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# Hepatic Resection for Breast Cancer Liver Metastases

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## Abstract

**Aim:** To review the experience of a single Oncological Surgery Centre regarding the benefit of hepatic resection in breast cancer liver metastases (BCLM) patients with unique focus in overall survival rate, and compare these results with matched individuals of other group of BCLM patients treated only with chemotherapy and/or hormonal regimens.

**Patients and methods:** Between July 2007 and July 2015, a total of 260 female patients with BCLM were entered prospectively into a database of our Surgical Oncological Centre, and were all evaluated by their Multidisciplinary Team. Two groups of patients were enlisted: 1) Surgical Group (SG) enrolled by 36 patients which were suitable to receive a hepatic resection; 2) Non-Surgical Group (NSG) integrated by 20 that could receive medical treatment alone. Patients with 5 or more liver metastases and/or uncontrolled extra hepatic metastatic disease were excluded in this series. However, patients with slight extra hepatic disease that were treated and were deemed stable or certainly improving were included.

**Results:** Concerning with SG there was no postoperative mortality and perioperative complications occurred in 11 out of 36 patients (30.5%). Histopathological examination confirmed in all cases free tumor margin (R0). Follow-up of 100% for all patients. Median overall survival was 55.2 months in the SG vs 23.6 months in the NSG. Actuarial 1-year, 3-year and 5-year survival rates were 100%, 84% and 61.6% respectively in the SG vs 65%, 28% and 0% respectively in the NSG (p=0.000).

**Conclusions:** Surgical treatment is only indicated in a select group of patients and can improve long-term outcomes. In this study, significantly better survival rates were observed in the surgical group that encourage continuing in this line of multimodal treatment. Surgical therapy can act as an effective adjuvant treatment to systemic therapies, providing selected patients a survival benefit as well as the hope for cure.

**Keywords:** Breast Cancer; Liver Metastases; Hepatic Metastases; Surgery; Liver Resection; Hepatectomy; Metastasectomy

## Background

Breast cancer is one of the most common malignancies in women and represents the second highest cause of cancer mortality in the United States [1-3]. We define, as breast cancer liver metastases (BCLM), all cases of adenocarcinoma of the breast with documented secondary sites in the liver. BCLM are responsible for the high number of breast cancer-related deaths in women diagnosed with this malignancy worldwide [4]. BCLM was generally considered as disseminated disease with a poor prognosis. But, currently in selected patients hepatic resection may be an important adjunct to systemic treatment. Because death is related primarily to metastatic spread, strategies to treat BCLM are of considerable importance. For this reason, in the last twenty years different schemes of non-surgical treatment based on systemic chemotherapy, anti-hormonal therapy and targeted therapy were widely used. However the reported survival after those current modern multimodal approaches remains very poor, ranging from 3 to 15 months of overall survival [5,6]. When benefits of liver resection were widely demonstrated in cases with hepatic metastases from colorectal primaries, now the attention has been focused on a possible benefit of hepatic resection for BCLM. Many authors have shown that the 5-year survival rate is comparable to colorectal cancer liver metastases resection [5,7]. But, the reported results after BCLM remain heterogeneous with 5-year overall survival rates ranging between 25-75% [8,9].

The aim of the present study was to review the experience of a single Surgical Oncological Centre regarding the benefit of hepatic resection in BCLM patients with unique focus in overall survival rate, and compares these results with matched individuals of other group of BCLM patients treated only with chemotherapy and/or hormonal regimens.

## Patients and Methods

Between July 2007 and July 2015, a total of 260 female patients with BCLM were entered prospectively into a database of the Oncological Surgery Centre of UNACIR HPB (Associated Units in Hepato-Pancreato-Biliary Surgery) at the Sanatorio San Lucas of San Isidro (Provincia de Buenos Aires, Argentina), and were all evaluated by their Multidisciplinary Team. From this population, 2 groups of patients were enrolled in this study: the first is the so-called Surgical Group

(SG) that was integrated by 36 patients (13.8%) which were suitable to receive a hepatic resection with curative intent, with a mean of 51.2 years (range 32-66 years). The second is the so-called Non-Surgical Group (NSG) that was integrated by 20 patients (7.7%) which were treated only with chemotherapy and/or hormonal regimens, with a mean age of 52.1 years (range 29-69 years).

