

ORIGINAL ARTICLE

Prognostic Factors Related to Surgical Outcome of Liver Metastases of Breast Cancer

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Purpose: The role of hepatectomy for patients with liver metastases of breast cancer (LMBC) remains controversial. The purpose of this study is to share our experience with hepatic resection in a relatively unselected group of patients with LMBC and analyse the prognostic factors and indications for surgery. **Methods:** In 2000 to 2006, 42 female patients with a mean age of 58.2 years (range, 39 to 69 years) with LMBC diagnosed by means of abdominal ultrasound, computed tomography and/or magnetic resonance imaging in the hospital. They were considered for surgery because of limited comorbidities, presence of seven or fewer liver tumors and absence of (or limited and stable) extrahepatic disease on preoperative imaging. Patients' demographics, metastatic characteristics as well as clinical and operative parameters were being studied. Overall actuarial 1-, 3-, and 5-year survival rates were calculated since the hepatic resection onwards using the Kaplan-Meier method. **Results:** Metastatic tumor size of ≤ 4 cm ($p=0.03$), R0 resection ($p=0.02$), negative

portal lymph nodes ($p=0.01$), response to chemotherapy ($p=0.02$), and positive hormone receptor status ($p=0.03$) were associated with better survival outcomes on univariate analysis. However, it did not show survival benefits on multivariate analysis. The disease-free survival and overall survival are 29.40 and 43 months, respectively. The 1-, 3- and 5-year survival rates were 84.61%, 64.11%, and 38.45%, respectively. **Conclusion:** Selected patients with isolated LMBC may benefit from surgical management; although, indications remain unclear and the risks may outweigh the benefits in patients with a generally poor prognosis. Improvements in preoperative staging and progressive application of new multimodality treatments will be the key to improved survival rates in this severe disease. The careful selection of patients is associated with a satisfactory long-term survival rate.

Key Words: Breast neoplasms, Hepatectomy, Neoplasm metastasis

INTRODUCTION

Approximately 50% of all women diagnosed with breast cancers develop metastatic disease [1,2]. Their average survival time following the diagnosis ranges to approximately 18 to 30 months. Their overall prognosis is poor, with treatment options limited to chemotherapy or hormone replacement therapy. Isolated liver metastases appear in only 4% to 5% of the patients with metastatic breast cancer [3,4]. A poor effect of chemotherapy alone in patients with liver metastases has often been reported in the literature available [5]. Currently, with the recent chemotherapy and hormone therapy regimen,

the median survival of such patients is close to 24 months [6]. It is well known that chemo or hormone regimen should be changed when resistances such as tumor progression or severe adverse event develops [7]. Patients with liver metastases have the potential to be managed surgically, with either hepatic resection or radiofrequency ablation (RFA). The first series reporting hepatectomy for breast cancer patients has occurred two decades ago [3]. Some investigators used aggressive approaches including liver resection and achieved good results within highly selective patients. Several case series have reported an improvement in survival rates for patients who underwent hepatic resection for liver-only metastatic disease, with 5-year survival rates ranging from 9% to 61% [8].

The majority of patients treated with liver resection presented with limited disease, usually, less than four tumors distributed advantageously to allow for complete tumor resection. Many patients with liver metastases are, however, poor candidates for a major surgical intervention. In these cases,

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RFA is a minimally invasive procedure that offers a low-risk alternative to hepatectomy for the definitive treatment of liver malignancy. Improvements in surgery and anesthesiology which result in a reduction of mortality and morbidity rates have expanded the indications for hepatectomy concerning patients with liver metastases [9].

However, the role of liver resection is insufficiently defined and controversial for liver metastases of breast cancer (LMBC) patients. Hence, the present study was performed to analyze the outcome after hepatic resection for LMBC in one center, to define the factors that predict survival rates and to facilitate appropriate patient's selection.

METHODS

The study was being approved by the ethics committee of the Naval Hospital of Varna (No19, December 2012). From December 2001 to December 2007, 42 females with LMBC were considered for surgical management. Their mean age was 58.2 years (range, 39-69 years). All the procedures were performed by a single surgeon. Patients with a preoperative diagnosis of diffuse or multiple confluent metastases were excluded from the analysis.

Registered data

Hepatectomy involved procedures in which excision of a part of the liver was performed using anatomic techniques according to Couinaud's segmentation and Brisbane 2000 terminology [10]. Preoperative work-ups included the patient's history, clinical examination, comprehensive blood analysis as well as complete metabolic panels and tumor marker studies. The extent of disease was assessed by imaging studies such as abdominal ultrasound, computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients were typically considered for surgical management if they had limited comorbidities, seven or fewer liver metastases and no (or limited and stable) extrahepatic diseases on preoperative imaging. Synchronous liver lesions were defined as the simultaneous development of a primary breast cancer and liver metastasis, or metastasis occurrence within 3 months following the resection of the primary breast cancer [11]. Radiological images were interpreted in a multidisciplinary meeting involving abdominal surgeons, oncologists, radiologists, and pathologists. Patients who were not forwarded to hepatectomy were preferably considered for laparoscopic RFA if they had significant comorbidities, two or fewer liver metastases all of which ≤ 4 cm in size, metastases located > 1 cm from the central biliary structures and no (or stable) extrahepatic disease on preoperative imaging.

