Impact of primary tumor resection in patients with metastatic breast cancer

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Abstract

Objective: Evaluate the impact of modified radical mastectomy on overall survival and progression free period of patients with stage IV breast cancer treated at the ISSEMyM State Cancer Center. **Material and Methods:** An observational, retrospective, and historical cohort study where patients with metastatic breast cancer from the ISSEMyM State Cancer Center were reviewed. The efficacy of surgical treatment of the primary tumor with Kruskal-Wallis test was evaluated. Comparing overall survival and progression-free survival in both groups. OS and PFS were calculated at 5 years with Log-Rank test plotted on Kaplan and Meier curves. Cox multivariate analysis was used to calculate the adjusted risks expressed with Hazard ratio (HR) 95% confidence interval (CI). **Results:** We identified 96 patients with metastatic breast cancer. 46 (48%) were excluded because they received surgical management prior to referral, unjustified suspension of established medical-surgical management and/or failure to continue with regular follow-up. Of the 50 (52%) patients included for the analysis, 34 (65%) underwent surgery and 16 (35%) did not. The mean age was 54 years ($s = \pm 13$). No metastasectomy. All with radiotherapy to the surgical bed at doses of 32.6-60 Gy. The overall survival, reported in months and according to the univariate analysis, was higher for the operated ones than for those that did not (28.5 months [range 6-74.[3] vs. 9.7 months [range 0.8-39.[2], $p = 0.001$). Similarly PFS was higher for patients operated on [20].6 months (range 5.7-77.3)] than for the non-operated 7.5 months (range 0.7-17.0)] ($p < 0.0001$). However, in the multivariate analysis "marginal" and non-statistical significance of the surgery in the OS were identified (HR = 0.35, 95% CI 0.12-1.03 [$p = 0.057$]); but a positive impact on PFS (HR = 0.2, 95% CI 0.07-0.56 [$p = 0.0021$]). Surgery improved PFS in oligomethasic disease (HR = 0.361, 95% CI 0.14-0.93 [$p = 0.035$]). And offered worse OS for the molecular subgroups: Triple negative (HR = 5.56, 95% CI 1.03-29.97 [$p = 0.045$]) and Luminal B/ with Her2 + overexpression (HR = 8.9, 95% CI 1.28-61.83 [$p = 0.027$]). **Conclusions:** Our findings suggest that resection of the primary tumor in patients with metastatic breast cancer treated in the ISSEMyM State Cancer Center has a favorable impact on its PFS and borderline overall survival, particularly benefiting patients with oligomethasic disease in whom although the surgery did not help them to live longer we could say that it impact in favor of a greater PFS. In addition, the findings obtained in this study suggest that such intervention should be avoided in patients with a Luminal B profile with Her2+ overexpression and triple negative because they lack benefit in both OS and PFS, since the aggressive biology of these neoplasms, does not seem to give enough time for the mastectomy to add any benefit to the OS and/or PFS.

Key words: Metastatic breast cancer. Palliative mastectomy. Metastasectomy. Survival stage IV breast cancer.

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Introduction

Approximately 3-4% of women with breast cancer present with metastatic disease at diagnosis, with a median survival of 18 to 24 months; with infrequent complete remissions with systemic chemotherapy, only a fraction of these women achieve complete responses and remain progression-free for a prolonged period^{3,15}. Overall survival (OS) and progression-free survival (PFS) are the main objectives in therapeutic decision-making for this group of patients. Modern systemic therapy has evolved and, currently, it significantly contributes to improve survival in these patients, bringing up the subject of avoiding locoregional, non-controlled disease adverse effects with special attention. In this regard, observational studies have suggested that surgery of the primary tumor (with and without radiotherapy [RT])¹⁶ can improve survival, and means of 18 to 42 months have been reported versus 28.7 months in patients not receiving locoregional management⁷⁻¹⁴. In these series, the use of surgery is relatively common, ranging from 40 to 60%, in spite of a lack of consensus¹⁵. Local disease is considered to be a focus of tumor stem cells and, therefore, it has been suggested that elimination of the primary tumor might reduce micrometastatic populations hematogenous spread. Surgical resection of necrotic tumor areas that are inaccessible to systemic therapy can control or even eliminate the advent of resistant tumor stem cells. Another theoretical advantage is based on the notion that best response of the disease, survival and time to progression are associated with lower numbers of circulating tumor cells^{17,18}. It has also been proposed that tumor spread can jeopardize the immune system, since the primary tumor can produce immunosuppressive factors that can help cancer cells to escape eradication by the immune system. In this context, surgical resection can reduce the tumor burden and decrease deleterious immunosuppression. Finally, the relatively low risks of surgery-associated morbidity and mortality represent another advantage that supports its justification in the metastatic breast cancer setting^{5,6}.

