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Survival in patients with stage IV breast cancer with systemic and surgical management

Supervivencia en pacientes con cáncer de mama estadio IV con manejo sistémico y quirúrgico

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ABSTRACT

Introduction: Systemic therapy is the standard treatment in patients with metastatic breast cancer at debut. However, combined therapy (systemic therapy plus local/locoregional surgery) is under investigation to determine if it offers additional benefit on oncologic outcomes. Randomized clinical trials (RCTs) have yielded contradictory reports regarding overall survival (OS), while retrospective studies show a favorable impact. This investigation aims to describe the OS and progression-free survival (PFS) of patients with metastatic breast cancer at debut, treated with systemic therapy only or combined therapy. **Materials and method:** A retrospective cohort study of patients with metastatic breast cancer at the debut treated in a specialized cancer care center in Colombia. Two groups were evaluated: EST vs CT, i.e., systemic therapy and breast surgery, respectively. The primary outcomes were PFS and OS, calculated using Kaplan-Meier survival functions and adjusted for confounding variables with Cox models. **Results:** 174 patients received EST, and 88 patients received CT. Median follow-up was 58.38 months; PFS was 38.56 months in the EST group vs 72.25 months in the CT group. OS was 42.4 months (95% CI 33.23-51.56) in the EST group vs. 82.33 (95% CI 62.1-102.55) in the CT group; both results were statistically significant for the surgical group. **Conclusion:** In patients with metastatic breast carcinoma at debut, OS and PFS were better in those treated with CT than in those managed with EST.

Keywords: Breast neoplasms, surgery, survival, therapeutics.

RESUMEN

Introducción: El manejo sistémico es el pilar del tratamiento en las pacientes con cáncer de mama metastásico al debut. Sin embargo, la terapia conjunta (sistémica con cirugía local/locorregional) es objeto de investigación para determinar si ofrece un beneficio adicional en los resultados oncológicos. Los ensayos clínicos aleatorizados tienen reportes contradictorios en cuanto a supervivencia global, mientras que los estudios retrospectivos muestran un impacto favorable. Esta investigación tuvo como objetivo describir la supervivencia global y la supervivencia libre de progresión de pacientes con carcinoma de mama metastásico al debut, tratadas con terapia sistémica exclusiva o terapia conjunta. **Materiales y método:** Estudio retrospectivo de una cohorte de pacientes con carcinoma de mama metastásico al debut de una clínica de referencia oncológica. Se evaluaron dos grupos de manejo: con terapia sistémica exclusiva vs. terapia conjunta. Los resultados principales evaluados fueron la supervivencia libre de progresión y la supervivencia global, calculados mediante las funciones de supervivencia de Kaplan-Meier y ajustados a las variables confusoras con modelos de Cox. **Resultados:** Recibieron terapia sistémica exclusiva 174 pacientes y 88 pacientes, terapia conjunta. La mediana de seguimiento fue de 58,38 meses; la supervivencia libre de progresión fue de 38,56 meses en el grupo de terapia sistémica exclusiva vs. 72,25 meses para el grupo de terapia conjunta. La supervivencia global fue de 42,4 meses (IC

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95 % 33,23-51,56) en terapia sistémica exclusiva vs. 82,33 (IC 95 % 62,1-102,55) en terapia conjunta, ambos resultados estadísticamente significativos para el grupo quirúrgico. **Conclusión:** En pacientes con carcinoma de mama metastásico al debut, la supervivencia global y la supervivencia libre de progresión fueron mejores en los tratados con terapia conjunta que en los manejados con terapia sistémica exclusiva.

Palabras Clave: cáncer de mama, cirugía, supervivencia, tratamiento.

1. Introduction

It is estimated that 3-8% of patients diagnosed with breast cancer may be diagnosed with metastatic disease [1]. The standard treatment for these cases is systemic therapy with significantly improved OS and PFS, especially in patients with positive hormone receptors and/or HER2 [2,3].

Surgery has been conceived as a therapeutic approach aimed at relieving symptoms and preventing complications associated with the local progression of the disease [3]. However, it has also been suggested that it has a beneficial effect in prolonging patient OS through various mechanisms such as reduction of tumor load, elimination of cancer stem cells, reversal of tumor-induced immunosuppression, reduction in clonal heterogeneity, discontinuation of primary tumor self-seeding, interruption of multidirectional tumor cell movement between primary and distant tumor sites, and decrease in tumor promoter activities mediated by cancer stem cells [4].