Procedure details

Liver resection was considered if the known disease was technically resectable with an adequate hepatic functional reserve and if the patient's general condition permitted surgery. An anatomic resection (with or without the Pringle manoeuvre) using an open or laparoscopic approach was conducted after the completion of laparoscopic staging. The ligamentous attachments of the liver were divided for complete mobilization. Extraparenchymal division of the portal pedicle and hepatic venous outflow was performed and the parenchyma was divided with a combination of ultrasonic coagulation, electrocautery, or surgical stapling. Drains were used routinely and removed postoperatively if there was no evidence of bile leakage or bleeding between postoperative days 2 and 5.

Laparoscopic RFA is a minimally invasive technique that offers a low-risk alternative to liver resection. RFA probe is placed into the tumor under ultrasonographic guidance and deployed into the tumor bed. The tumor tissue is heated to at least 60°C to achieved complete cell death. The goal of the treatment is to destroy both the tumor and a 1-cm margin of normal tissue circumferentially.

Postoperative management

Routine nasogastric drainage was not being employed. Refeeding was initiated 24 hours after surgery if the patient presented signs of gastrointestinal transit resumption and no nausea. Antibiotic prophylaxis was used for 24 hours perioperatively. Routine liver tests were monitored after surgery on days 1, 3, and 5 and as required according to the patient's clinical status.

Follow-up

Postoperatively, all the patients were being followed-up radiologically, clinically and biochemically up to five years after the surgery. The patients were then referred back to their oncologist for consideration of systemic chemotherapy. Clinical and biochemical surveillance was performed every 3 months during the first year, every 4 months in the second year, every 6 months for the third year, and yearly thereafter until the fifth year. Thoracic and abdominal CT scans were done annually for 5 years after surgery.

Chemotherapy details

Following hepatic resection, all the patients received systemic therapy. Accordingly chemotherapeutic regimens included anthracyclines in 38.1%, taxanes in 64.28%, vinorelbine in 14.3%, and trastuzumab in 26.2% of cases. In addition, 54.8% of the patients were administered with antihormonal therapy. The majority of these patients were treated with aro-

matase inhibitors combined with different chemotherapy protocols.

Variables

Patients' demographics, metastases characteristics, clinical and operative parameters were analyzed. The following variables were assessed as prognostic factors: age (≤ 58.2 years vs. > 58.2 years), positive vs. negative axillary lymph nodes, interval between surgery for a primary tumor and liver resection (< 1 year vs. ≥ 1 year), number of metastases (1 vs. > 1), maximum metastasis diameter (≤ 4 cm vs. > 4 cm), presence of extrahepatic disease (yes vs. no), type of liver resection (< 3 segments vs. ≥ 3 segments), site of liver metastases (bilobar vs. unilobar), status of the resection margin (negative vs. involved), response to chemotherapy vs. no response to chemotherapy, positive vs. negative hormone receptor status, and presence of positive vs. negative portal lymph nodes. Definition of responses to and no responses to chemotherapy was based on the Response Evaluation Criteria in Solid Tumors formerly introduced to practice. Chemotherapy effects were evaluated based on serial CT scans 4 to 6 weeks following the completion of the therapies and then again in every 1 to 3 months. Complete tumor disappearance was regarded as complete remission, a tumor size decrease by more than 50% as partial remission, a reduction less than 50% or no change as stable disease, and a further progression as progressive disease. None of the respondents to chemotherapy were the patients whom encountered progressive, or stable diseases.

A R0 resection was defined as curative resection and presence of a negative microscopic resection margin but R1 is recognized as a positive microscopic resection margin. Major liver resection was defined as resection of more than three Couinaud's segments. The overall actuarial 1-, 3-, and 5-year survival rates were calculated since the hepatectomy. Mortality data were described as 30-, 60-, and 90-days of mortality rates.

Statistical analysis

The overall survival rate was calculated according to the survival curve analysis using the Kaplan-Meier method. Survival comparisons between the high-risk groups was being compared with a log-rank test and the significance was assigned at 0.05. SPSS version 17.0 statistical software (SPSS Inc., Chicago, USA) was used for statistical analysis.