Disadvantages of locoregional surgical treatment

The role of surgical treatment of the primary tumor in patients with metastatic breast cancer is controversial, since it is an invasive procedure the benefit of which has not been clearly established. Systemic therapy is the main treatment for this group of patients, and it

should not be delayed at the expense of locoregional treatment. A theoretical disadvantage of local therapy is based on the hypothesis that it is possible for the primary tumor to secrete substances that inhibit the formation of new blood vessels. This way, primary disease elimination might induce angiogenesis and promote the progression of metastases¹⁹. Furthermore, there are some who believe that surgery and anesthesia-induced trauma can generate cytokines that stimulate neoplastic proliferation by compromising the immune system integrity²⁰.

Clinical impact of locoregional surgical control at clinical stage IV

The studies with the largest patient samples that were first published on this subject emerged from the analysis of national and institutional cancer registries. The first and largest study was published by Khan et al., who analyzed more than 16,000 patients with metastatic breast cancer registered between 1990 and 1993 in the American College of Surgeons National Cancer Database, and in whom primary tumor complete surgical resection with free margins was associated with a significant survival improvement (5-year OS with free margins: 18 vs. 7% without surgery; $p < 0.001$). Even after adjusting for possible confounding variables associated with survival, margin-free surgery continued to be associated with better survival (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.58-0.65)⁷. Another large study reported by Gnerlich et al. assessed 9,734 patients with metastatic breast cancer identified in the SEER database from 1988 to 2003; median survival was longer in those patients treated with surgery (36 vs. 21 months; $p < 0.001$). In the multivariate analysis, women with breast cancer who underwent surgical resection of the primary tumor were found to have lower mortality risk than women who did not undergo surgery (HR: 0.63; 95% CI: 0.60-0.66)⁹. These results were corroborated by a series based on a Geneva clinical data registry where 300 women were assessed from 1977 to 1996; an association was also found between survival improvement and complete primary tumor resection in breast cancer at clinical stage IV (HR: 0.6; 95% CI: 0.4-1.0; $p < 0.05$ "borderline")⁸. Researchers of the University of Washington in the US evaluated 409 patients with metastatic breast cancer treated between 1996 and 2005. After adjusting for variables associated with survival in the univariate analysis, median survival was longer in patients treated with surgery than in those who did not undergo surgical resection

(32 vs. 15 months; HR: 0.53; 95% CI: 0.42-0.67; $p < 0.001$)¹⁰. Similarly, University of Texas researchers observed a longer mean survival in those patients treated with surgery (27 vs. 17 months; $p < 0.001$). In the multivariate analysis, surgical intervention was associated with better OS (HR: 0.71; 95% CI: 0.56-0.91; $p = 0.006$)¹¹. Investigators of the British Columbia Cancer Agency, in Canada, reported an analysis of 733 women with metastatic breast cancer at diagnosis between 1996 and 2005: primary disease locoregional treatment with surgery and/or radiotherapy (RT) was associated with better 5-year OS (21 vs. 14%; $p < 0.001$) and better locoregional progression-free survival (72 vs. 46%; $p < 0.001$). In the Cox regression analysis, locoregional treatment was associated with better survival (HR: 0.78; 95% CI: 0.64-0.94; $p = 0.009$)²¹. Another study, carried out at the Cancer Comprehensive Center of the Netherlands, in Amsterdam, reported better 5-year survival in those patients who underwent surgery of the primary tumor (24 vs 3%; $p < 0.0001$). In the multivariate analysis, surgery maintained a significant survival improvement (HR: 0.62; 95% CI: 0.51-0.76)¹³. Researchers of the National Hospital and Cancer Center in Okayama (Japan) analyzed 344 patients treated from 1962 to 2007 and found a higher mean survival in patients with metastatic disease treated with surgery (27 vs. 22 months; $p = 0.049$)¹⁴.

