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Surgical treatment of the primary tumor in patients with stage IV breast cancer

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Abstract: Objective: To analyze the impact on survival in patients with stage IV breast cancer underwent surgical treatment of the primary tumor in the service of mammary pathology of our service in the period 2006-2016. Method: Retrospective, longitudinal study, analytical and descriptive. The sample consisted of 106 patients diagnosed with stage IV breast cancer, treated at the breast pathology service, meeting the inclusion criteria, taking into account the histories available in the medical histories service.All the patients fulfilled initial systematic treatment based on anthracyclines and taxanes, selecting 71 patients for surgical treatment. The tabulation and processing of the information was done through a database in excel, and statistical system SPSS22 . Results: 71 patients underwent surgery (66.98 %), 35 (33.2 %) only to chemotherapy. The most frequent histological subtype was the ductal 80.2%, 68.9% were T4, 43.4% N1, the most frequented site of metastasis was bone, oligo-metastatic 84%, the most performed surgery was total mastectomy 32.1%, not palliative 84%. The overall survive was 69.9 vs. 30.6 months inpatients operated and not operated. The progression free period was 47.3 in operated patients vs. 11.02 months in non-operated patients. Associated with the risk of death and survival, lymph node status, surgical treatment, metastasis in more than two organs and other than bone localization. Conclusion: This study showed benefit in terms of overall survive and free survival whiteout progression with the surgical treatment of the primary tumor.

Key words: cancer; breast; stage IV; primary tumor surgery; survival

1 Introduction

According to statistics, up to 6% of breast cancer (BC) is diagnosed at stage IV (metastatic) with an overall survival (OS) of 40 months on average, adversely influenced by factors such as multiple metastases and involvement of different organs [1]. For this reason, metastatic breast cancer (MBC) has been considered an incurable disease with low 5-year survival. Consequently, the goal of systemic treatment has been focused on alleviating symptoms and improving quality of life, reducing surgery on the primary tumor in these patients as a means of preventing or treating local complications such as bleeding, infection, or tumor ulceration. However, it is true that with the new treatment modalities developed over the past 25 years, the median OS has increased (3%–30%), suggesting that this group of patients may achieve better OS and disease-free survival (DFS) rates, especially in patients with single and limited metastases, with DFS rates extending up to 20 years [2].

The natural history of MBC is changing; the diagnosis of disease with a low tumor burden and the development of new systemic treatments has led to higher overall survival (OS) and disease-free survival (DFS) rates. The paradigm of surgery for MBC as a palliative treatment is being widely questioned based on multiple retrospective reviews over the past decade,

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which have suggested a survival benefit in women with resected intact primary tumors. These reviews may contain biases such as younger age, low tumor burden, and more favorable biological characteristics, but this has led to multiple randomized trials to evaluate the value of local treatment of the primary tumor in patients with distant disease [3] .

These studies have suggested that surgical resection of the primary tumor in patients with MBC may improve survival. This finding is intriguing, as it may offer a treatment option for a disease that has historically been considered untreatable [3].

There is now compelling evidence that surgical resection of the primary tumor as an initial treatment described for other metastatic cancers (kidney, colon, melanoma), provides a benefit in terms of OS and PFS [1]. In MBC, the benefit in terms of OS has been extensively investigated in the context of demographic factors, histopathology, metastatic burden, and type of surgery performed.

Another widely studied factor has been lymph node status. It has been postulated that the value of fine needle aspiration (FNA) lies in its ability to determine which patients require axillary staging, thereby avoiding axillary surgery in stage IV patients. The study also compared the outcomes of sentinel lymph node biopsy (SLNB) versus axillary lymph node dissection (ALND). It was demonstrated that positive axillary ultrasound was associated with a lower number of patients selected for surgery; as expected, patients with positive FNA were associated with axillary dissection, avoiding SLNB, without demonstrating an additional survival benefit with axillary dissection over local treatment and SLNB alone; previous studies have reported similar results [4].

The NSABP-B4 study compared radical mastectomy with total mastectomy, questioning the survival benefit of ALND. While a benefit has certainly been observed with ALND in patients with extensive axillary disease but no distant metastases; however, it has not been shown to provide a statistically significant benefit in terms of overall survival once distant metastases have occurred. Since there is a potential survival benefit associated with surgery in metastatic patients, it would appear that all patients who do not present symptoms of disseminated disease or extensive metastatic disease should undergo local surgery and ALND; therefore, omitting FNA with axillary ultrasound (if the disease is low volume) and performing axillary dissection is safe without affecting the outcome in the absence of distant metastasis, although most studies have been retrospective [5].

