https://doi.org/10.1177/1049732318763351
16. Senkus E, Kyriakides S, Ohno S, et al.; ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26 Suppl 5:v8-30. https://doi.org/10.1093/annonc/mdv298
17. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. https://doi.org/10.1016/j.ejca.2008.10.026
18. Sznol M. Reporting disease control rates or clinical benefit rates in early clinical trials of anticancer agents: useful endpoint or hype? *Curr Opin Investig Drugs*. 2010;11(12):1340-1341.

19. Shen T, Siegal GP, Wei S. Clinicopathologic factors associated with de novo metastatic breast cancer. *Pathol Res Pract*. 2016;212(12):1167-1173. https://doi.org/10.1016/j.prp.2016.09.007
20. Co M, Ng J, Kwong A. De-novo metastatic breast cancers with or without primary tumor resection - a 10-year study. *Cancer Treat Res Commun*. 2019;19:100118. https://doi.org/10.1016/j.ctarc.2019.100118
21. Lobbezoo DJA, van Kampen RJW, Voogd AC, et al. Prognosis of metastatic breast cancer: Are there differences between patients with de novo and recurrent metastatic breast cancer? *Br J Cancer*. 2015;11:1445-1451.
22. Chen L, Romond E, Chokshi S, et al. A prognostic model of early breast cancer relapse after standard adjuvant therapy and comparison with metastatic disease on initial presentation. *Breast Cancer Res Treat*. 2012;136(2):565-572. https://doi.org/10.1007/s10549-012-2265-4
23. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/csr/1975_2014
24. Tripathy D, Brufsky A, Cobleigh M, et al. De novo versus recurrent HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from the SystHERs registry. *Oncologist*. 2020;25(2):e214-e222. https://doi.org/10.1634/theoncologist.2019-0446
25. Wang R, Zhu Y, Liu X, et al. The clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. *BMC Cancer*. 2019;19:1091.
26. Neuman HB, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer*. 2010;116(5):1226-1233. https://doi.org/10.1002/cncr.24873
27. He ZY, Lian CL, Wang J, et al. Incorporation of biologic factors for the staging of de novo stage IV breast cancer. *NPJ Breast Cancer*. 2020;6:43. https://doi.org/10.1038/s41523-020-00186-5
28. Lin C, Wu J, Ding S, et al. Subdivision of M1 Stage for de novo metastatic breast cancer to better predict prognosis and response to primary tumor surgery. *J Natl Compr Canc Netw*. 2019;17(12):1521-1528. https://doi.org/10.6004/jnccn.2019.7332
29. Press DJ, Miller ME, Liederbach E, Yao K, Huo D. De novo metastasis in breast cancer: occurrence and overall survival stratified by molecular subtype. *Clin Exp Metastasis*. 2017;34(8):457-465. https://doi.org/10.1007/s10585-017-9871-9
30. Piñeros M, Sánchez R, Perry F, et al. Demoras en el diagnóstico y tratamiento de mujeres con cáncer de mama en Bogotá, Colombia [Delay for diagnosis and treatment of breast cancer in Bogotá, Colombia]. *Salud Publica Mex*. 2011;53:478-485.
31. De Vries E, Buitrago G, Quitian H, et al. Access to cancer care in Colombia, a middle-income country with universal health coverage. *J Cancer Policy*. 2018;15:104-112.
32. Bafford AC, Burstein HJ, Barkley CR, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. *Breast Cancer Res Treat*. 2009;115(1):7-12. https://doi.org/10.1007/s10549-008-0101-7
33. Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM. Association of surgery with improved survival in stage IV breast cancer patients. *Ann Surg*. 2008;247(5):732-738. https://doi.org/10.1097/SLA.0b013e3181656d32
34. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery*. 2002;132(4):620-6; discussion 626. https://doi.org/10.1067/msy.2002.127544
35. Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. *Ann Surg Oncol*. 2006;13(6):776-782. https://doi.org/10.1245/ASO.2006.03.033
36. Gnerlich J, Jeffe DB, Deshpande AD, et al. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER Data. *Ann Surg Oncol*. 2007;14:2187-2194.
37. Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. *Breast Cancer Res Treat*. 2010;120(1):9-16. https://doi.org/10.1007/s10549-009-0670-0
38. Harris E, Barry M, Kell MR. Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. *Ann Surg Oncol*. 2013;20:2828-2834.
39. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: An open-label randomised controlled trial. *Lancet Oncol*. 2015;16:1380-1388.
40. Soran A, Ozmen V, Ozbas S, et al. Abstract S2-03: Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01). *Cancer Res*. 2013;73:24 (suppl: abstract nr S2-03).
41. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. *Ann Surg Oncol*. 2018;25:3141-3149.
42. King TA, Lyman JP, Gonen M, et al. A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). *J Clin Oncol*. 2016;34(suppl):1006.
43. Fitzal F, Balic M, Bjelic-Radisic V, et al. Primary operation in synchroneous metastasized invasive breast cancer patients: first oncologic outcomes of the prospective randomized phase III ABCSG 28 POSYTIVE trial. *J Clin Oncol*. 2017;35(suppl):557.
44. Khan SA, Zhao F, Solin LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2108). *J Clin Oncol*. 2020;38(suppl):LBA2-LBA2.
45. Lane WO, Thomas SM, Blitzblau RC, et al. Surgical resection of the primary tumor in women with de novo stage IV breast cancer: contemporary practice patterns and survival analysis. *Ann Surg*. 2019;269(3):537-544. https://doi.org/10.1097/SLA.0000000000002621
46. AlJohani B, AlMalik O, Anwar E, et al. Impact of surgery on survival in stage IV breast cancer. *Breast J*. 2016;22(6):678-682. https://doi.org/10.1111/tbj.12662
47. Magnoni F, Colleoni M, Mattar D, et al. Contralateral axillary lymph node metastases from breast carcinoma: is it time to review TNM cancer staging? *Ann Surg Oncol*. 2020;27(11):4488-4499. https://doi.org/10.1245/s10434-020-08605-4
48. Ministerio de Salud de Colombia, Profamilia: Encuesta Nacional de Demografía y Salud – ENDS; 2015.. Available from: https://profamilia.org.co/investigaciones/ends.
49. Soares LR, Freitas-Junior R, Curado MP, Paulinelli RR, Martins E, Oliveira JC. Low overall survival in women with de novo metastatic breast cancer: does this reflect tumor biology or a lack of access to health care? *JCO Glob Oncol*. 2020;6:679-687. https://doi.org/10.1200/JGO.19.00408
50. de Lemos LLP, Carvalho de Souza M, Pena Moreira D, et al. Stage at diagnosis and stage-specific survival of breast cancer in Latin America and the Caribbean: a systematic review and meta-analysis. *PLoS One*. 2019;14:e0224012.
51. Pardo C, de Vries E. Breast and cervical cancer survival at Instituto Nacional de Cancerología, Colombia. *Colomb Med (Cali)*. 2018;49(1):102-108. https://doi.org/10.25100/cm.v49i1.2840