Institutional series suggesting there is no association between locoregional treatment and survival

Unlike the above-described studies, which suggest that survival leans in favor of the group of patients undergoing locoregional surgical treatment, other studies have reported little or no association between locoregional treatment and survival in patients with clinical stage IV breast cancer. In a multivariate analysis carried out at MD Anderson Cancer Center in Texas (USA), primary disease surgery was associated with better progression-free survival (HR: 0.54; 95% CI: 0.38-0.77; $p < 0.001$), but with no statistical significance for OS (HR: 0.50; 95% CI: 0.21-1.19; $p = 0.12$)²⁴. Similarly, in an analysis conducted at Memorial Sloan-Kettering Cancer Center in New York, Neuman et al. also failed to find an OS improvement with surgery (HR: 0.71; 95% CI: 0.47-1.06; $p = 0.10$)²². In another study at Harvard University in Massachusetts, no positive impact on survival was identified to be associated with the group of primary tumor surgical intervention when the groups were adjusted for and analyzed by age, year

of diagnosis, metastatic disease localization, estrogen receptors and use of systemic therapy¹⁶. Finally, in a report of the Massey Cancer Center in Virginia (USA), patients treated with surgery appeared to have better survival than their peers treated without surgery (25 vs. 13 months). However, this survival benefit disappeared once data were adjusted for the use of chemotherapy in the multivariate analysis²⁵. One caveat of many studies is the lack of information about chemotherapy and the inability to control for this variable as an important factor of treatment. In addition, it should be highlighted that these series of studies were carried out prior to the advent of modern chemotherapeutic treatments and didn't take the specific chemotherapy regimen, dose intensity, response to systemic therapy and the moment patients underwent locoregional surgical treatment with regard to chemotherapy into account.

Biases of retrospective studies

When interpreting data originating in national databases and institutional series, the limitations of retrospective analyses should be considered. These limitations include bias in patient selection and assigned treatment. The reasons why some women, but not other, were offered locoregional treatment were often unclear. Most studies tried to control for confounding variables by means of multivariate analysis. However, the use of surgery was more common in specific groups of patients, with those selected to undergo primary tumor surgery having more favorable clinicopathological characteristics, including the following: younger age, Caucasian ethnicity, less comorbidities, smaller tumors, limited lymph node disease and estrogen receptor positive status. They also had more limited metastatic disease burden (oligometastases) and higher rates of chemotherapy use. In addition to these selection biases, some authors have also recognized the impossibility to assess other important factors that contribute to the analysis of the impact on survival owing to insufficient information about variables such as molecular sub-classification, the chemotherapy scheme, histologic grade and hormone receptors.

Current issues and prospective studies

In the American Society of Clinical Oncology (ASCO) annual meeting, in June 2016, two studies assessing the effect of primary tumor resection on OS in women with stage IV breast cancer, both arriving to conflicting conclusions, were presented. The prospective randomized

trial carried out in Turkey arrived to the conclusion that there is a 5-year survival benefit⁵, whereas the other study, which resorted to the USA database, showed a lack of benefit⁶.

The former trial⁵ included 274 Turkish women presenting with stage IV breast cancer. Based on disease extension, the patients received surgery at an average of 4 weeks post-chemotherapy ($n = 138$), or only chemotherapy ($n = 136$). Surgery was performed with a breast-preservation approach (with whole breast RT), or else it was a mastectomy (with or without RT based on disease extension and institutional practices). Patients with positive lymph nodes underwent axillary dissection, and hormone therapy and/or trastuzumab (anti-HER2) was given if it was indicated. Baseline characteristics were similar in both groups. Most patients had differentiation degree II-III, T2-3 and infiltrating ductal carcinoma. Approximately 30% of each group had HER2+ disease. In the surgery group, hormone receptor-positive disease occurred more commonly (86%) than in the systemic therapy group (73%), and there was less triple-negative disease (7 vs. 17%). Approximately 50% of patients had only bone metastases. At 3 years' follow-up, OS was 68% for the surgery group and 51% for the group only with systemic therapy, with the difference not being statistically different ($p = 0.10$). However, there were differences identified at up to 5 years of follow-up: 41.6% of patients in the surgery group were alive in comparison with 24.4% of the group that only received systemic therapy (HR: 0.66; $p = 0.005$). Mean OS at that moment was 46 and 37 months, respectively. It was concluded that surgery of the primary tumor added 7 extra months of life in patients with positive estrogen/progesterone receptors, 12 months in HER2- patients, 14 months in patients < 55 years of age and 10 months in patients with single bone metastasis. In addition, locoregional relapse was 11-fold lower for the group with surgical management (1 vs. 11%), and there was a 39% reduction in relapse.