RESULTS

Demographics

A metachronous liver lesion was identified within all the patients. All the patients had undergone a resection of their

primary breast cancer before the liver metastases diagnosis. Fourteen patients (33.3%) had undergone previous treatments with systemic chemotherapy and radiation for their primary breast cancer (Table 1). Twelve patients (28.6%) had positive axillary lymph nodes at the time of the resection for primary breast cancer. Nineteen patients (45.2%) had primary tumors that were estrogen receptor-positive while four patients (9.5%) had progesterone receptor-positive breast cancer. The human epidermal growth factor receptor 2 (HER2) status was available for all patients, 9 (21.4%) of which were HER2-positive. Targeted therapy with trastuzumab was administered to patients with HER2-positive tumor cells. Twenty-two patients (52.4%) had metastatic disease confined to the liver, 16 patients (38.1%) had concurrent metastases to the bone and four patients (9.5%) had a concurrent metastasis to the lung and pleura. Extrahepatic disease had been stable on preoperative imaging for more than 6 months before surgery. Patient's clinical status, fitness, hormone receptor status, and age determined the most appropriate treatment. Between one and four different chemotherapy regimens was being administered to all the patients combined with hormone replacement therapy in 23 ones (54.8%). The chemotherapy was administered to all patients indicating a total of 84 various courses. No response to chemotherapy was discovered within 10 patients (23.8%).

Table 1. Clinical characteristics of patients (n=42)

Characteristic	No. (%)
Primary breast surgery	
Lumpectomy	28 (66.7)
Mastectomy	14 (33.3)
Histologic finding	
Ductal carcinoma	37 (88.1)
Lobular carcinoma	5 (11.9)
Positive axillary nodes	12 (28.6)
Estrogen receptor-positive	19 (45.2)
Progesterone receptor-positive	4 (9.5)
Human epidermal growth factor receptor 2-positive	9 (21.4)
Months between primary diagnosis of liver metastases < 12	9 (21.4)
Chemotherapy and radiation for primary tumor	14 (33.3)
Chemotherapy for liver metastases	42 (100.0)
Chemotherapy and hormone therapy for liver metastases	23 (54.8)
Targeted therapy	9 (21.4)
Concurrent distant metastasis	20 (47.6)
Major liver resection	29 (69.1)
No. of liver metastases	
1	22 (52.34)
2-4	12 (28.6)
5-7	8 (19.0)
Diameter of lesions > 4 cm	13 (30.9)
R0 liver resection	35 (83.3)

Table 2. Type of hepatectomy according to Brisbane terminology in liver metastases of breast cancer patients (n=42)

Type of hepatectomy	No. (%)
Left lateral sectionectomy	4 (9.5)
Right posterior sectionectomy	5 (11.9)
Left hepatectomy and segmentectomy 1	4 (9.5)
Right hepatectomy	23 (54.8)
Extended right hepatectomy	1 (2.4)
Extended left hepatectomy	1 (2.4)
Right posterior sectionectomy and segmentectomy 2	1 (2.4)
Laparoscopic radiofrequency ablation	3 (7.1)

Surgical treatment

The type of surgical intervention was based on individual patient's needs. The most frequent procedure was the right hepatectomy performed in 23 patients (54.8%). This was followed by right posterior sectionectomy and left hepatectomy conducted in five (11.9%) and four (9.5%) patients, respectively (Table 2). Left lateral sectionectomy was performed in four patients (9.5%), three of whom underwent a laparoscopic procedure. Interval between surgery for a primary tumor and liver resection < 1 year was noticed in 9 patients (21.4%). Major liver resection was undertaken in 29 patients (69.1%). Ten patients (23.8%) were presented with bilobar disease. Three of them underwent complete ablation of the metastatic lesions with laparoscopic radiofrequency ablation. Presence of positive portal lymph nodes was seen in 14 patients (33.3%).

Final histological examinations of the resected specimen confirmed the number of liver metastases ranging from one to seven with the mean as being one. Twenty-two patients (52.4%) were presented with a solitary metastasis. In all the patients, there was a histomorphological evidence of LMBC. Immunohistochemical analysis of liver metastases demonstrated hormonal patterns and HER2 status analogous to those of the primary tumor.

Metastatic tumor size of > 4 cm was observed in 13 patients (31.0%). Metastasis maximum diameter of the largest lesion was 5.1 cm (range, 1.4-9 cm). A R0 resection was successfully achieved in 35 patients (83.3%) while the R1 resection was accomplished in the remaining 7 patients (16.7%). There were no R2 resections at all.

There was a significant morbidity rate following hepatectomy in 15 patients (35.7%). One patient presented with intra-abdominal bleeding requiring relaparotomy. Another patient developed a bile leakage managed by biliary stenting and percutaneous drainage. Wound infections in two patients required drainage. Two patients developed intra-abdominal collections necessitating percutaneous radiologically guided drainage. A chest infection was diagnosed within five patients (11.9%). Small-for-size syndrome and renal failure were

proved in two patients each. And both patients needed renal replacement therapy.

Survival and recurrence rates

There was no perioperative mortality. One patient (2.3%) died within 30 days after liver resection of multiorgan failure. The 60- and 90-day mortalities were two patients (4.8%) each. These patients dropped out of the study. As a result, only 39 patients were being followed-up. The median length of follow-up for patients who underwent surgical treatment with hepatic resection was 60.0 months. The disease-free survivals and overall survivals were 29.4 and 43.0 months, respectively. The 1-, 3-, and 5-year survival rates were 84.6% (n = 33), 64.1% (n = 25), and 38.5% (n = 15), respectively (Figure 1A).