Given the many unanswered questions regarding the treatment of MBC, we set out to analyze the impact on survival in patients with stage IV breast cancer who underwent surgical treatment of the primary tumor in the breast pathology service of the IVSS Oncology Hospital Service.

2 Method

2.1 Type of study

This study was conducted using a retrospective, longitudinal, analytical, and descriptive design. The study population consisted of patients with stage IV breast cancer treated in the Oncology Department of the Padre Machado Oncology Hospital from January 2006 to December 2016.

The sample was selected using a non-probabilistic, purposive, or judgmental sampling technique, taking into account the medical records available in the medical records department that met the inclusion criteria.

The inclusion criteria were: patients diagnosed with breast cancer and distant metastases confirmed by biopsy or imaging studies, patients under 90 years of age with adequate cardiac and hepatic function, a life expectancy of at least one year and eligible for systemic treatment with anthracyclines, hormone therapy, and/or targeted therapies; patients with stage IV breast cancer and measurable disease; patients with stage IV breast cancer who had a partial or complete response or stable disease following initial systemic treatment and were eligible for surgery on the primary tumor.

The exclusion criteria for study participants are as follows: patients who have received prior treatment before admission to the SOH IVSS breast pathology unit (surgery, chemotherapy, or radiation therapy); patients with local or distant disease progression during induction chemotherapy; and patients with impaired liver, cardiorespiratory, or renal function who are not eligible for surgery.

A written request for medical records was submitted to the SOH IVSS statistics department. Once the review schedule was completed, the dates of the admission medical records and case discussions were cross-checked to verify that they fell within the study period.

The following data were then collected: date, age at diagnosis, sex, type of diagnosis, clinical stage, immunohistochemistry report, tumor size, lymph node status, presence of metastasis, surgical procedure performed, survival, post-treatment status, and date of last follow-up.

The data were obtained by applying the instrument designed as the patient's medical record. Subsequently, the data were organized, and information was gathered to verify compliance with the specific research objectives, according to the indicators outlined in the operationalization of the variables.

The information, collected retrospectively and expressed as means with standard deviations, with variables compared using tables, percentage charts, and line graphs, was stored in a computerized database (Microsoft Office Excel 2010) and subsequently analyzed in the SPSS 22 statistical software, enabling the respective conclusions to be drawn.

Therefore, the author recorded the relevant clinical information in a tool designed for this purpose, linked to the operationalization of variables; this results data was related to other studies to present the relevant discussion and conclusions.

For survival data, the Kaplan-Meier formula was applied according to subtypes: pk = pk-1. (Rk-L)/rk; progression-free survival and overall survival curves were correlated with relapse type and intrinsic subtypes and are presented in a survival plot generated using Excel and SPSS 22.

3 Results

The study included 106 patients with stage IV breast cancer who were seen in the breast pathology clinic at our center between 2006 and 2016, with an average follow-up of 33.6 months (range 3–102). all of whom received initial systemic therapy based on a regimen of anthracyclines and taxanes for 6 cycles; of these, 71 patients (66.98%) were selected for surgical treatment of the primary tumor, and 35 cases (33.2%) continued with systemic therapy and radiotherapy as needed.

The mean age of the patients with metastatic breast cancer included in the study was 54.9 years (range 25–88); 24.5% (n = 26) were under 45 years of age, and 75.5% (n = 80) were over 45 years of age.

Table 1. Ages

Age		
N	Valid	106
	Missing	0
Mean		54.92

Table 2. Frequency, Cumulative %

		Frequency	%	Valid %	Cumulative %
Valid	<45	26	24.5	24.5	24.5
	>45	80	75.5	75.5	100.0
	Total	106	100.0	100.0	

The most common histological subtype was ductal (80.2%, n=85), followed in order of frequency by the lobular subtype (12.3%, n=13); less common subtypes included the papillary histological subtype (1.9%), micropapillary (1.9%), and ductal-lobular (1.9%), as well as one case of metaplastic breast cancer and one case of mammary stromal sarcoma (both 0.9%).

Based on side distribution, stage IV breast cancer was observed in the left breast in 58.5% of cases (n =62) and in the right breast in 41.5% of cases (n=44).