The North American study⁶ included 112 patients with intact primary tumors, diagnosed between 2009 and 2012 at 14 institutions. After first-line systemic therapy, selected according to each treating physician's judgment, patients with clinical response to chemotherapy were then considered for elective surgery (its type and extent depended on treating physician's judgment). Median age was 51 years, average tumor size was 3.2 cm, most patients had positive estrogen/progesterone receptors and some were HER2-. Bone disease was only identified in 46% of cases, and metastatic disease was observed to be confined to a single organ in 57%. With a median

follow-up of 54 months, 3-year OS was 70% and median survival was 69 months. A total of 94 patients (85%) responded to first-line therapy (to later undergo surgery or not), whereas 17 patients (15%) failed to respond. In order to correct for potential bias in the survival comparison between responders and non-responders, the investigators carried out the analysis only among those patients who were still alive at 6 months of systemic therapy (patients who respond to first-line treatment are known to achieve better survival than those who don't). Median survival was 65 months among responders, with a 30-month survival rate of 78%, in comparison with only 13 months for non-responder patients, who had a 30-month survival rate of 24% ($p < 0.001$). Among the 94 responder patients, 39 underwent elective surgery (median time: 7 months after chemotherapy). These patients had larger tumors and most of them had metastatic disease to a single organ; other factors were not different between both groups. In the multivariate analysis, primary tumor surgery did not improve OS among those patients who responded to systemic therapy, who had a mean survival of 71 months versus 65 months for the group of those who did not receive surgical intervention. This finding translates into survival rates of 77 and 76%, respectively, at 30 months of follow-up ($p = 0.85$). No particular molecular subgroup could be identified where there was clear benefit of surgical intervention.

Patient selection for locoregional treatment

In an analysis published by Rapiti et al., complete surgical resection of the primary tumor was associated with improved survival, especially in women only with bone metastases (HR: 0.2; 95% CI: 0.1-0.4; $p = 0.001$)⁸. In another study conducted in Japan, OS was longer in surgery-treated patients, especially in those younger than 50 years ($p = 0.02$) and in those with oligometastasis ($p = 0.01$)¹⁴. In an exploratory analysis, Neuman et al. identified an association between better survival and primary tumor surgery, which was restricted to patients with positive hormone receptors or amplified HER2/neu ($p = 0.004$), whereas surgery was not identified to be associated with better survival in triple-negative patients ($p = 0.44$)²². Finally, an analysis of the British Columbia Cancer Agency found that, among patients treated with locoregional therapy, most favorable survival was observed in subsets of younger age, good performance status, positive estrogen receptor, free resection margins and distant disease limited to one site (bone metastatic disease or less than 4 metastatic lesions)²¹. As

a whole, these data suggest that locoregional treatment can reasonably be considered in groups of patients with favorable risk factors.

Material and methods

After the COE ISSEMyM Ethics on Research Committee approval, in this retrospective, historical cohort observational study, the medical records of all female patients attended to at the institution until the year 2016 or until the moment of death, and that were met for the first time with a diagnosis of metastatic breast cancer in the period encompassed between January 2009 and December 2012, were reviewed. This study assessed primary tumor surgical treatment efficacy: modified radical mastectomy (MRM) to improve OS and/or PFS as part of initial comprehensive oncological management, comparing these outcomes with those of non-operated patients. Demographic characteristics, variables of disease extension and information on pathology specimens were recorded.

Definitions

- Progression-free survival: time elapsed from the moment of cancer diagnosis to objective identification of disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1^{1,2}.
- Overall survival: time elapsed from the moment of cancer diagnosis until death, regardless of the cause¹.
- Metastatic breast cancer: it is considered to be a breast cancer at clinical stage IV when at the moment of initial diagnosis tumor activity distant to the site of origin has been documented according to criteria established by the American Joint Committee on Cancer (AJCC) clinical guidelines (7th edition, 2010)³.
- Oligometastasis: intermediate state of cancer distant extension, characterized by a spectrum of metastases limited by number (less than 5) and by site (one to 3 organs)⁴.