As a result, the combined use of systemic therapy and surgical management in patients with stage IV breast cancer has been investigated. RCTs report contradictory results in terms of OS for those receiving both therapies [3,5-7], while retrospective studies, resulting from real-life experiences, show an improvement in this parameter [3,8-12]. It provides relevant evidence in therapeutic decision-making.

Our research aims to describe the OS and PFS of patients with early-stage IV breast cancer, who received CT and EST at a specialized cancer care center in Medellín - Colombia.

2. Methods

An observational retrospective cohort study was carried out using information from Fundación Colombiana de Cancerología Clínica Vida (FCCCV) database in Medellín, between 2013 and 2021. Data collection was carried out from 1 October 2022 to 15 January 2023. Data of individuals who met the inclusion criteria were recorded, so the sample corresponded to the total number of patients.

2.1. Patients

The inclusion criteria were: 1) Patients over 18 years of age with infiltrating stage IV breast cancer at diagnosis; 2) Histological confirmation of primary disease; 3) Clinical or imaging confirmation for metastatic disease; 4) Management with systemic therapy only and/or local or regional surgery, considering any type of breast or axillary surgery. 270 patients met the criteria and were reviewed. Exclusion criteria were considered as follows: medical histories with more than 10% of the data lost, stage IV disease by progression, pregnancy, lactation, metachronous breast cancer, and breast cancer as second primary.

2.2. Variables

The primary result was OS calculated from the start of treatment to the last follow-up or death from any cause. PFS was a secondary outcome calculated from the start of treatment to the date of last follow-up or at which progress was documented.

Variables were evaluated in two groups of patients: exclusive systemic therapy and combined therapy (systemic treatment plus breast and/or axillary surgery). Characteristics of individuals at the time of diagnosis were collected in both groups: age, menopausal status, and body mass index (BMI). The characteristics of the tumor were also recorded: histological type and grade molecular subtype,

tumor size, clinical and pathological classification of regional nodules according to TNM classification [13], site and number of metastases, date, and site of first progression.

The date of diagnosis was the one described in the first study that documented the disease remotely; if this information was not available, the date of the biopsy report; and, if none of the previous were available, the data provided in the institution's database. The date of progression of the disease for the first study was recorded. Finally, the cutoff date for assessing the OS was 8 January 2023 via the Adres platform (www.adres.gov.co/consulte-su-ep).

2.3. Statistical methods

A univariate analysis was carried out to characterize the study population. In the case of quantitative variables, the Kolmogorov-Smirnov normality test was applied to determine whether they presented averages or medians. Qualitative variables were determined using absolute and relative frequencies. Median survival was calculated using the Kaplan Meier curve.

For bivariate analysis, survival associations with each factor were calculated independently; for qualitative variables, chi square of independence; for quantitative variables, student's t-test or Mann-Whitney U test (quantitative – qualitative). The differences in covariable survival were calculated using the Logrank test.

A multivariate analysis was performed to measure the association between covariables and the event occurrence time using a Cox regression. A p value less than 0.05 was considered statistically significant.

As a sensitivity analysis of the possible effect of confounding by indication, a Propensity Score analysis was performed using a logistic regression model, estimating the expected effect throughout the sample. The probability difference is presented with its respective confidence interval.

All analyses were carried out by the STATA software version 16.1.

3. Results

A total of 270 patients met the inclusion criteria, eight cases with unknown start date were excluded, thus obtaining a final group of 262 patients: 174 receiving EST, and 88 receiving CT.

Characteristics of the disease are presented in Table 2. CT patients showed significantly more oligometastases and inflammatory tumors, while EST patients had significantly higher bone, pleural, liver metastases, and T4b tumors. The other characteristics were balanced.

Table 1. Demographic characteristics

Characteristic	Systemic treatment (N = 174)	Systemic + surgical treatment (N = 88)	P
Age, average ± Standard deviation	56.6 (13,4)	56.3 (14)	0.17
Menopausal status			
Premenopausal	48 (27.6)	26 (29.5)	0.77
Postmenopausal	122 (70.1)	61 (69.3)	
Unknown	4 (2.3)	1 (1.1)	
Body mass index			
Low weight:<18.5	18 (10.3)	6 (6.8)	0.19
Normal: 18.5 – 24.9	74 (42.5)	27 (30.7)	
Overweight25 – 29.9	45 (25.9)	29 (33)	
Obesity: > 30	17 (9.8)	14 (15.9)	
Unknown	20 (11.5)	12 (13.6)	

Table 2.