## Patient selection

All of the population had 1 to 4 liver metastases diagnosed by ultrasonography (100%), and with computed tomography (CT-scan) and/or magnetic resonance imaging (MRI). In the NSG, diagnosis was confirmed by percutaneous liver biopsy. All patients were evaluated with a total body bone scintigraphy with Tc 99 and with the serum level measure of CA 15-3, which is the specific breast tumour marker. In the SG, the CA 15-3 was measured 1 to 3 days before surgical exploration and proved to be elevated in all patients (sensitivity 100%). Since 2009, all patients underwent a positron emission tomography with the combination of computed tomography (PET-CT). Patients with 5 or more liver metastases and/or uncontrolled extra hepatic metastatic disease that were detected with imaging studies were excluded in this series. However, patients with extra hepatic disease that were treated and were deemed stable or certainly improving were included. In the SG, chemotherapy was administered in all patients before hepatic resection, and chest CT-scan, abdominal/pelvic MRI and measuring of CA 15-3 were performed every 3 cycles and immediately before surgical intervention.

## Characteristics of the primary breast neoplasm

In both groups, patients underwent breast-conserving surgery for treatment of their primary breast cancer. In the SG, 32 (88.9%) out of 36 of the primary neoplasms were infiltrating ductal carcinoma, and the TNM status was: T1 (33.3%), T2 (47.2%) and T3 (19.4%); N0 (27.8%), N1 (38.9%) and N2 (33.3%); and M0 (100%). Most breast cancers were poorly dierentiated (G3): 21 (58.3%). The primary neoplasms were evaluated by immunohistochemistry: 28 patients (77.8%) with estrogen receptor (ER) positive, 22 (61.1%) with progesterone receptor (ProR) positive, and 20 (55.6%) with neoplasms that were identified as HER-2/-neu (HER2) positive. In the NSG, 16 (80%) out of 20 of the primary neoplasms were infiltrating ductal carcinoma, and the TNM status was: T1 (35%), T2 (40%) and T3 (25%); N0 (25%), N1 (45%) and N2 (30%); and M0 (100%). The majority of the breast cancers were poorly differentiated (G3): 13 cases (65%). The primary neoplasms were evaluated by immunohistochemistry: 15 patients (75%) with estrogen receptor (ER) positive, 11 (55%) with progesterone receptor (ProR) positive, and 8 (40%) with neoplasms that were identified as HER-2/-neu (HER2) positive (Table 1).

| **Patient and Tumor Characteristics** | | |
|---|---|---|
| | **Surgical (N= 36)** | **Non-surgical (N= 20)** |
| Mean age (years) | 51.3 (32-66) | 52.1 (29-69) |
| Mean number of BCLM | 1.8 (1-4) | 1.7 (1-3) |
| Concomitant extrahepatic disease | 22.2% | 25% |
| Chemotherapy | 100% | 100% |
| Time to BCLM (months) | 44 (15-123) | 46.3 (21-72) |
| Primary Tumor | | |
| T Stage | | |
| T1 | 33.3% | 35% |
| T2 | 47.2% | 40% |
| T3 | 19.4% | 25% |
| N Stage | | |
| N0 | 27.8% | 25% |
| N1 | 38.9% | 45% |
| N2 | 33.3% | 30% |
| Differentiation | | |
| G2 | 41.7% | 35% |
| G3 | 58.3% | 65% |
| Hormone Receptor | | |
| ER (+) | 77.8% | 75% |
| PR (+) | 61.1% | 55% |
| Her-2 (+) | 55.6% | 40% |