The frequency by molecular subtype was: Triple-negative 28.3% (n=30), Luminal A 26.4% (n=28), Luminal B HER2-negative 22.6% (n=24), HER2 neu +++ 11.3% (n=12), and Luminal B HER2-positive 10.4% (n=11).

Table 3. Histological subtype

		Frequency	%	Valid %	Cumulative %
Valid	Ductal	85	80.2	80.2	80.2
	Ducto-lobular	2	1.9	1.9	82.1
	Lobular	13	12.3	12.3	94.3
	Metaplastic	1	0.9	0.9	95.3
	Micropapillary	2	1.9	1.9	97.2
	Papillary	2	1.9	1.9	99.1
	Stromal sarcoma	1	0.9	0.9	
100					

Table 4. Molecular subtype

Valid	Her2	12	11.3	11.3	11.3
	Luminal	28	26.4	26.4	37.7
	Luminal	24	22.6	22.6	60.4
	Luminal	11	10.4	10.4	70.8
	No	1	0.9	0.9	71.7
	Triple	30	28.3	28.3	100.0
	Total	106	100.0	100.0	

Regarding the "T" in the TNM staging system of the 7th edition of the AJCC, 68.9% (n=73) were T4, 14.2% (n=15) were T3, 12.3% (n=13) were T2, and 4.7% (n=5) were T1.

Upon evaluating lymph node status at diagnosis, it was observed that 43.4% (n=46) were N1, 38.7% (n=41) were N2, and 16% (n=17) were N3.

The sites of metastasis, in order of frequency, were bone 43.4% (n=46), lung 20.8% (n=22), liver 5.7% (n=6), and contralateral axilla 1.9% (n=2); with 84% being oligometastatic (n=90) and 15% being polymetastatic (n=16).

51.9% (n=55) had a Ki67 score of less than 25% on immunohistochemical analysis, while 48.1% (n=51) had a score

greater than 25%.

Table 5. Tumor size

		Frequency	%	Valid %	Cumulative %
Valid	T1	5	4.7	4.7	4.7
	T2	13	12.3	12.3	17.0
	T3	15	14.2	14.2	31.1
	T4	73	68.9	68.9	100.0
	Total	106	100.0	100.0	

Table 6. Lymph node status

		Frequency	%	Valid %	Cumulative %
Valid	N0	2	1.9	1.9	1.9
	N1	46	43.4	43.4	45.3
	N2	41	38.7	38.7	84.0
	N3	17	16.0	16.0	100.0
	Total	106	100.0	100.0	

Table 7. Metastasis

		Frequency	%	Valid %	Cumulative %
Valid	Oligometastasis	90	84.9	84.9	84.9
	Polimetastasis	16	15.0	15.0	100.0
	Total	106	100.0	100.0	

The histological differentiation grade in the evaluated patients was G2 66% (n=70), G3 31.1% (n=33), G1 2.8% (n=3).

Of the total number of patients evaluated, 28.3% (n=30) had comorbidities; hypertension 24.5% (n=26), type 2 diabetes mellitus 1.9% (n=2), both 0.9% (n=1), and one case of hepatitis B 0.9% (n=1).

Regarding the type of surgical treatment performed following partial or complete response, stable disease, or for palliative purposes in the evaluated patients, total mastectomy accounted for 32.1% (n=34), modified radical mastectomy (Madden type) 17.9% (n=19), partial mastectomy 9.4% (n=19), modified radical mastectomy (Forrest type) 4.6% (n=5), partial mastectomy with axillary dissection 1.9% (n=2), and total mastectomy plus pectoralis major muscle window 0.9% (n=1).

Table 8. Surgical procedures performed

QT + Mastectomy	10	9.4	9.4	42.5
QT + Total mastectomy	34	32.1	32.1	74.5
QT + Modified radical mastectomy, Forrest type	5	4.7	4.7	79.2
QT + Modified radical mastectomy, Madden type	19	17.9	17.9	97.2
QT + Partial mastectomy + Axillary dissection	2	1.9	1.9	99.1
QT + Total mastectomy + wide window	1	0.9	0.9	100.0
Total	106	100.0	100.0	

Of the total number of patients who underwent surgery for the primary tumor (66.8%), 84.5% (n=60) had a non-palliative indication; whereas palliative surgery was performed in 15.5% (n=11).