Characteristics	Systemic treatment (N = 174)	Systemic + surgical treatment (N = 88)	P
Laterality			
Unilateral	165 (94.8)	83 (94.3)	0.53
Bilateral	9 (5.2)	5 (5.7)	
Histological type			
Infiltrating ductal carcinoma	144 (82.8)	81 (92)	0.26
Infiltrating lobular carcinoma	13 (7.5)	5 (5.7)	
Mixed	2 (1.1)	0	
Other	5 (2.9)	0	
Occult carcinoma	3 (1.7)	0	
Unknown	7 (4)	2 (2.3)	
Histological grade			
1	17 (9.8)	8 (9.1)	0.15
2	73 (42)	32 (36.4)	
3	65 (37.4)	35 (39.8)	
Occult carcinoma	6 (3.4)	0	
Unknown	13 (7.5)	13 (14.8)	
ER status			
Positive	131 (75.3)	60 (68.2)	0.45
Negative	42 (24.1)	27 (30.7)	
Unknown	1 (0.6)	1 (1.1)	
PR status			
Positive	108 (62.1)	50 (56.8)	0.7
Negative	64 (36.8)	37 (42)	
Unknown	2 (1.1)	1 (1.1)	
Her 2 status			
Positive	34 (19.5)	19 (21.6)	0.82
Negative	138 (79.3)	68 (77.3)	
Equivocal, not FISH	1 (0.6)	0	
Unknown	1 (0.6)	1 (1.1)	
Ki 67, median + IQR	36.4 + 22	38.7 + 25.3	0.70
Subtype IHC			
Luminal A	30 (17.2)	15 (17)	0.16
Luminal B	85 (48.9)	31 (35.2)	
Triple negative	25 (14.4)	20 (22.7)	
Luminal-HER2	18 (10.3)	13 (14.8)	
HER2 positive	16 (9.2)	8 (9.1)	
Unknown	0	1 (1.1)	
Number of metastases			
<4	18 (10.3)	32 (36.4)	<0.001
>4	155 (89.1)	54 (61.4)	
Unknown	1 (0.6)	2 (2.3)	

Table 2. (Continued)

Metastatic site			
Bone	123 (70.7)	51 (58)	0.02
No	51 (29.3)	37 (42)	
Lung	59 (33.9)	27 (30.7)	0.35
No	115 (66.1)	61 (69.3)	
Liver	39 (22.4)	6 (6.8)	0.001
No	135 (77.6)	82 (93.2)	
NCS	6 (3.4)	2 (2.3)	0.46
No	168 (96.6)	86 (97.7)	
Distance	49 (28.2)	22 (25)	0.34
No	125 (71.8)	66 (75)	
Pleural	19 (10.9)	4 (4.5)	0.06
No	155 (89.1)	84 (95.5)	
Other	19 (10.9)	3 (13.6)	0.02
No	155 (89.1)	865 (96.6)	
Tumor size			
T1	4 (2.3)	2 (2.3)	0.02
T2	32 (18.4)	14 (15.9)	
T3	19 (10.9)	13 (14.8)	
T4a	2 (1.1)	5 (5.7)	
T4b	80 (46)	34 (38.6)	
T4C	5 (2.9)	3 (3.4)	
T4d	17 (9.8)	17 (19.3)	
TX	9 (5.2)	0	
Unknown	6 (3.4)	0	
Focality			
Unifocal	157 (90.2)	81 (92)	0.17
Multifocal	7 (4)	3 (3.4)	
Multicentric	3 (1.7)	2 (2.3)	
Multifocal and multicentric	0	2 (2.3)	
Occult	5 (2.9)	0	
Unknown	2 (1.1)	0	
Clinical N			
N1	58 (33.3)	29 (33.3)	0.16
N2	58 (33.3)	28 (31.8)	
N3	29 (16.7)	24 (27.3)	
N0	14 (8)	6 (6.8)	
Nx	8 (4.6)	0	
Unknown	7 (4.1)	1 (1.1)	

When evaluating the treatment characteristics, significant differences between groups were found in almost all the variables. Thus, CT patients presented significantly higher requirements for cytotoxic therapy, polychemotherapy, and the use of Anthracycline drugs with taxans. While patients with EST received significantly more endocrine therapy with aromatase inhibitors (AI) and the combination of AI with cyclin-dependent kinase inhibitor (CDKI). Radiation therapy was administered significantly more in the CT group. There were no differences between the groups regarding the use of anti-Her therapy and suppression of ovarian function. (Table 3).