**Table 1:** Characteristics in surgical and non-surgical groups.

## Characteristics of the BCLM

BCLM were defined as metachronous if the interval between resection of the primary breast tumour, and first diagnosis of liver metastases was longer than 4 months. Such interval time had a median of months of 44.1 and 46.3 in the SG and NSG respectively. Initially, the intention to treat in the SG series was of 43 patients which were considered candidates for surgical approach. All of them were operable (comorbidities compatible with complex surgical treatment and performance status of 0 or 1). But, finally only 36 patients were eligible for surgery because a second exclusion of other 7 patients was carried out during surgery when initial abdominal exploration, by inspection and palpation of the hepatic surface plus a liver intra-operative ultrasound revealed the presence of 5 or more metastases and/or unresectable hepatic lesions not identified on preoperative imaging studies and/or extra hepatic malignant disease. Before surgical exploration: 17 (47.2%) out of 36 patients, BCLM was a solitary lesion; 12 (33.3%) had 2 lesions; 5 (13.9%) had 3, and 2 (5.5%) had 4 lesions. Furthermore, in 19 patients (52.8%) after surgical exploration some new metastases were identified but only were included in this series because the sum of all such lesions in such patients was 4 or less as had been stipulated in this paper. In addition, in the same surgical exploration, in 13 patients (36.1%) the so-called satellites metastases were also detected, and included in this series, and were defined as lesions located at no more than 20 mm of the main metastasis and/or with less than 10 mm in diameter each.

Also, in 16 patients (44.4%) the metastases had a bilobar distribution and the mean size of the main metastases was of 39.8 mm in diameter (range 24-82 mm), and 26 (72.2%) of these lesions were of less than 50 mm in diameter (Table 2). In the NSG series, medical treatment was administered according to their hormone receptor status and oncologic stage and to evidence-based protocols available at

the time. All patients of the NSG were candidates for liver resection but they not received surgical treatment because were managed by different clinical oncologists that were not convinced of the usefulness of the surgical treatment, and they chose the chemotherapy and/or hormonal regimens as the best options.

| **Hepatic Resections Characteristics** | | |
|---|---|---|
| | **Mean** | |
| Preoperative CA 15.3 | 72.2 U/mL | |
| Preoperative BCLM number | 1.8 | |
| Intraoperative non-expected BCLM | 0.6 | |
| BCLM size | 39.8 mm | |
| Patients (N=36) | | |
| Bilobar | 41.7% | |
| Number of liver segments completely resected | | |
| | 1 | 13.9% |
| | 2 | 25% |
| | 3 | 8.3% |
| | 4 | 11.1% |
| Number of metastasectomies | | |
| | 1 | 11.1% |
| | 2 | 38.9% |
| | 3 | 16.7% |
| Post-operative stay mean | 6,7 days | |
| Post-operative complications (Clavien) | 30.5% (11 patients) | |
| | I | 18.2% |
| | II | 54.5% |
| | IIIa | 18.2% |
| | IIIb | 9.1% |
| | IV | 0% |
| | V | 0% |
| Survival mean (months) | 55.2 (CI 49.9-60.5) | |
| Recurrence | 80% (29 patients) | |
| Hepatic recurrence | 30% (11 patients) | |
| Mean time to recurrence (months) | 37.1 | |
| Survival | | |
| | 1 year | 100% |
| | 3 years | 84% |
| | 5 years | 61.6% |

**Table 2: Hepatic Resections Characteristics.**

## Surgical techniques

Surgical procedures for liver resection were selected according to the disease extent and tumor location: Metastasectomy was the most frequent surgical resection, carried out in 24 patients (66.7%). Anatomical resection of one segment (5/13.9%) or two segments (9/25%) were performed as a unique technique or associated in the same patient with metastasectomies according to each surgical case. Seven cases (19.4%) of the hepatic resections were majors, which were defined as those in which 3 or more Couinaud segments were removed (Table 2). In this surgical series, local ablation with radiofrequency or microwaves was not taken into account, and no patient received such therapy. A R0 resection was defined as curative resection when it specimen had a negative microscopic resection margin. Such surgical specimens were evaluated according to size, grade, margin, and hormone receptor status.

## Extra hepatic disease

Eight (22.2%) out of 36 patients in the SG had pulmonary and/or bony metastases under clinical control: 4 patients with sub-centimetre lung lesions, 3 with bone metastases, and 1 with lung and bone lesions. All of them, were treated and were deemed stable or in better condition before hepatic surgery. Five (25%) out of 20 patients of the NSG had pulmonary and/or bony metastases under clinical control: 2 patients with sub-centimetre lung lesions, 2 with bone metastases, and 1 with lung and bone lesions (Table 1).

## Follow-up

Surgeons and oncologists of our group perform jointly at the Tumour Board, the follow-up of all patients of this series. From the second postoperative month (new baseline) include: routine lab blood tests, serum CA 15-3 level, abdominal ultrasonography carried out by the surgeon, chest CT scan and pelvic/ abdominal MRI. Later, subsequent follow-up every 3 months for 2 years include the repetition of blood tests and imaging studies, and then every 6 months until 5 years the same schema with the addition of a total body bone scintigraphy with Tc 99. Finally, from the sixth year, the same evaluation but once per year.