Variables

- Independent: primary tumor surgical treatment (MRM).
- Dependent: time of PFS and to death (OS) in months.
- Group identifier variables: age, metastatic disease localization and volume (oligometastasis), molecular classification, histologic grade and lymph node

involvement, both for the group undergoing surgery and for the one that does not.

Inclusion criteria

Any female patient older than 18 years of age newly diagnosed with clinical stage IV breast cancer attended to at COE ISSEMyM until the year 2016 or until the moment of death and that was first met in the period encompassed between January 2009 and December 2012 (i.e., with at least 3 years of follow-up).

Exclusion and non-inclusion criteria

Patients with metastatic breast cancer who had already received primary tumor radical surgical management prior to referral to our hospital.

Elimination criteria

Patients in whom, for any reason, medical-surgical management standardized in the medical practice guidelines established at COE ISSEMyM would have been discontinued or interrupted.

Statistical analysis

The Kruskal-Wallis test and the chi-square test for dichotomous variables were used in the univariate analysis in order to compare OS and PFS of operated versus non-operated patients. Clinical stage IV breast cancer OS at 5 years and PFS were calculated comparing the operated with the non-operated group with the log-rank test, and were displayed on Kaplan-Meier survival curves. Cox proportional risks multivariate analysis was used to calculate crude and adjusted disease progression and mortality risks, expressed with the risk rate or HR with a 95% CI. To assess each variable's independent contribution to OS and PFS, known covariates and covariates reported in the literature that are known to be associated with metastatic cancer prognosis were included in the Cox multivariate analysis. Using the Epi InfoTM data collection program, a Microsoft[®] Excel file was generated, which was imported from Statistical Analysis System-SAS/STAT[®] to carry out statistical analysis.

Bioethical implications and conflicts of interests

Up to date there isn't any prospective, randomized multicenter study demonstrating that surgical treatment

impacts with sufficient and statistically significant evidence as to recommend widespread and routine use of primary tumor surgery in patients with metastatic breast cancer with the purpose to improve OS and/or PFS, except for systemic cytotoxic or hormone treatment and/or targeted therapy, and bioethical conflicts are therefore ruled out for the group of patients who did not receive surgical treatment of the primary tumor and, instead, remained only under surveillance.

On the other hand, it should be mentioned that there were no conflicts of interests relative to the present study.

Results

During the reviewed period, 96 patients diagnosed with clinical stage IV breast cancer were identified, out of which 46 were excluded for having received some surgical management prior to their referral to our hospital, for having discontinued standard medical-surgical management established by our institution and/or for not continuing with regular follow-up (dropouts). Of the 50 patients who met the criteria for inclusion in the analysis, 34 underwent MRM and 16 had no surgical management at all. Average age at diagnosis was 54 years ($s = \pm 13$ years). Presence of oligometastatic disease was identified in 91% of operated and in 9% of non-operated patients. No patient underwent metastasectomy. All operated patients received RT to the surgical bed (complete mammary cycle) at 32.6 to 60 Gy doses. Similarly, all patients with bone metastatic disease and/or metastasis to the central nervous system (CNS) underwent palliative RT at a dose of 30 Gy in 10 fractions. All patients received standard systemic treatment according to their molecular profile. Twenty percent of them were found to be younger than 45 years at diagnosis. Ninety-six percent of patients had ductal carcinoma with no specific pattern and, the rest, classic-pattern lobular carcinoma. Up to 32% had lymph node clinical disease limited to cN0-N1, whereas 68% had extended lymph node disease ranging from cN2a to cN3c. With regard to the degree of differentiation, grade I (well differentiated) accounted only for 10% of total pathology specimens (Table 1).

When operated patients' molecular groups were compared with those in non-operated patients, 16% versus 8% were found to be luminal A; 14% versus 2%, luminal B/with HER2+ overexpression; 14% versus 10%, luminal B/HER2-; 10% versus 2%, with HER2+ overexpression, and 14% versus 10%, triple-negative, respectively. OS, reported in months and according to the univariate analysis with Kruskal-Wallis test, was longer and statistically significant for patients who underwent MRM in