Characteristics of surgical treatment are presented in Table 4.

Table 3. Characteristics of the treatment

Characteristics	Systemic treatment (N = 174)	Systemic + surgical treatment (N = 88)	P
Cytotoxic therapy			
Monochemotherapy	61 (35.1)	20 (22.7)	0.002
Polychemotherapy	70 (40.2)	56 (63.6)	
No CT/do not accept	43 (24.7)	12 (13.6)	
Chemotherapy drug			
Taxans	53 (30.5)	13 (14.8)	0.001
Anthracyclines	14 (8)	2 (2.3)	
Platinum	0	1 (1.1)	
Capecitabine	1 (0.6)	1 (1.1)	
Taxans and platinum	10 (5.7)	7 (8)	
Taxans y Anthracyclines	38 (21.8)	40 (45.5)	
Taxans and others	6 (3.4)	3 (3.4)	
Antracyclic and others	2 (1.1)	1 (1.1)	
Platinum and others	1 (0.6)	0	
Taxans, anthracyclines and platinum	3 (1.7)	3 (3.4)	
Others	3 (1.7)	6 (6.8)	
Do not require	43 (24.7)	11 (12.5)	
Endocrine Therapy			
Tamoxifen	16 (9.2)	17 (19.3)	0.01
Aromatase inhibitor	60 (34.5)	26 (29.5)	
Fulvestrant	4 (2.3)	5 (5.7)	
Cycline and aromatase inhibitor	37 (21.3)	6 (6.8)	
Cycline and fulvestrant inhibitor	2 (1.1)	0	
Fulvestran anastrozole	1 (0.6)	0	
Do not receive	11 (6.3)	4 (4.5)	
Do not require	43 (24.7)	30 (34.1)	
Suppression of ovarian function			
Surgical	19 (10.9)	7 (8)	0.47
Medicine	6 (3.4)	6 (6.8)	
Radiotherapy	3 (1.7)	3 (3.4)	
Do not receive	8 (4.6)	2 (2.3)	
Do not require	138 (79.3)	70 (79.5)	

Table 3. Characteristics of the treatment (Continued)

Anti HER2 Therapy			
Trastuzumab	10 (5.7)	10 (11.4)	0.4
Pertuzumab	2 (1.1)	0	
Tratuzumab + Pertuzumab	25 (14.4)	12 (13.6)	
Do not receive	1 (0.6)	0	
Do not require	136 (78.2)	66 (75)	
Locoregional radiotherapy			
Breast	7 (4)	2 (2.3)	<0.001
Breast and locoregional nodules	5 (2.9)	6 (6.8)	
Rib cage	0	8 (9.1)	
Rib cage and y locoregional nodules	0	9 (10.2)	
Axial	1 (0.6)	1 (1.1)	
Do not receive	156 (89.7)	35 (39.8)	
Unknown	5 (2.9)	27 (30.7)	
Radiotherapy to metastasis			
Yes	70 (40.2)	21 (23.9)	0.04
No	102 (58.6)	67 (76.1)	
Unknown	2 (1.2)	0	

Table 4. Surgical and systemic treatment characteristics

Characteristics	**Systemic + surgical treatment (N = 88)**
Average N positive by pathology	5.3 + 6.2
First management	
Systemic	78 (88.6)
Surgical	10 (11.4)
Cause of surgery	
Hygienic	24 (27.3)
Systemic but non-local response, albeit stable	21 (23.9)
Complete clinical response	11 (12.5)
No systemic or local response	1 (1.1)
Stable systemic disease and local progression	1 (1.1)
Others	10 (11.4)
Unknown	20 (22.7)
Type of Surgery	
Modified radical mastectomy	71 (80.7)
Simple mastectomy	2 (2.3)
Conservative surgery and axillary dissection	10 (11.4)
Conservative surgery	1 (1.1)
Conservative surgery and sentinel ganglion biopsy	2 (2.3)
Axillary dissection	2 (2.2)

4. Survival Analysis

The 262 patients provided a total of 6910.92 months of follow-up with an average of 58.38 months (range 48.6 - 68 months) and a median of 36.17 months (95% CI 26.91-45,42).