Sixteen patients (41.0%) developed disease recurrence within the liver. Most commonly, recurrence disease patterns within the liver were confluent multiple liver metastasis. All of these patients took the systemic chemotherapy for further disease management. The mean survival rate of the patients with a recurrence in the liver was 8.6 months (range, 0.5-38.0 months). Only one patient underwent a repeated liver resection for recurrent disease within the liver. The right hepatectomy was performed on her for metachronous metastases. She developed recurrence in segment 3 of the liver 10 months later and required another nonanatomic liver resection. However, patient remained disease-free, and died 55 months later due to unrelated reasons. Cerebral metastases were proved in 14 patients (35.9%). The mean survival of these patients after the diagnosis of liver metastasis was 9.5 months (range, 0.8-27.2 months) while it was 2.25 months after the diagnosis of cerebral metastasis 2.3 months (range, 0.8-19.2 months) despite the treatment with cranial irradiation and steroids. Nine remaining deceased patients (23.1%) developed disease recurrence within the lung and brain, the mean rate after the diagnosis of disease recurrence only 1.1 months (range, 0.5-11.2 months) only. Axillary lymph node recurrence was noted in one patient 2 years after the mastectomy for primary breast cancer. Seven years later this patient developed liver metastasis requiring hepatectomy.

Prognostic factors

Among all the factors that predict patient's survival rates on univariate analysis, five variables, namely, metastatic tumor size of ≤ 4 cm ($p=0.03$), R0 resection ($p=0.02$), negative portal lymph nodes ($p=0.01$), response to chemotherapy ($p=0.02$), and positive hormone receptor status ($p=0.03$) were associated with better survival outcomes on univariate analysis, however, they did not show any survival benefit on multivariate analysis (Table 3, Figure 1B-F).