comparison with those who received no primary tumor surgical management (28.5 [range: 6-74.[3] vs. 9.7 months [range: 0.8-39.[2]; $p = 0.001$). Similarly, PFS was longer and statistically significant in the multivariate analysis with Kruskal-Wallis test for operated than in comparison with non-operated patients (20.6 [range: 5.7-77.[3] vs. 7.5 months [range: 0.7-17.0]; $p < 0.0001$) (Fig. 1). However, when Cox multivariate analysis was carried out, a "marginal" impact with no statistical significance of MRM on OS was identified (HR: 0.35; 95% CI: 0.12-1.03; $p = 0.057$), as well as a positive impact on PFS (HR: 0.2; 95% CI: 0.07-0.56; $p = 0.0021$). With regard to the analyzed variables and those already known for having higher impact on OS and PFS according to reports in the literature for the group of patients with metastatic breast cancer^{7,14}, in the Cox multivariate analysis of our population undergoing MRM, only one factor was identified to have a statistically significant impact on PFS: oligometastatic disease, a group in which surgery improved PFS (HR: 0.361; 95% CI: 0.14-0.93; $p = 0.035$). On the other hand, in the multivariate analysis for MRM impact on OS, surgical intervention was found to have a marginal impact with no statistical significance (HR: 0.353; 95% CI: 0.121-1.03; $p = 0.057$), with particular benefit being shown in oligometastatic disease (HR: 0.219; 95% CI: 0.07-0.61; $p = 0.004$), but a negative impact for the triple-negative (HR: 5.56; 95% CI: 1.03-29.97; $p = 0.045$) and luminal B/with HER2+ expression (HR: 8.9; 95% CI: 1.28-61.83; $p = 0.027$) molecular subgroups (Tables 2 and 3).

Discussion

According to data published by the World Health Organization (WHO) at its last 2012 update through its website www.globocan.iarc.fr, breast cancer is at first place both in terms of incidence and mortality in the female gender worldwide. In developing countries such as Mexico, a large part of these women are first diagnosed with metastatic disease (9.6% according to the Breast Cancer Foundation [FUCAM – *Fundación del Cáncer de Mama A.C.*²⁷]) and at an average age of up to 10 years younger than their peers in other countries such as USA (SEER¹⁵). Therapeutic options' sequence defines their survival; therefore, the impact surgical intervention of the primary tumor has demonstrated on progression-free survival in this group of patients is of high importance to justify its routine practice^{23,26}. In this study, we found that MRM positively impacted, favoring PFS in women with metastatic breast cancer; however, it wasn't found to favor OS (actually, it showed a

Table 1. Analyzed population demographics

Demographic characteristic	Group						Cox multivariate analysis					
	Operated		Non-operated		Total		PFS			OS		
	n	%	n	%	n	%	HR	95% CI	p-value	HR	95% CI	p-value
Age												
< 45	9	18%	1	2%	10	20%	0.865	0.3-2.0	0.74	0.616	0.2-1.4	0.279
≥ 45	25	50%	15	30%	40	80%	—	—	—	—	—	—
Lymph node involvement												
cN0-1	14	28%	2	4%	16	32%	—	—	—	—	—	—
cN2a-3c	20	40%	14	28%	34	68%	1.312	0.52-3.3	0.565	1.928	0.6-5.4	0.212
Pathology												
Ductal (no specific pattern)	24	48%	24	48%	48	96%	—	—	—	—	—	—
Lobular (classic pattern)	2	4%	0	0%	2	4%	—	—	—	—	—	—
Grade I	4	8%	1	2%	5	10%	—	—	—	—	—	—
Grades II and III	29	58%	11	22%	40	80%	1.480	0.19-11	0.706	0.372	0.07-1.96	0.244
Luminal A	8	16%	4	8%	12	24%	—	—	—	—	—	—
Luminal B HER2-	7	14%	5	10%	12	24%	3.727	0.59-23	0.160	8.907	1.28-61	0.027
Luminal B HER2+	7	14%	1	2%	8	16%	—	—	—	—	—	—
HER2+	5	10%	1	2%	6	16%	2.649	0.42-16	0.294	5.090	0.7-36	0.103
Triple-negative	7	14%	5	10%	12	24%	3.050	0.51-18	0.218	5.563	1.03-29	0.045
Oligometastases												
Yes	21	91%	2	9%	23	46%	0.361	0.14-0.9	0.035	0.219	0.07-0.6	0.004
No	13	9%	14	91%	27	54%	—	—	—	—	—	—

Figure 1. Operated and non-operated women PFS Kaplan-Meier curves.

“marginal” benefit [$p = 0.057$], but perhaps larger benefit might be reached by broadening the sample size).