## Statistical analysis

Statistical analysis was processed with IBM SPSS v 22 statistical software. Survival time was calculated from date of BCLM diagnosis to death or censored date. Surviving patients were censored at the date of last known contact. Survival was measured in months with the use of median values. Patients who died from BCLM were treated as event observations, whereas patients who were alive at the point of last follow-up were treated as censored observations. The Kaplan-Meier method was used to produce survival curves, which were compared by the log-rank test $p<0.05$ was considered to be statistically significant.

## Results

Concerning with SG there was no postoperative mortality. The mean duration of hospital stay was 6.7 days. Postoperative complications were classified according to the Clavien scheme and occurred in 11 out of 36 patients (30.5%) and include: 4 biliary leakage, 3 neuropathy, 2 urinary infections, 1 wound hematoma and 1 wound infection. Eight of them were minor complications and were solved with no invasive intervention, and 3 complications have required invasive therapeutic maneuvers for definitive treatment including 2 percutaneous drainages and 1 laparoscopic surgery due to 2 biliary collections and 1 intra-abdominal abscess respectively (Table 2). Histopathological examination confirmed in all cases the presence of BCLM with free tumor margin (R0).

The liver metastases were evaluated by immunohistochemistry and 26/72.2% had metastases positive for ER, 19/52.8% had metastases positive for ProR, and 15/41.7% had metastases positive for HER2. All patients of both groups (56 cases) are under medical supervision with a follow-up of 100%. Median overall survival was 55.2 months (CI: 49.9-60.5) in the SG vs 23.6 months (CI: 16.4- 30.8) in the NSG. Actuarial 1-year, 3-year and 5-year survival rates were 100%, 84% and 61.6% respectively in the SG vs 65%, 28% and 0% respectively in the NSG (p=0.000) (Figure 1).

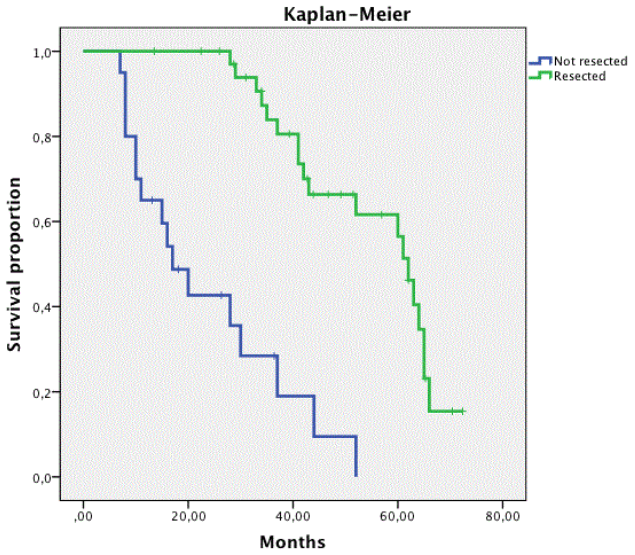


**Figure 1:** Kaplan-Meier analysis of overall survival rates aer BCLM treatment Surgical Group (resected patients) and Non-Surgical Group (non-resected patients).

## Discussion

Breast cancer is the most frequent malignant tumour and the leading cause of cancer-related death in females [6,10]. Following a breast cancer diagnosis, 20% of patients develop metastases, and the main sites of recurrence after breast cancer surgery are the bones (85%), liver (40-50%), pleura (20%), lung (15-25%) and brain (6-16%) [4,10-12]. In contrast to colorectal cancer, isolated liver metastasis in the absence of extrahepatic disease is rare in breast cancer, occurring in approximately 5-10% of cases [2,5,11,13].

Although rare, this event might be a more favorable condition suitable for an aggressive protocol including liver resection [7,13]. BCLM are responsible for the high number of breast cancer-related deaths in women diagnosed with this malignancy worldwide and were traditionally associated with a negative impact on survival of patients with breast cancer [5,6,10]. In such patients, metastases seed the liver via systemic circulation, and thus a microscopic dissemination may be present in multiple sites. The presence of distant metastases was usually considered a sign of systemic disease that is associated with the

presence of malignant cells in the blood stream, with an extremely poor prognosis and the reported survival of this untreated patients ranging between 3 to 6 months [6,11].