Table 9. Intention of surgery

Valid	Non-palliative	60	56.6	84.5	84.5
	Palliative	11	10.4	15.5	100.0
	Total	71	67.0	100.0	
Missing	System	35	33.0		
Total		106	100.0		

When evaluating OS using Kaplan-Meier curves in the patients in this study, an estimated 10-year survival of 30.6 months was observed in the group of patients who did not undergo surgery; while the group of patients who underwent surgery had 69.9 months, with a 95% confidence interval of (21.7–39.5) and (59–80.8), respectively (P=0.00).

The OS of all patients evaluated in the study was 59.4% (n=63), with 28.6% (n=10) in the non-operated group and 74.6% in the operated group (n=53).

The mean duration of SLP in months for the group of patients treated without surgery was 11.02 months (95% CI 6.1–15.9), and for the group of patients who underwent surgery, 47.3 months (95% CI 38.09–56.51) (P=0.00).

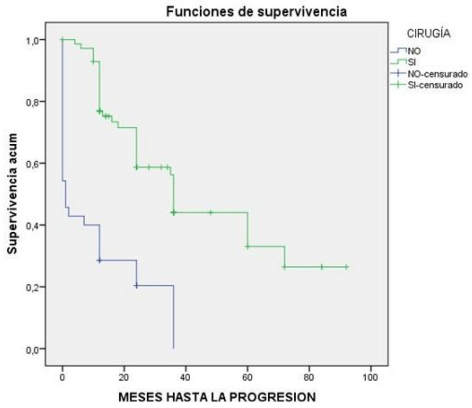

Figure 1. Survival. Months to progression

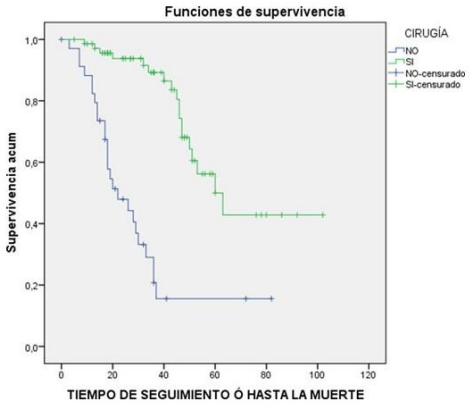

Figure 2. Follow-up time to death

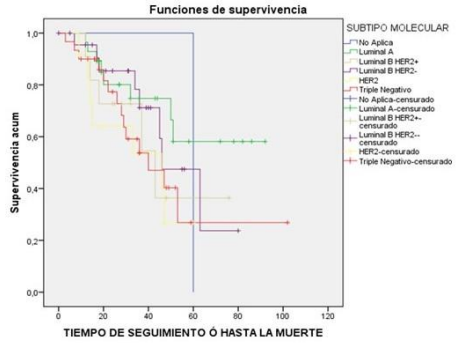

Figure 3. Survival. According to molecular subtype

Upon applying multivariate Cox regression analysis, the risk of death or impact on survival was statistically significant in patients with positive lymph nodes, for N1 (hazard ratio [HR] 0.00; 95% CI 0.00), N2 (HR 0.4; 95% CI 0.17–1.07), and N3 (HR 1.38; 95% CI 0.6–3.09; p=0.01), in patients with polymetastatic disease vs. oligometastatic disease (HR 0.49, 95% CI 0.25–0.99) (P=0.04), visceral metastases or metastases in sites other than bone and visceral sites (HR 5129.3; 95% CI 0.00–3.43), bone and visceral (HR 17,847.4; 95% CI 0.00–1.19), visceral and contralateral lymph node (HR 16,752.1; 95% CI 0.00–6.44) (P=0.02), and in the surgery group (HR 6.027; 95% CI 3.1–11.36) (P=0.00).