To date, no randomized, prospective, multicenter studies have been published offering evidence with sufficient strength of recommendation as to consider generalized and routine use of mastectomy at clinical stage IV. However, in June 2016, at the ASCO meeting, a discussion of two prospective works with opposite conclusions took

place: the Turkish study MF07-015, with results in favor of surgical intervention at clinical stage IV (presented since the 2013 San Antonio Breast Cancer Symposium and without formal publication of its conclusions until this year), and the North American trial TBCRC 013⁶, which only recommends it in the setting of a clinical trial and not routinely. Our retrospective review is consistent with international series –also retrospective– that lean in favor of

Table 2. Cox multivariate analysis for surgery impact on PFS estimation

Variable	HR	Limits of confidence		p-value
		with risk rate at 95%		
Surgery (MRM)	0.205	0.075	0.563	0.0021
Age < 45	0.865	0.364	2.056	0.7429
Oligometastasis	0.361	0.14	0.934	0.0357
HER2 overexpression*	2.649	0.428	16.399	0.2948
Luminal B with HER2 overexpression*	3.727	0.594	23.388	0.1603
Triple-negative*	3.05	0.516	18.033	0.2188
cN2-3†	1.312	0.52	3.311	0.5652
Degree of differentiation II-III‡	1.48	0.192	11.398	0.7064

*In comparison with luminal A.

[†]Relative to cN0-N1.[‡]In comparison with grade I according to Scar-Bloom-Richardson Score.**Table 3.** Cox multivariate analysis for surgery impact on OS estimation

Variable	HR	Limits of confidence		p-value
		with risk rate at 95%		
Surgery (MRM)	0.353	0.121	1.033	0.0573*
Age < 45	0.616	0.256	1.481	0.2792
Oligometastasis	0.219	0.078	0.616	0.004
HER2 overexpression [†]	5.09	0.717	36.151	0.1037
Luminal B with HER2 overexpression [†]	8.907	1.283	61.834	0.027
Triple-negative [†]	5.563	1.033	29.965	0.0458
cN2-3 [‡]	1.928	0.687	5.41	0.2123
Degree of differentiation II-III [§]	0.372	0.07	1.967	0.2445

**"Borderline" significance.

[†]In comparison with luminal A[‡]Relative to cN0-N1.[§]In comparison with grade I according to Scar-Bloom-Richardson Score.

surgical intervention with the purpose to increase progression-free survival¹⁷⁻¹⁴, together with systemic cytotoxic or hormone treatment and/or targeted therapy, without leaving aside –and this is already well known– that it is the molecular group that defines disease biological behavior. In this regard, in this study we found that patient groups with the triple-negative and luminal B with HER2+ overexpression molecular profiles were associated with shorter OS and PFS (HR: 5.56; 95% CI: 1.03-29.97; p = 0.045; and HR: 8.9; 95% CI: 1.28-61.83; p = 0.027, respectively) than those with the luminal A molecular profile

as reference group. Additionally, we observed a propensity of the group with HER2+ overexpression to progress to the CNS, which directly affects patient survival and quality of life. On the other hand, in our series, in line with current knowledge^{5,6,16}, we also identified that not all cases of metastatic disease behave the same way, since clinical behavior depends on the number and localization of metastases, which demonstrates that oligometastatic disease favorably impacts on both OS ("borderline") and PFS (HR: 0.353; 95% CI: 0.121-1.03; p = 0.057 and HR: 0.361; 95% CI: 0.14-0.93; p = 0.035, respectively).

Conclusions

Our findings suggest that primary tumor resection in patients with metastatic breast cancer treated at COE IS-SEMyM favorably impacts on PFS and in a borderline manner on OS, particularly benefiting patients with oligo-metastatic disease; although surgery did not help the latter group of patients to live longer, we could claim that it favorably impacted on longer PFS, which in turn had a positive impact on this group of patients' quality of life. In addition, findings obtained in this study suggest that said intervention should be avoided in patients with the luminal B with HER2+ overexpression and triple-negative molecular profiles, since there is no benefit both in terms of OS and PFS.

Suggestions

The present study has the weakness of being a small population sample and of bias in the selection of patient candidates to surgery by the treating physician and, although it doesn't provide enough evidence offering a high degree of recommendation for its routine and generalized use, it does offer important information to support a prospective, randomized trial in a well selected subgroup of patients with factors that enable assessing its long-term impact in our population.

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