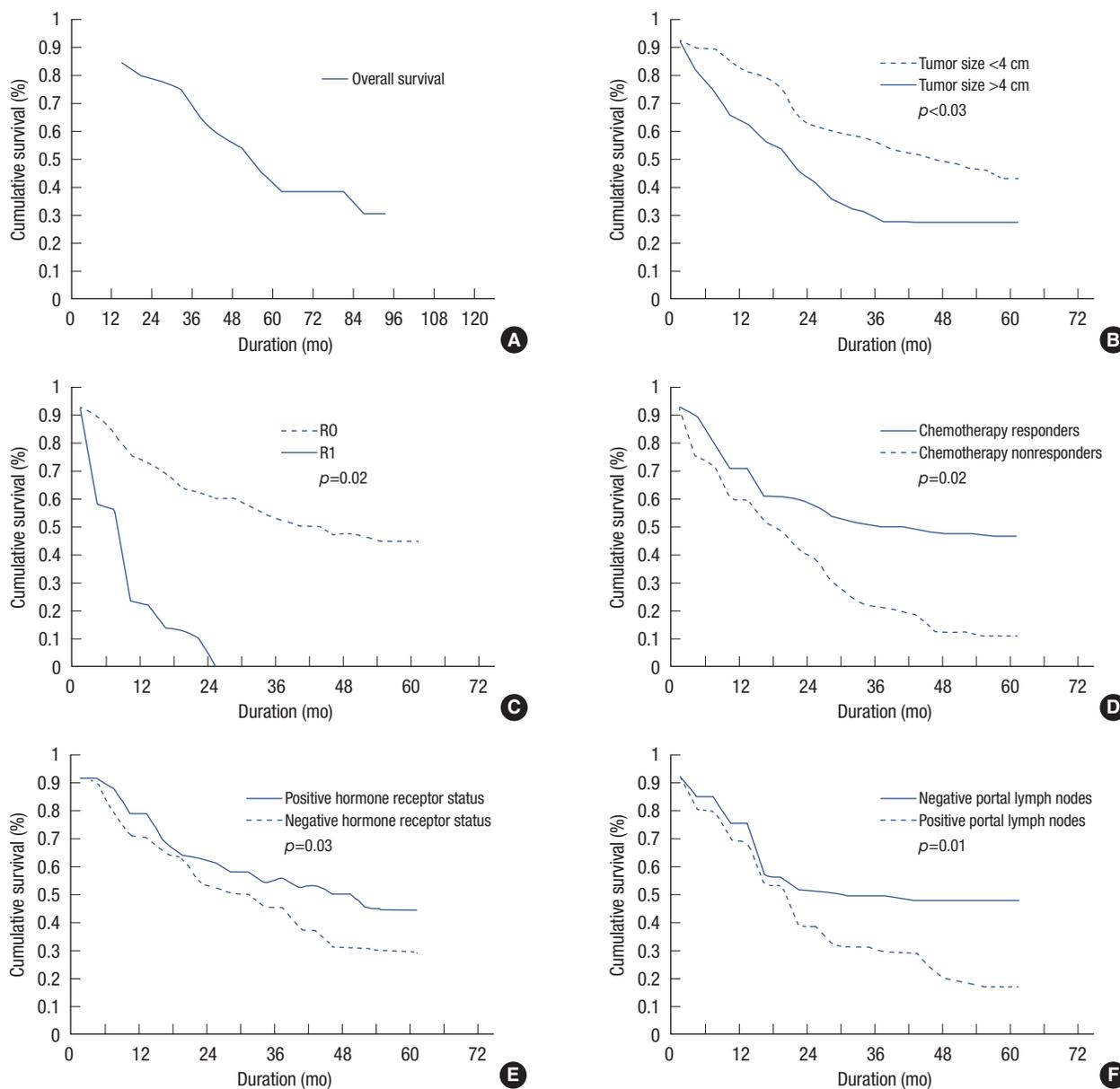


Figure 1. Survival curves according to tumor characteristics. (A) Overall survival curve for patients who underwent a hepatectomy for liver metastases of breast cancer (LMBC) calculated since surgery onwards ($p=0.03$). (B) Cumulative survival curves compare metastasis size of ≤ 4 cm and > 4 cm ($p=0.03$). (C) Cumulative survival curves compare R0 and R1 resections ($p=0.02$). (D) Cumulative survival curves compare chemotherapy responders and nonresponders ($p=0.02$). (E) Cumulative survival curves compare positive and negative hormone receptor status ($p=0.03$). (F) Cumulative survival curves compare negative and positive portal lymph nodes ($p=0.01$).

The negative predictive factors were further individually analyzed to define their impact on 5-year survival. This survival dropped from 42.9% for a tumor size of ≤ 4 cm to 27.3% for a tumor size of > 4 cm. Similarly, it was 44.5% for a R0 resection in contrast to 0% for a R1 one. This survival decreased from 46.7% for chemotherapy respondents to 11.1% for non-respondents. It was 45.5% for patients with positive hormone receptor status in contrast to the 29.4% for negative ones. This

decreased from 48.1% for patients with negative portal lymph nodes to 16.7% for those with positive ones. There was no prognostic significance concerning other variables. On the multivariate analysis, however, none of these variables have significantly affected surgery outcome. Any direct comparison between endocrine- and chemotherapy-treated patients was not appropriate as patients selected for such treatments differed in age and fitness.

Table 3. Univariate analysis of variables predicting the hepatectomy outcome (n=39)

Variable	No. (%)	95% CI	p-value	HR
Age (yr)			0.75	0.42
≤58.2	19 (48.7)			
>58.2	20 (51.3)			
Axillary lymph nodes			0.09	0.52
Positive	11 (28.2)			
Negative	28 (71.8)			
Interval between primary tumor surgery and hepatectomy (yr)			0.48	0.00
<1	8 (20.5)			
>1	32 (82.1)			
No. of metastases			0.29	0.39
1	20 (51.3)			
>1	19 (48.7)			
Size of metastasis (cm)		0.81-7.93	0.03	1.19
≤4	28 (71.8)			
>4	11 (28.2)			
Presence of extrahepatic disease			0.83	0.02
Yes	19 (49.7)			
No	20 (51.3)			
Type of liver resection			0.09	0.91
Major	27 (69.2)			
Minor	12 (30.8)			
Site of metastases			0.32	0.46
Bilobar	10 (25.6)			
Unilobar	29 (74.4)			
Status of the resection margin		1.13-10.01	0.02	1.25
Negative	33 (84.6)			
Involved	6 (15.4)			
Response to chemotherapy		2.15-13.04	0.02	1.64
Yes	30 (76.9)			
No	9 (23.1)			
Hormone receptor status		1.38-11.22	0.03	1.89
Positive	22 (56.4)			
Negative	17 (43.6)			
Portal lymph nodes		2.40-13.74	0.01	1.27
Positive	12 (30.8)			
Negative	27 (69.2)			

CI= confidence interval; HR=hazard ratio.

DISCUSSION

Breast cancer is the most common malignancy among women. One of eight women will develop breast cancer during her lifetime [12]. Approximately 50% of all patients will present distant metastases during the course of their disease [7,13]. Despite significant progress in the multidisciplinary management of breast cancer patients, the development of distant metastases continues to be associated with very poor prognosis. As liver metastases occur in the setting of widely disseminated disease, systemic treatment is commonly suggested for this condition which is, unfortunately, palliative and has a mean survival rate of 2 to 14 months only [13,14]. The

liver is the third most common site of distant metastases in breast cancer patients, following the bones and the lungs. This type of cancer is generally considered to be more easily metastasizing to visceral organs. The presence of metastatic disease isolated to the liver is a rare finding occurring in only 4% to 5% of the cases [3,4]. In cases of disseminated disease, systemic management behavior includes combinations of chemotherapy and hormone therapies. However, they are less effective against liver metastases, which tends to be hormone-receptor negative [13]. Generally, the chemotherapy is proposed as first-line treatment of visceral metastases. Liver metastases are considered less responsive to chemotherapy than metastases of other locations. This may partly explain why liver metastases patients have a shorter survival rate as compared to those with metastases at other sites [14]. Survival in liver metastases patients (19 months) or in those with liver and bone metastases (17 months) is longer than that in patients with metastases of other sites (12 months) [13]. These authors conclude that the presence of isolated liver metastases may not indicate any poor prognosis as previously believed.