When BCLM received standard chemotherapeutic regimens, a median overall survival that varies between 6 to 26 months has been reported from different publications [5,10,12,13]. Due to this fact, and correlated to the benefits reported after liver resection for colorectal hepatic metastases attention has been focused on determining which are the patients who could benefit most after liver resection for BCLM [10,11]. In contrast to liver metastases from colorectal cancer, in which surgery emerged as the only effective first-line treatment option due to a lack of useful medical treatment and for which the value of peri-operative chemotherapy was subsequently demonstrated, BCLM are always treated by first-line chemotherapy, even when the disease is readily resectable from the onset [2,10].

Criteria for liver resection for BCLM have changed throughout the last three decades [10,12]. At the beginning, the majority of the surgeons were reluctant to operate on patients who developed BCLM [12,13]. However, over time, progress in different types of chemotherapies regimens has enabled the disease to be stabilized in certain patients. Since the mortality and morbidity associated with hepatic resection have decreased significantly during the last decade, the indications for surgery for BCLM have been widened [14,15]. Thus, together with the improvement in our own results in liver surgery, since 2007 we started to operate on systematically the BCLM. By the end of the 90 decade, it was considered that in contrast to hepatic colorectal metastases, resection of BCLM was often not contemplated as a therapeutic option, because it was considered a systemic disease involving multiple sites, and the majority of patients with BCLM were treated with systemic chemotherapy without hepatic resection [16,17]. But, along the last two decades it has been shown, even in cases of a clinically relevant response, the cure of BCLM is not achieved when using systemic chemotherapy alone [6,10,18]. Because of this lack of curative effectiveness by chemotherapeutic regimens, is that in the last years there has been a progressive increase in the interest in hepatic resection for appropriately selected patients with BCLM, and surgery has been proposed as a useful adjunct to medical oncological therapy [6,19,20]. It is notable that 25 years after the first report of a series of hepatic resection for BCLM made by Elias, D and colleagues [21], many authors currently think that the doubts about the role of surgery are in process of being clarified and standardized [2,5,22]. In 2006, a study published by the French multicentre retrospective cohort in order to determine the utility of hepatic resection in the treatment of patients with non-colorectal and non-endocrine liver metastases has shown that the overall survival rates after surgical treatment were 41% and 22% at 5 and 10 years respectively, and remarking that the prognosis of BCLM was better than that of many other metastatic non-colorectal and non-endocrine cancers [13,17,23]. Currently, there is increasing evidence that liver resection associated with systemic chemotherapy may provide survival benefit in a subset of patients with BCLM [1-3,12,23].

Synchronous liver disease was defined as hepatic metastases diagnosed at the time of the primary breast neoplasm and is included within the stage IV of disease [13]. On the contrary, metachronous liver disease was defined as hepatic metastases diagnosed after completion of therapy for the primary breast neoplasm, with a time interval longer than 4 months, and it is considered as an event related to tumour recurrence [10,24]. Both variants are commonly associated with synchronous extra hepatic tumour spread especially to and/or lungs [23]. Several investigators have shown that in cases presenting synchronous liver metastases, a decreased survival can be expected when compared to those with metachronous lesions [5,24]. For that reason, it is that in both groups of our series all the enrolled patients were of the first three stages of breast cancer disease (I, II or III). It has been shown for several authors that long progression-free intervals between primary breast cancer surgery and liver metastases diagnosis, positive hormone receptor status, absence of extrahepatic tumoral burden, response to preoperative chemotherapy and R0 liver resection are all favorable prognostic factors influencing the overall survival in patients with BCLM [24,25]. In the other hand, it has been demonstrated that the variables associated with poor outcome after liver resection for BCLM include short progression-free survival between breast cancer surgery and detection of liver lesions, non-controlled extrahepatic disease at the resection time, multiple liver metastases (5 or more lesions), negative hormone-receptors and negative HER-2/ neu status [8,25]. Currently, the surgical decision for BCLM is straightforward for young women. But, for older women, the negative hormone receptor status acts like a relative contraindication to hepatic resection [7,26]. However, new systemic treatments will probably could modify this scheme and must be tested in association with hepatic resection [25,27].

