Outcome of liver resection in breast cancer liver metastases

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Received 20 April 2015
Accepted 13 June 2015

The Egyptian Journal of Surgery
2015, 34:230–237

Introduction
Women with visceral metastases of breast cancer are usually considered to have a poor prognosis. A small subgroup of patients, however, present with liver metastases as the only manifestation of recurrence. The discussion whether this subgroup might benefit from an aggressive approach including liver resection is still ongoing and remains controversial. The decrease in mortality and morbidity rates has led to a broadening of the indication for hepatic resection.

Design
This was a case series study.

Methodology
Between January 2011 and December 2013, nine adult female patients underwent liver resection for liver metastases from breast cancer. Patients were considered for surgical management if they were fit for major operation; hepatic resection can be performed with adequate residual liver volume, intact inflow and outflow, and biliary drainage, and no extrahepatic disease on preoperative imaging except for limited and stable bone metastases. Hepatic resection was performed using standard techniques for either anatomic or nonanatomic resection. The type and length of the surgical procedures, intraoperative blood loss and transfusion, postoperative complications, ICU stay, and hospital stay were recorded. These patients were followed up in clinic 2 weeks postoperatively to record early postoperative complications. At subsequent follow-up visits every 3 months, chest radiography, abdominal ultrasound, and evaluation of carcinoembryonic antigen and CA 15-3 were carried out. Triphasic computed tomography of the abdomen was performed every 6 months and bone scan was performed case by case according to the patient's complain. The follow-up period was 2 years.

Results
All patients underwent tumorectomy with safety margins, except for two cases for which combined segmentectomy and tumorectomy with safety margins was performed. All patients underwent R0-resections. The mean operating time for hepatic resection was 150 ± 17 min, and blood loss was 360 ± 95 ml. Six patients were admitted to the ICU for 1 day and the main hospital stay was 5 ± 2 day. There was an overall morbidity rate of 33%, with one patient (11%) had grade 1 complication and two patients (22%) had grade 2 complications according to Clavien–Dindo score, and no postoperative mortality was detected. The mean follow-up period was 21 ± 2.7 months. One patient was presented with disease recurrence in the liver and brain at 8 months, and died at 10 months postoperatively (1-year survival, 88%). A second patient had local breast recurrence and died at 19 months postoperatively (2 years survival, 77%).

Conclusion
This approach represents a valid cytoreductive procedure for many patients with isolated liver metastases and may be curative for some of them. This benefit was obtained with a low morbidity rate and no mortality.

Keywords:
cancer breast, liver metastases, outcome

Egyptian J Surgery 34:230–237

1110-1121

Introduction

Breast cancer accounts for 1.38 million cancer diagnoses and 458 000 cancer deaths in women annually, making it the most frequently diagnosed cancer and the leading cause of death among women worldwide [1].

Approximately 50% of all women with breast cancer develop liver metastases [2,3]. In the majority of patients, this is associated with tumor deposits at other sites, indicating advanced disease with poor outcome and a short overall survival of 1–4 months [4]. However, a small proportion of patients (1–3%), present with isolated liver metastases [5,6].

Surgical approaches in the treatment of metastatic disease are still contradictory and some hold the view that only chemotherapy and/or hormone therapy are

indicated in such conditions. However, hormonal therapy is generally of limited use because most hepatic metastases are hormone receptor negative [7]. Neither chemotherapy nor radiotherapy represents a curative treatment in this condition and long-term survival rarely observed, with reported median survivals that range from 15 months when responding to chemotherapy to as low as 3 months when not responding [8,9].

Several case series have reported an improvement in survival for patients who underwent hepatic resection for liver-only metastatic disease, with 5-year survival rates ranging from 9 to 61% [10].

The primary endpoint of our study was to detect liver recurrence after liver resection with an intention to treat isolated breast cancer liver metastases compared with a review of the existing published literature, and the secondary endpoint was to prove its survival advantage.

Patients and methods

Between January 2011 and December 2013, nine adult female patients underwent liver resection for liver metastases from breast cancer diagnosed based on the triphasic abdominal computed tomography (CT) and MRI scan criteria. The diagnosis was confirmed with postoperative histopathology.

Clinical and pathologic parameters evaluated included age at diagnosis of breast metastases, primary breast surgery, lymph node status, chemotherapy and/or radiation of the primary tumor, interval from diagnosis of the primary tumor to the discovery of metastases, and the number, size, and location of the metastases.