4.2. Progression-free survival

114 progression events occurred, 85 in the EST group and 29 in the CT group. The average PFS in the EST group was 38.56 months (range 29.89–47.24); while for the CT group it was 72.25 (rang 60.92.83.37), i.e., a statistically significant result (p<0.001) (Figure 1A).

PFS at the year of diagnosis was 79.6% (95% CI 72.2–85.2%) and 90.2% (95 % CI 81.4–95%); at 5 years of age 11.5% (4.6–21.8% CI 95%) and 54.6% (30.8–67.9%) for EST vs. CT, respectively.

4.3. Overall survival

118 deaths occurred, 92 in the EST group and 26 in the CT group. The median OS for the entire population was 48.63 months (95% CI 40.43-56.82): for the EST group, it was 42.4 months (93% CI 95% 33, 23-51.56); and for the CT group, 82.33 (95 % CI 62.1-102.55), i.e., a statistically significant difference (p<0.001) (Figure 1B).

OS at the year of diagnosis was 85.7% (CI 95 %: 79.4-90,2%) and 96.4% (CI 95%: 89.1-98.8%). After 5 years of follow up, OS was 30% with 95% CI 20.8-39.7% and 59.9% with 95% CI 44.5-72.2% for the EST group and the CT group, respectively.

4.4. Confounding Factor Adjustment

Based on the results of the study and data from the literature, we considered as confounding variables for adjustment: age, menopausal status, tumor size, site of metastasis, number of metastases, status of hormone and HER2 receptors, molecular subtype, cytotoxic and endocrine systemic management.

The PFS shows an unadjusted analysis with HR 0.34 CI 95 % 0.22-0.52 (p<0.001) and the OS of 0.33 CI 95% 0.21–0.52 (p <0.001) (Table 5).

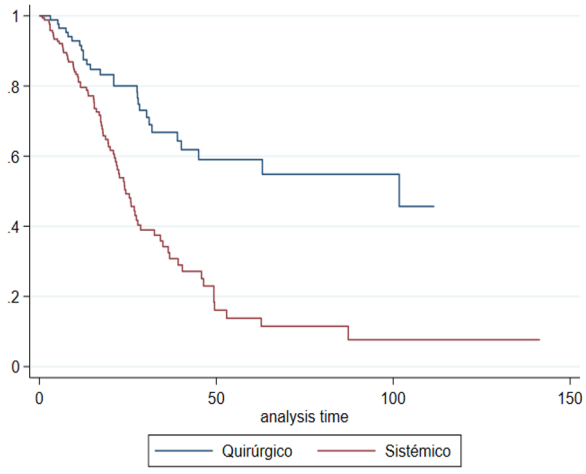

Fig. 1A. Progression free survival according to treatment group

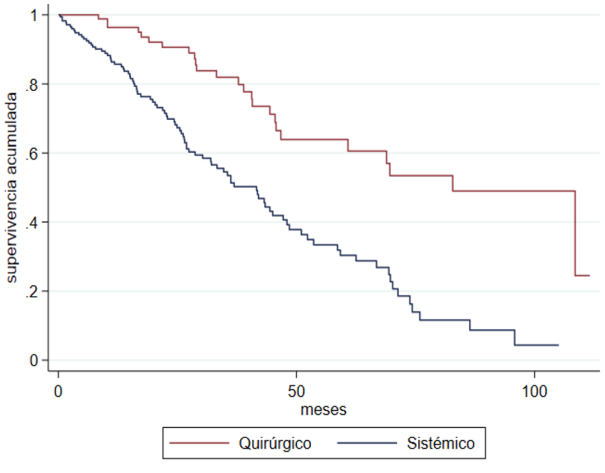

Fig. 1B. overall survival according to treatment group

The adjusted results can be seen in Table 6, showing that for both PFS and OS there is a statistically significant association in favor of CT. In the adjusted estimates, PFS showed a significant association with triple-negative subtype, the presence of liver metastasis and tumor size, T4b being of higher risk. Although T4a, T4d, and Tx showed significant results, the patient group for each of these categories was small and the confidence intervals wide. The same occurred with endocrine management and the use of CDKI and fulvestrant. As for the clinical staging of the nodules, confidence intervals for these categories were also wide.