Hormone receptor status was analyzed by several authors and most studies found them to be without significance, but there were divergent results [28]. Further work is required to clarify this issue, as hormone drugs are an important part of breast cancer therapy and hormone receptor status has been associated with a good prognosis in previous studies of metastatic disease [19,28]. In 2016, Qiu, J and colleagues, have published a study where they found that triple-negative breast cancer was a distinct subgroup of breast cancer with particular clinic-pathological behavior and compared with the non-triple-negative was characterized by more aggressive behavior, and lower progression-free survival and overall survival rates [29]. BCLM arising from triple-negative breast cancer confers the worst prognosis, and novel agents capable of controlling intrahepatic and extrahepatic triple-negative breast cancer are needed [6,25,29,30]. Elias et al. reported HER2 positivity of the primary tumour to be the only predictor of prolonged survival after surgery for BCLM. In accordance with other studies, we saw no correlation between the hormone receptor status and survival after liver resection, but there was a clear survival benefit for patients with strong HER2 expression in metastatic tumour cells [1,20,21,27,30].

In this presentation, the 2 groups were similar in patient age (SG: 51.2% and NSG: 52.1%). The other matching group criteria were: a majority of the population with infiltrating ductal carcinoma, TNM status: T1 to T3, breast cancer hormone receptor and limited extra hepatic disease. Further, interval time between breast cancer diagnosis and liver metastasis was similar in both groups with a median of months of 44.1 and 46.3 in the SG and NSG respectively, and it is similar to a systematic review that were reported in 2012 by Chua, T and colleagues, where median time was of 40 months. However, others publications have shown a more average of time ranged between 55 to 80 months [9,17,31,32].

All of SG patients in our study received chemotherapy treatment, and only from such patients with stable disease or disease responding to medical treatment were selected for hepatic resection. A subset of the SG had a radiological objective response to chemotherapy and/or hormonal therapy, as have also been reported by other investigators

[6,17,21,32]. On the contrary, those cases with liver progression after chemotherapy treatment were excluded to be candidates for surgery.

As in others publications, the majority of patients in our series harboured single metastases [2,13,31,33]. Seventeen metastases (47.2%) in the SG were unique, but after the surgical exploration other new lesions were detected by inspection and palpation of the hepatic surface. So, is very important an accurate exploration throughout the liver. Further, the use of intra-operative ultrasound in order to running out the hepatic surface is mandatory, before the liver surgeon makes the decision of the surgical technique that could be used in each case. In this series we have changed our preoperative strategy in 19 patients (52.8%). Other intraoperative issue could be the finding of satellites metastases that in most of cases are thin and flat lesions, generally range between 5-10 mm in diameter, and located over the hepatic surface close to a main lesion. In this series we have detected them in 13 patients (36.1%) and all of them were included in the hepatic resections. This issue is important whereas in some intraoperative exclusion cases this kind of metastases are detected as scattered spots in different places of the hepatic surface. Concerning with the size of tumor and the bilobar liver distribution of the lesions that were shown as predictor factors of long-term survival after liver resection, the conclusions vary widely between the different published studies [6,32].

Presence of non-controlled and/or extensive extrahepatic disease is relevant as prognostic factor. Kim, J and colleagues, have published in 2014, the 1-year and 3-year overall survival rates of patients without extrahepatic metastasis that were 83.3% and 66.7% respectively vs those patients with extrahepatic metastasis that were 80.0% and 0.0% respectively (p=0.001) [21]. This significant difference keeps the controversy to offer the surgical resection to this subset of patients. Extrahepatic disease was handled very differently in the studies. Some centers have excluded for surgery all patients with any extrahepatic metastases [6,22]. In our two groups were enrolled patients with slight extrahepatic disease that were treated and deemed stable or improving before treatment, and the long-term outcome had not difference with those cases of this series without extrahepatic disease. The traditional dogma that surgical therapy has no role in the treatment of BCLM patients with minimal and controlled extrahepatic disease is no longer valid [7,26]. In this series, the measuring of serum CA 15-3 level has not only a high sensitivity for diagnosis but it is also very useful for the follow-up of patients with liver resection because it normalizes after surgery. Further, could increase with the emergence of new hepatic and/or extrahepatic metastases [15].