The hepatic involvement is a life threatening prognostic indicator, therefore, early local or regional treatment is a viable option to improve survival. This necessitates the development of new and better treatment strategies. In 1991, the first series reporting hepatectomy for LMBC has been published [3]. Since then, reports on the role of liver resection in liver metastases patients contain minimal cases [1,8,15-19]. Less than 20% of such patients treated by a multidisciplinary approach are candidates for hepatectomy. The real impact on patient-survival is very difficult to evaluate due to the absence of randomization. It is important to identify the prognostic factors which predict more favorable outcomes after liver resection for attempted cure.

In the present study, tumor size > 4 cm ($p=0.03$), R1 resection ($p=0.02$), nonresponsiveness to chemotherapy ($p=0.02$), negative hormone receptor status ($p=0.03$), and positive portal lymph nodes ($p=0.01$) possess negative prognostic values concerning liver metastases patient's survival on univariate analysis. However, our results fail to reach significance on multivariate analysis because of the small number of patients.

Prognostic factors in LMBC are difficult to validate after liver resection owing to the small number of patients involved. There are only few reports that examine the outcome following hepatectomy in more than 50 patients [15,17,20]. Investigations of outcome predictors [8,17] indicate that a disease-free interval shorter than 1 year from primary breast cancer to liver metastases diagnosis and positive hepatic resection margin diminishes the probability of long-term survival. The disease-free interval between treatment of the primary neoplasm

and liver metastases development is considered a tumor biology marker. The analysis on 53 out of 86 patients (61.6%) with a solitary LMBC and tumor size of ≤ 5 cm (in 73 patients, 84.9%) following hepatectomy demonstrates that the disease-free survivals and overall survivals are 14 and 57 months at a 62-month median follow-up, respectively [20].

The observation of a longer disease-free interval being possibly associated with less aggressive tumor biology is supported by studies demonstrating longer survivals in patients with disease-free intervals of more than 12 or 24 months [21]. However, most of the larger series describe a R0 that significantly correlates with superior survival [17,22]. Therefore, achieving the complete macroscopic resection represents an important selection criterion for patients whom are suitable for hepatectomy.

Hormone-receptor status is another key variable when determining the treatment for LMBC [14]. It has been the only significant prognostic factor for patient's survival [15]. This status is, classically, one of the main prognostic factors in any studies concerning survival of LMBC patients. On univariate analysis, estrogen receptor/progesterone receptor status of the primary breast cancer, best radiographic response, and preoperative radiographic response are associated with overall survival. On multivariate analysis, estrogen receptor-negative primary breast cancer ($p=0.009$; hazard ratio, 3.3; 95% confidence interval [CI], 1.4-8.2) and preoperative progressive disease ($p=0.003$; hazard ratio, 3.8; 95% CI, 1.6-9.2) are related to decreased overall survival [20]. However, the studies on prognostic impact demonstrate equivocal results [16,23].

The presence of extrahepatic disease prior to hepatectomy is the only significant prognostic factor [16]. Positive hilar lymph nodes are present in 33% of the cases and have a significant prognostic impact on overall survival [15]. This suggests that hepatectomy for LMBC is only a cytoreductive surgery and thus can't be considered a definitive and isolated treatment option. In a large patients' contingent, multivariate analysis determines four factors associated with the poor survivals such as time to metastases, extrahepatic location, progressions under chemotherapy treatment, and incomplete resection [18].

The opinions about the lymph node status at the time of the primary breast cancer resection are still controversial. The presence of symptoms relating to the metastases such as pain or weight loss correlates with poor survivals in the study of untreated liver metastases patients [24]. There is a significant correlation between LMBC vascular invasion and poor patient's survival. It might be a useful selection parameter in patients with macroscopically detectable vascular invasion and for decisions on further adjuvant chemotherapy [22].

The response to chemotherapy correlates significantly with survivals after liver resection thus demonstrating the important role of systemic therapy in the multimodal treatment of LMBC patients [17]. Response rates to salvage chemotherapy regimens, once hormonal and first-line chemotherapy have been exhausted, are extremely poor and short-lived. The prognosis of non-respondents, who comprise the majority of patients, is much worse. In our series, the median overall survival calculated from the time of hepatic resection, is 43 months, the 1-, 3- and 5-year survival rates are 84.6% ($n=33$), 64.1% ($n=25$), and 38.5% ($n=15$), respectively, while the median disease-free interval after liver resection is 29.4 months.