In the adjusted estimates for OS, significant associations were found in luminal B subtypes, triple-negative, and tumor staging; however, when reviewing the confidence intervals, they were all very wide.

When the sensitivity analysis is carried out by the propensity score considering the characteristics that differed significantly between the groups by indication of treatment (pre-T, number of metastases, and site of the metastasis), the adjusted progression-free survival curves (Figure 2A) and global (Figure 2B) are drawn, and the significant difference in favor of joint management in terms of OS and PFS continues to be observed.

Table 5. Crude analysis of progression free survival and overall survival

	Observed estimate					
	Progression free survival			**Overall survival**		
	HR	CI95%	P value	HR	CI95%	P value
Type of treatment						
Systemic	Ref.			Ref		
Surgical + systemic	0.34	0.22 - 0.52	<0.001	0.33	0.21 - 0.52	<0.001

Table 6. Adjusted analysis of Progression free survival and Overall Survival

	Adjusted estimates							
	Progression free survival				**Overall survival**			
	HR	**CI95%**		**P value**	**HR**	**CI95%**		**P value**
Type of treatment								
Systemic	Ref.				Ref.			
Surgical + systemic	0.28	0.16 - 0.5	<0.001		0.23	0.13 - 0.43		<0.001
Molecular Subtype								
Her 2	Ref.				Ref.			
Luminal A	1.3	0.2	9.4	0.814	6.8	1.0	48.3	0.056
Luminal B	4.5	0.7	29.3	0.116	29.7	4.7	189.0	<0.001
Triple negative	3.5	1.3	9.1	0.010	13.3	4.9	36.1	<0.001
Luminal - Her 2	2.6	0.4	16.6	0.313	3.9	0.6	23.6	0.138
Liver Metastasis								
No	Ref.				Ref.			
Yes	2.2	1.2	4.0	0.009	1.6	0.9	2.7	0.078
Number of metastasis								
1-3 metastasis	Ref.				Ref.			
> 4 metastasis	2.4	1.2	4.8	0.016	1.7	0.9	3.3	0.117
Ct stage								
T1	Ref.				Ref.			
T2	5.2	1.4	19.5	0.015	6.3	1.2	33.3	0.030
T3	4.3	0.9	19.3	0.059	8.9	1.6	50.8	0.014
T4a	9.3	1.3	67.1	0.027	62.3	8.4	461.6	<0.001
T4b	4.7	1.2	18.2	0.023	10.8	2.1	56.7	0.005
T4c	34.2	5.6	207.9	<0.001	61.2	8.6	434.9	<0.001
T4d	4.5	1.2	17.9	0.030	10.7	2.0	57.6	0.006
Tx	15.1	2.1	108.4	0.007	4.2	0.3	51.4	0.263

Table 6. Adjusted analysis of Progression free survival and Overall Survival (Continued)

Cn stage								
Nx	Ref.				Ref.			
N1	8.8	1.7	47.1	0.011	1.3	0.3	6.1	0.774
N2	14.3	2.7	76.4	0.002	2.1	0.4	10.1	0.359
N3	20.1	3.5	114.0	0.001	1.8	0.3	9.1	0.487
N0	7.8	1.2	50.3	0.032	1.4	0.2	7.9	0.704
Type of chemotherapy								
Polychemotherapy	Ref.				Ref.			
Monochemotherapy	1.6	1.0	2.7	0.057	1.6	1.0	2.7	0.067
Did not receive	1.1	0.6	2.3	0.700	1.8	0.9	3.4	0.077
Initial endocrine therapy								
AI+ CDKI	Ref.				Ref.			
Tamoxifen	2.5	1.0	6.6	0.060	1.3	0.5	3.7	0.622
AI	2.3	1.0	5.3	0.052	1.8	0.8	4.2	0.176
Fulvestrant	3.5	1.0	11.9	0.042	2.7	0.8	9.2	0.111
CDKI +Fulvestrant	17.8	3.2	97.9	0.001	NE			
Fulvestrant + AI	NE				NE			

NE: Non estimable; Ref. reference category; AI: aromatase inhibitor; CDKI: Cyclin-dependent kinase inhibitors