Currently recommendations concerning with benefits of hepatic surgery for selected BCLM patients are: 1) Young patients; 2) Low operation risk; 3) Long interval (more than one year) between breast cancer surgery and liver metastases; 4) Positive hormone receptor status of primary tumour; 5) No extrahepatic disease (except minimal pulmonary and/or bony metastases); 6) Less than 5 metastases; 7) Demonstrated disease regression or stability with systemic chemotherapy and/or hormonal treatment before resection; 8) Normal liver function tests; 9) Resection with intent of a complete (R0) resection of liver metastases [3,10,13,25-27,32]. As other authors, we found in our series a high risk of recurrent disease (intrahepatic and/or extrahepatic) after liver resection, and data indicate that patients should be given further adjuvant chemo-and/or hormone therapy [8,15,19,29,31]. In addition, based on the little information about re-hepatectomy in case of recurrence of disease in the remaining liver after initial liver resection, one could argue that this might be a valuable treatment to prolong survival [4,10,33].

In selected patients with BCLM, repeat hepatectomy for liver recurrence combined with systemic treatment could provide survival rates comparable to those cases that received first hepatectomy [33]. It is not the aim of this study analyze the prognostic and/or predictors of long-term survival factors, recurrence and progression-free survival rates because will be the issue of other publication.

In 2012, Chua, T and colleagues, examined 19 studies, including 553 patients that received surgical resection for BCLM and have shown that the median overall survival was 40 months (range: 15-74), and the median 5-year survival rate was 40% (range: 21-80%) [33]. Hepatic resection for BCLM show consistent results with superior 5-year survival for selected patients with isolated liver metastases and in those with well controlled extrahepatic disease [8,10,18,33]. There is increasing evidence that patients with oligometastases, defined as metastases limited to one organ with a small number of lesions, may be good candidates for surgical therapy with a favourable clinical outcome [31,33]. Current literature does not establish clearly which patients are candidates for hepatic resection for BCLM. But it seems that hepatic resection should be considered as a valid and safe therapeutic option [9,10]. In this surgical series, local ablation with radiofrequency or microwaves was not taken into account and no patient received such therapy, nevertheless in some other series were published the combination of resection plus ablation for BCLM [12,19,34].

In the SG, median overall survival was 55.2 months (range: 14–72 months) and is clearly better than the 23.6 months of the NSG. Further, these data are similar to other non-randomized retrospective studies published in the literature [6-8,17,32,34].

The overall survival rates after hepatic surgery that have been published by others authors in the last 3 years ranged from 90-100% at 1 year, 68-86% at 3 years and 65-40% at 5 years [5,8,17,22,33,35]. In our study, it is notable the statistical difference in actuarial 1-year, 3-year and 5-year survival rates between the 2 groups (SG: 100%, 84% and 61.6% respectively vs. NSG: 65%, 28% and 0% respectively) (p=0.000). Therefore, concerning the NSG it is clear that none of the 20 patients that have received systemic chemotherapy alone are alive after 5 years of treatment. Fourteen (82.4%) out of 17 surgical patients in the SG that were operated on since 2011, are up-to-date alive. The surgical treatment of BCLM remains the method of choice in a selected group of patients [13,31,33,35] but, in spite of the good outcomes of this study, we think that results of future randomized controlled trials could give better level of evidence whether liver surgery for BCLM truly improves long-term survival.

Planning the right therapeutic approaches for individual patients is becoming more complex, and it requires a close multidisciplinary collaboration between surgical and medical oncologists [14,25,35]. This interdisciplinary team so-called tumor committee or tumor board is handled by a case-manager and integrated by liver surgeons, clinical oncologists, pathologists, and specialists in image-study diagnosis, in order to discuss altogether the oncologic cases studies which they are presented at each meeting. A relevant message for the management of BCLM is the importance of a strong and interactive multidisciplinary team to plan the diagnosis, treatment and follow-up for these patients.

Finally, in our opinion hepatic resection is safe but must be done by liver surgeons in specialized high-volume centres, with almost no mortality and with low morbidity rates.

## Conclusions

Surgical treatment is only indicated in a select group of patients and can improve long-term outcomes. In this study, significantly better survival rates were observed in the surgical group that encourage continuing in this line of multimodal treatment.

In these cases, surgical therapy can act as an effective adjuvant treatment to systemic therapies, providing selected patients a survival benefit as well as the hope for cure.

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