Previously reported series reveal favorable 5-year overall survival rates ranging from 21% to 61% and a median overall survival reaching 57 months for R0 [8,16]. With the classic nonoperative treatment, there are no survivals after five years. Our study also confirms these results. Patients with LMBC who underwent classic nonoperative treatment only had 1- and 3-year survival rates of 72% and 36%, respectively, with no patients surviving after 3.5 years. However, these reports describe only small patients' cohorts and all the investigators notes considerable heterogeneity in the presentation and progression of metastatic disease.

Published studies on ablative therapies such as RFA demonstrate disappointing results with high recurrences at short-term follow ups [25]. Outcomes for RFA are not comparable to liver resection, therefore, RFA must be considered a palliative procedure in LMBC. It represents an inferior alternative treatment option for high-risk patients and those with stable extrahepatic disease are not candidates for hepatectomy. Data in the literature available suggest a subgroup of patients who may benefit from surgery, however, only few reports the transcatheter arterial chemoembolization [1]. Nowadays, this procedure is used in a variety of clinical settings and proves to be effective in prolonging the survivals in liver metastases patients. However, these results have not yet been confirmed in cases with LMBC. A laparoscopic approach allows for more accurate staging with direct visualization and, typically, requires only two 10-mm incisions. Smaller lesions or peritoneal metastasis, which may not enhance on preoperative imaging can be intraoperatively identified only under direct visualization. Incidences of untreatable disease diagnosed during staging laparoscopy and intraoperative ultrasound is high among most LMBC series [17]. Laparoscopic hepatic resection or RFA are safe surgical treatments in selected liver metastases patients [19].

A literature review shows that thermal ablation procedures such as RFA, laser-induced thermotherapy (LITT) and microwave ablation (MWA) are an alternative treatment for LMBC.

They result in median survivals of 10.9 to 6 months using RFA, 51 to 54 months after LITT and 41.8 months after MWA. Five-year survival rates are 27% to 30%, 35%, and 29%, respectively [26]. According to the response evaluation criteria in solid tumor, there is partial response in 29 out of 52 liver metastases patients (55.7%), a stable disease in 18 (34.6%) and a progressive disease in 5 ones (9.6%) after ^{90}Y radioembolization. The median overall survival is 11.5 months. ^{90}Y radioembolization is safe, well-tolerated and effective for liver metastases [27]. The application of CT-guided high-dose-rate brachytherapy ablation in 35 LMBC patients results in a median overall survival of 18 months (range, 3-39 months). This therapeutic modality is safe and effective as it provides a high rate of local tumor control evaluated by gadoteric acid-enhanced liver MRI [28].

In the past decade, hepatectomy has become a fairly common therapeutic option for such patients because mortality with this procedure has declined as a result of improved preoperative imaging, patient's selection, anesthetics, critical care management and understanding of liver anatomy. In order to further enhance the prognosis of liver metastases patients, early diagnosis is essential. Positron emission tomography will, obviously, play a progressively crucial role in the selection of the patients for improving surgery at preoperative staging of the disease. Staging laparoscopy could be another useful tool in this respect. No treatment is available for patients who display specific symptoms and signs such as hepatomegaly, jaundice and abdominal pain, and therefore their prognosis is extremely poor. As a whole, our data suggest the possibility of a curative, multidisciplinary therapeutic approach for at least a fraction of patients with limited LMBC. Definitive evidence from controlled prospective randomized trials is missing; although available data are from retrospective series, relatively few patients were enrolled.

Liver resection offers the only chance of cure in patients with a variety of primary and secondary liver tumors. For LMBC, the natural history of this condition is poorly defined and the management remains controversial. The results are particularly difficult to interpret and do not allow clear conclusions to be drawn regarding the true indications for hepatectomy in liver metastases patients. It appears logical to propose liver resection for women with LMBC when the six following conditions are absolutely confirmed: 1) a positive response to chemotherapy and endocrine therapy; 2) a completely resectable liver metastases; 3) a negative hilar lymph nodal status; 4) a size of liver metastases < 4 cm; 5) a low operative risk, and 6) no extrahepatic disease, except for bone metastases which are easily controlled.

This study proves that survival factors may be useful in pre-

dicting the duration of survivals for LMBC patients. The careful selection of patients is associated with a satisfactory long-term survival. Improvement in preoperative staging and progressive application of new multimodality treatments will be the key to improved survivals in this severe disease. The surgical treatment of LMBC is only of beneficial to a minority of the patients and should be practiced more extensively in the future.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