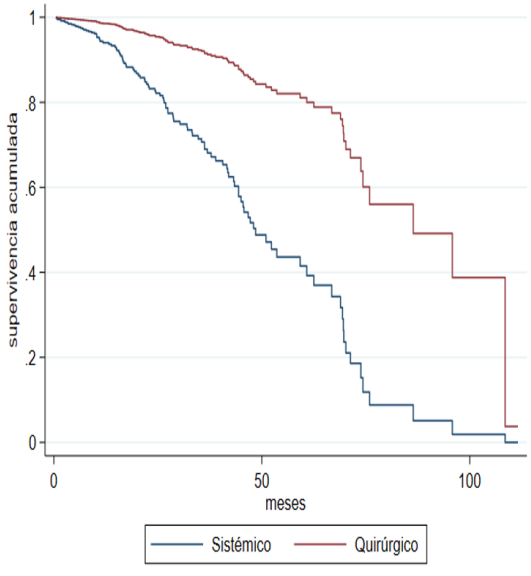

Fig. 2A. Adjusted Overall Survival

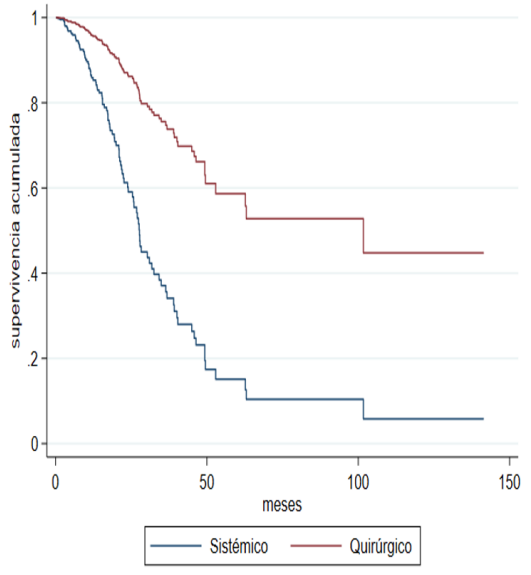

Fig. 2B. Adjusted Progression-Free Survival

5. Discussion

Stage IV breast cancer is a heterogeneous and incurable disease, its management is aimed at prolonging survival and palliation of symptoms, systemic therapy being the main pillar. However, multiple studies have been conducted to assess whether CT offers any additional benefit in oncological outcomes. The present study looked at this group of patients as well as those treated with EST.

Our study population had an average age of 56 years and a predominance of menopausal patients, consistent with what is in the literature. Nationally, Diaz and Cols had an average age of 58.8 years and a 62.9% postmenopausal [14]. And international studies, in general, report an average age of >50 years [1, 6-9, 15-18] and most menopausal patients [5, 7, 12, 17].

The main type of carcinoma in our cohort was the infiltrating subtype, moderate to high grade, hormone-positive, ductal, which is consistent with the global literature [6-9,11,14,17-19]. However, the triple negative subgroup, which has the lowest occurrence in various studies [6,7,12], took the second place in our cohort. Both in the literature and in our study, tumors were mainly classified at stage T4 [6, 8, 11, 14,16, 20]. Although, Soran and Cols [6] and Thomas and Colls [18] reported a higher frequency of small T2 stage tumors in their clinical trials.

Most of our patients received EST as in many of the retrospective studies [8, 11, 16-18]; this is supported by research results showing that surgical treatment is not associated with a higher rate of OS [1, 7, 12, 19]. It is important to note the clinical trial E2108 [7], where they randomized 256 patients to EST and CT, allowed the use of contemporary systemic therapies and showed the absence of effect on OS; thus, a better locoregional control in the CT group.

Our research showed that there were better results in OS and PFS in patients with CT, even after adjusting confounding variables. This is consistent with the findings of several retrospective descriptive studies and even an RCT [6, 8, 11, 12, 14-19]. The survival benefits of locoregional surgery in stage IV patients are supported in multiple hypotheses: some studies suggest that index lesion may behave as a reservoir of sick stem cells and removing it would decrease the likelihood of developing new sites of distant disease [21]. Resection of the primary tumor can increase angiogenesis by sensitizing it to chemotherapy and facilitating the entry of the drug into cancer cells [22,23]. Removing necrotic and tumor tissue eliminates chemoresistant tissues, restores host immunocompetence, and reduces growth of metastases [24, 25] thus resulting in increased patient survival [26]. Although there is the hypothesis that surgery in this group of patients may stimulate the progression of the disease by increased release of local growth factors [27], these can accelerate the proliferation of circulating tumor cells in peripheral blood and affect the OS and PFS [24, 25, 28-30].