In this same multivariate analysis, no effect on survival or association between the cumulative risk of death and the independent variables Ki67 ≥ 25% (HR 1.03, 95% CI 0.5–1.9) (P=0.9), Her2neu overexpression (HR 0.5; 95% CI 0.27–1.04) (P=0.06), estrogen receptors (HR 1.7; 95% CI 0.9–3.1) (P=0.08), progesterone receptors (HR 1.6; 95% CI 0.99–3.01) (P=0.10), triple-negative molecular subtype (HR 0.83, 95% CI 0.42–1.62) (P=0.5), presence of comorbidities (HR 1.2; 95% CI (0.6–2.7%) (P=0.49), age group 45 years or older versus younger than 45 years (HR 1.1; 95% CI 0.5–2.1) (P=0.72), tumor size: T2 (HR 0.00; 95% CI 0.0), T3 (HR 0.17; 95% CI 0.043–0.74), T4 (HR 0.6; 95% CI 0.25–1.68) (P=0.11), histological grade G2 (HR 1.9; 95% CI 0.68–5.3) and G3 (HR 0.7; 95% CI 0.3–1.4) (P=0.13), or axillary dissection as a factor associated with improved survival (HR 0.4; 95% CI 0.05–3.37) (P=0.25). The median survival calculated by survival curve for the molecular subtypes was 66.8 months for the Luminal A subtype, 51.7 months for Luminal B HER2-negative, 50.6 months for triple-negative, 46.1 months for HER2- positive Luminal B, and 36.6 months for the HER2-neu-positive subtype (95% CI 48.8–66.5; P=0.38).

Table 10. Age, histological type, grade of differentiation, tumor size

	Inferior	Superior	
Age ≤45/>45 years	1.1	0.58-2.11	0.7
Histological type			
Ductal			0.99
Lobular	0.9	0.12-6.7	0.93
Ducto-lobular	1.1	0.14-9.7	0.86
Micropapillary	0.88	0.055-14.3	0.93
Papillary	0.00	0.00-0.00	0.97
Metaplastic	0.87	0.05-14.1	0.92
Sarcoma	0.00	0.00	0.99
Histological grade			
G1			0.13
G2	1.9	0.6-5.3	0.21
G3	0.7	0.3-1.4	0.35
cT			
T1			0.11
T2	0.00	0.00	0.97
T3	0.17	0.043-0.748	0.01
T4	0.65	0.25-1.68	0.38
cN			
N0			0.016

4 Discussion

The impact of locoregional treatment on survival in patients with stage IV breast cancer has been extensively studied, with conflicting results; most studies have failed to demonstrate a benefit in overall survival, while others show improved OS in patients with certain characteristics such as age, performance status, and the presence of comorbidities, related to the tumor's biological behavior and anatomoclinical factors (tumor size, grade of differentiation, lymph node status, hormone receptor positivity, Her2 neu overexpression, cell proliferation index, response to chemotherapy, among others). The retrospective nature of the studies, the absence of inclusion criteria in many of the series, and the detection of selection biases in some of them mean that their conclusions are questioned, and controversy persists regarding the effect of surgery on survival.

In the breast pathology department at our center, as part of our standard protocol, all patients with stage IV breast cancer initially receive systemic treatment with regimens based on anthracyclines in combination with taxanes. During the 2006–2016 period, 106 patients who completed this chemotherapy regimen were identified as the study sample. Of these, 71 patients (66.98%) were selected for surgical treatment of the primary tumor for local control following a partial or complete response or stable disease; 84.5% (n=60) had a non-palliative indication; while palliative surgery was performed in 15.5% (n=11).

In the study we present, surgical treatment of the primary tumor was associated with longer survival (30.6 vs. 69.9 months) when compared to the group of patients who underwent no surgical procedure, with a mean follow-up of 33.6 months (range 3–102).

Other authors agree with our findings and conclude that locoregional surgery of the primary tumor improves survival in patients with metastatic breast cancer. In a retrospective study of 109 patients with metastatic breast cancer, 52 patients underwent surgery following chemotherapy, with significantly higher survival reported in the operated patients who had few metastatic sites (P=0.001), with no significant differences in the number of metastases (P=0.35), and this improvement in OS was maintained in a multivariate Cox regression analysis at 24 months follow-up, particularly in patients with oligometastatic disease who received chemotherapy [4,5]. Neuman et al., in their prospective study conducted between 2000 and 2004 on 186 patients with stage IV breast cancer, selected as candidates for surgery those patients who were HER2-negative (P=0.01), had smaller tumors (P=0.05) and solitary metastases (P=0.001), of whom 69 (37%) underwent surgery, reported a significant trend toward improved survival in patients who underwent surgery and were estrogen receptor-positive, progesterone receptor-positive, and HER2-negative, identified as predictive factors for improved survival. The median survival was 35 months (P=0.004), with no benefit in triple-negative patients, suggesting that the impact on local control is much better with the use of targeted therapies [6].