- Li XP, Meng ZQ, Guo WJ, Li J. Treatment for liver metastases from breast cancer: results and prognostic factors. *World J Gastroenterol* 2005;11:3782-7.
- Elias D, Di Pietroantonio D. Surgery for liver metastases from breast cancer. *HPB (Oxford)* 2006;8:97-9.
- Elias D, Lasser P, Spielmann M, May-Levin F, el Malt O, Thomas H, et al. Surgical and chemotherapeutic treatment of hepatic metastases from carcinoma of the breast. *Surg Gynecol Obstet* 1991;172:461-4.
- Díaz R, Santaballa A, Munárriz B, Calderero V. Hepatic resection in breast cancer metastases: should it be considered standard treatment? *Breast* 2004;13:254-8.
- Piccart MJ, Awada A, Hamilton A. Integration of new therapies into management of metastatic breast cancer: a focus on chemotherapy, treatment selection through use of molecular markers and newly developed biologic therapies in late clinical development. *Am Soc Clin Oncol Educ Book* 1999:526-39.
- Aapro MS. Combining new agents with anthracyclines in metastatic breast cancer: an overview of recent findings. *Semin Oncol* 1999;26(1 Suppl 3):17-21.
- Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast* 2012;21:242-52.
- Vlastos G, Smith DL, Singletary SE, Mirza NQ, Tuttle TM, Popat RJ, et al. Long-term survival after an aggressive surgical approach in patients with breast cancer hepatic metastases. *Ann Surg Oncol* 2004;11:869-74.
- Malassagne B, Goere D, Cherqui D, Fagniez PL. Surgical treatment of non-colorectal and non-endocrine liver metastases. *Gastroenterol Clin Biol* 2000;24:1177-85.
- Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB* 2000; 2:333-39. *HPB (Oxford)* 2002;4:99; author reply 99-100.
- Marudanayagam R, Sandhu B, Perera MT, Taniere P, Coldham C, Bramhall S, et al. Hepatic resection for non-colorectal, non-neuroendocrine, non-sarcoma metastasis: a single-centre experience. *HPB (Oxford)* 2011;13:286-92.
- Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66.
- Zinser JW, Hortobagyi GN, Buzdar AU, Smith TL, Frascini G. Clinical

- course of breast cancer patients with liver metastases. *J Clin Oncol* 1987;5:773-82.
14. Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A, Garcia-Conde J. Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 1999;56:67-78.
 15. Elias D, Maisonnette F, Druet-Cabanac M, Ouellet JF, Guinebretiere JM, Spielmann M, et al. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. *Am J Surg* 2003;185:158-64.
 16. Sakamoto Y, Yamamoto J, Yoshimoto M, Kasumi F, Kosuge T, Kokudo N, et al. Hepatic resection for metastatic breast cancer: prognostic analysis of 34 patients. *World J Surg* 2005;29:524-7.
 17. Adam R, Aloia T, Krissat J, Bralet MP, Paule B, Giacchetti S, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? *Ann Surg* 2006;244:897-907.
 18. Adam R, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg* 2006;244:524-35.
 19. Cassera MA, Hammill CW, Ujiki MB, Wolf RE, Swanström LL, Hansen PD. Surgical management of breast cancer liver metastases. *HPB (Oxford)* 2011;13:272-8.
 20. Abbott DE, Brouquet A, Mittendorf EA, Andreou A, Meric-Bernstam F, Valero V, et al. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. *Surgery* 2012;151:710-6.
 21. Earle SA, Perez EA, Gutierrez JC, Sleeman D, Livingstone AS, Franceschi D, et al. Hepatectomy enables prolonged survival in select patients with isolated noncolorectal liver metastasis. *J Am Coll Surg* 2006;203:436-46.
 22. Thelen A, Benckert C, Jonas S, Lopez-Hänninen E, Sehoul J, Neumann U, et al. Liver resection for metastases from breast cancer. *J Surg Oncol* 2008;97:25-9.
 23. Martinez SR, Young SE, Giuliano AE, Bilchik AJ. The utility of estrogen receptor, progesterone receptor, and Her-2/neu status to predict survival in patients undergoing hepatic resection for breast cancer metastases. *Am J Surg* 2006;191:281-3.
 24. Cady B, Stone MD, McDermott WV Jr, Jenkins RL, Bothe A Jr, Lavin PT, et al. Technical and biological factors in disease-free survival after hepatic resection for colorectal cancer metastases. *Arch Surg* 1992;127:561-8.
 25. Gunabushanam G, Sharma S, Thulkar S, Srivastava DN, Rath GK, Julka PK, et al. Radiofrequency ablation of liver metastases from breast cancer: results in 14 patients. *J Vasc Interv Radiol* 2007;18(1 Pt 1):67-72.
 26. Vogl TJ, Farshid P, Naguib NN, Zangos S. Thermal ablation therapies in patients with breast cancer liver metastases: a review. *Eur Radiol* 2013;23:797-804.
 27. Cianni R, Pelle G, Notarianni E, Saltarelli A, Rabuffi P, Bagni O, et al. Radioembolisation with (90)Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. *Eur Radiol* 2013;23:182-9.
 28. Colletini F, Golenia M, Schnapauff D, Poellinger A, Denecke T, Wust P, et al. Percutaneous computed tomography-guided high-dose-rate brachytherapy ablation of breast cancer liver metastases: initial experience with 80 lesions. *J Vasc Interv Radiol* 2012;23:618-26.