In several studies [6, 8, 14, 17] including ours, hormone receptor status was as an independent prognosis factor, suggesting that tumor biology is important in survival. In contrast, there are also reports where sub-group tests of the hormone receptor status or HER2 show no benefit in OS [7].

Polymetastatic disease characterized our population as in a previous Colombian study [14] and in the RCT [1,6,7]. The metastatic pattern, both in number and location of distant disease, has also been identified as an independent and significant variable for patient survival outcomes [6,9-12,15,17]. Soran and Cols [6] identified that patients with solitary bone metastasis undergoing surgery had a significant benefit in OS compared to those who did not undergo surgery, although in their multivariate analysis, that association proved to be marginal. Rapiti and Cols [10] informed that the surgical effect on survival was not different for patients with bone metastases vs. other sites; however, after stratification, they observed a positive effect of surgery with negative margins in those who had bone metastases exclusively. Moreover, there are also studies where survival did not differ according to the treatment independent of the metastasis pattern [1, 7, 12]. For instance, Badwe and Cols [1] concluded that surgical management had no impact on patient survival, but also did not identify any subgroup of patients likely to benefit from locoregional treatment. Our study found a significant association, with worse PFS, in those patients who had liver metastases and metastasis number >4, whereas OS showed no association with these variables.

As in the literature, the most widely used systemic treatment in our population was chemotherapy [1-9, 12,15-18, 20]. Non-administration of systemic therapy, when indicated, occurs in some retrospective studies [8, 9, 14, 16, 17], including at the Tata Memorial Hospital in India [1]. In the RCT, treatment with taxans and antiHER2 was limited to only a small number of patients, thereby affecting their survival results. This is not our case, the patients received almost entirely the indicated therapies, allowing us to observe the real impact of local control on the patient's survival with protocol management.

Due to the retrospective nature of the study, one of its limitations is the lack of randomization and thus the possible bias of selection for the treatment groups, this would explain the beneficial effect in OS and PFS in patients receiving CT. Retrospective studies showed that patients who underwent surgery had better prognostic characteristics [30-33] and some had responded to systemic treatment, which could then be the causes of better survival and not the surgical procedure itself [12]. In our study, patients undergoing surgery had a higher tumor load; it was also observed that when grouping surgical indications, most of them presented a complete or partial response to systemic therapy, leading us to consider that the benefit would be associated with systemic treatment. Similarly, the sample size is low, which does not allow us to establish a clinical recommendation.

As for the clinical records, some patients lacked information about their management, most evident in the early years. However, those were excluded so that they did not affect the results

6. Conclusion

In patients with metastatic breast cancer at debut, the additional benefit that locoregional surgical management can offer is controversial. The higher quality RCT argues that locoregional control does not offer a better OS, while retrospective studies, resulting from real-life experiences, like our research, report a benefit with surgical management.

7. Abbreviations

RCTs: Randomized clinical trials

OS: overall survival

PFS: progression-free survival

EST: exclusive systemic therapy

CT: combined therapy (systemic and local/locoregional surgery).

FCCCV: Fundación Colombiana de Cancerología Clínica Vida

AI: aromatase inhibitors

CDKIs: cyclin-dependent kinases inhibitors

8. Administrative information

8.1. Additional Files

None declared by the authors

8.2. Acknowledgments

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8.3. Author contributions

FERNANDA XIMENA BRAVO: Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **ELSA MARIA VÁSQUEZ TRESPALACIOS:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **ARNON OVIEDO:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **FERNANDO HERAZO MAYA:** Conceptualization, validation, visualization,

methodology, project management, writing: review and editing. **JAVIER MAURICIO CUELLO LÓPEZ:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. All authors read and approved the final version of the manuscript

8.4. Financing

The study was funded with the resources of each researcher.

8.5. Availability of data and materials

Data and materials are available upon request from the corresponding author. No other materials are reported.

8.6. Statements

8.6.1. Ethics committee approval

The protocol of this study was approved by the institutional committee of ethics of research in human beings of University CES (code Acta283Proy004) and Fundación Colombiana de Cancerología Clínica Vida. Since this is a retrospective study without any intervention in the care of the patients, no consent was required. Patient data were guaranteed to be anonymous and confidential.

8.6.2. Conflicts of interest

The authors declare that they have no conflict of interest.

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