The PFS (Progression-Free Survival) calculated using the Kaplan-Meier survival curve, demonstrated in this study that surgery resulted in a longer progression-free survival period for patients who underwent some form of surgical treatment of the primary tumor: 47.3 months (95% CI 38.09–56.51), (P=0.00) compared to patients who received only systemic therapy, with or without radiotherapy if indicated, which was 11.02 months (95% CI 6.1–15.9). Nguyen et al. demonstrated the benefit of locoregional treatment in patients with metastatic breast cancer compared to those who received only chemotherapy, with a 5-year OS rate of 21% vs. 14% and a progression- free survival of 72% vs. 46% (P<0.001 for both), which supports our findings [7] .

To establish criteria for selecting stage IV breast cancer patients who would benefit from surgical treatment of the primary tumor, a multivariate Cox regression analysis demonstrated a statistically significant association with lymph node-negative patients for N1 (hazard ratio [HR] 0.00; 95% CI 0.00), N2 (HR 0.4; 95% CI 0.17–1.07), and N3 (HR 1.38; 95% CI 0.6–3.09), (P=0.01), oligometastatic (HR 0.49, 95% CI 0.25–0.99) (P=0.04), whose metastasis site was exclusively bone (P=0.02), and who underwent surgical treatment (HR 6.027; 85% CI 3.1–11.36) (P=0.00).

Another study on surgical treatment in patients with metastatic breast cancer found benefits in overall survival, relapse-free rate, and progression-free survival in 75 oligometastatic patients treated between 1980 and 2010, with overall survival of 185 months and progression-free survival of 68.5 months—results superior to those obtained in our study; which is likely due to the fact that our study included patients with polymetastatic disease, reaffirming the benefit of surgery in patients with metastases in one or up to two organs who have responded to initial systemic treatment, considering this a subgroup of patients with longer survival and a better prognosis, with a reasonable probability of cure [8].

This study did not demonstrate a statistically significant influence or association in terms of survival or cumulative risk of death with the independent variables Ki67 greater than or less than 25% (HR 1.03, 95% CI 0.5–1.9) (P=0.9), HER2-neu overexpression (HR 0.5; 95% CI 0.27–1.04) (P=0.06), estrogen receptors (HR 1.7; 95% CI 0.9–3.1) (P=0.08), progesterone receptors (HR 1.6; 95% CI 9.9–3.01) (P=0.10), triple-negative molecular subtype (HR 0.83, 95% CI 0.42–1.62) (P=0.5), presence of comorbidities (HR 1.2; 95% CI 0.6–2.7) (P=0.49), age group older or younger than 45 years (HR 1.1; 95% CI 0.5 ‑ 2.1) (P=0.72), tumor size (P=0.11), histological differentiation grade (P=0.13), or axillary dissection as a factor associated with improved survival (HR 0.4; 95% CI 0.05 ‑ 3.37) (P=0.25); contradicting the findings of various studies, such as that by Rashaan et al., who concluded that women with more favorable prognostic factors (young, without comorbidities, with small tumors, hormone receptor-positive, and oligometastatic) underwent surgery more frequently, demonstrating an association between surgical treatment and survival [9].

Rapiti et al. obtained similar results, showing that women treated with surgery were younger, had smaller clinical tumor size (cT) and less clinical involvement of the axillary lymph nodes (cN), with a single metastatic site; they concluded that women with more favorable prognostic factors (young, without comorbidities, with small tumors, hormone receptor-positive, and oligometastatic) underwent surgery more frequently, demonstrating an association between surgical treatment and survival [10] .

We conclude that BC in metastatic patients in our country represents a significant percentage, due to the impossibility of early diagnosis or treatment, whether due to a lack of adequate screening programs or difficulty accessing the public health system. Although the surgical management of this subgroup of patients has been controversial.

This study, although retrospective, has demonstrated a clear benefit to performing non-palliative mastectomies in patients with stage IV breast cancer, particularly in those with oligometastatic disease; showing a clear benefit in both overall survival and disease-free survival.

Based on our results, we recommend offering the option of total mastectomy to all stage IV breast cancer patients, especially those with oligometastatic disease, once systemic treatment has been completed and there is clinical and imaging evidence of response and/or stable disease.

In the future, a prospective study will be proposed, in which the group of metastatic patients undergoes surgical management of the breast, and why not, of the axilla as well.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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