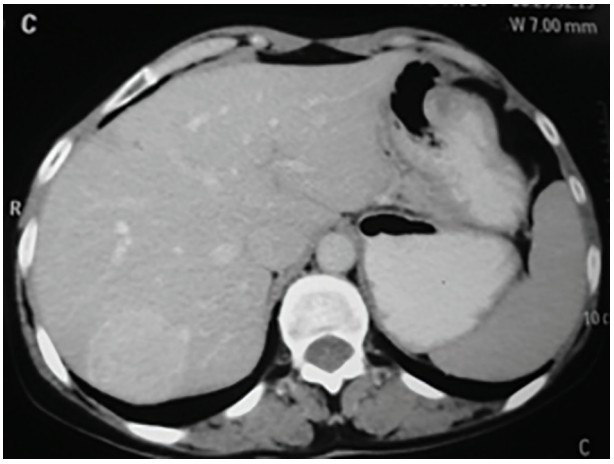
Preoperatively, all patients underwent a triphasic abdominal CT (Fig. 1) or MRI scan (Fig. 2) to assess tumor burden in the liver before surgery was considered. CT volumetry was requested if major resection was suspected. Additional distant metastases were excluded by renewed staging before liver surgery: bone scan and CT/MRI of the brain and chest and sometimes mammography.

Patients were considered for surgical management if they were fit for major operation; hepatic resection can be performed with adequate residual liver volume (35% residual liver volume), intact inflow and outflow, and biliary drainage. Patients included in the study were those with no extrahepatic disease on preoperative imaging except for limited and stable bone metastases for at least 6 months. Any patient with underlying liver disease was excluded.

Hepatic resection was performed using standard techniques for either anatomic or nonanatomic resection aiming at 1 cm safety margin (Fig. 3). All patients were taken to the operating room for a planned intraoperative ultrasound. Selective vascular clamping or Pringle maneuver was used to control intraoperative blood loss according to the intraoperative findings. A lymphadenectomy of the hepatoduodenal ligament was performed if the lymph nodes were intraoperatively considered suspicious for metastatic involvement for frozen examination and the procedure was canceled if proved to be positive. For patients who received chemotherapy the operation was performed 4–6 weeks from the last dose.

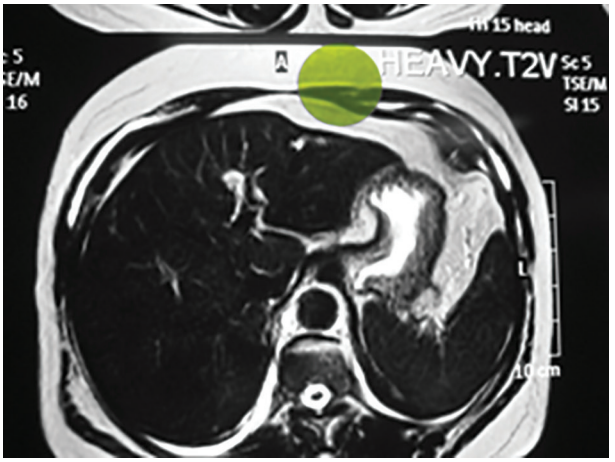
The type and length of the surgical procedures, intraoperative blood loss and transfusion, postoperative complications, ICU stay, and hospital stay were recorded.

Figure 1



Triphasic computed tomography showing hepatic focal lesion (HFL) in the right lobe.

Figure 2



MRI revealing HFL in the left lobe.

Postoperative chemotherapy was used at the discretion of a multidisciplinary tumor board.

These patients were followed up in clinic 2 weeks postoperatively to record early postoperative complications. At subsequent follow-up visits every 3 months, chest radiography and abdominal ultrasound was performed and carcinoembryonic antigen (CEA) and CA 15-3 were measured only in patients with previously elevated levels before management of the primary breast tumor. Triphasic CT of the abdomen was performed every 6 months and bone scan was performed case by case based on the patient's complain. The follow-up period was 2 years.

Curative resection was defined as removal of all macroscopically detectable disease and microscopically clear resection margins of the excised liver. Hepatectomies were classified into major and minor resections, as defined by resection of up to three segments for minor and corresponding more than three segments for major hepatectomies. Curative management of breast primary was considered if no vital tumor was evident at the site of previous tumor on MRI. Complications were classified according to the Clavien–Dindo classification of surgical complications [11]. All deaths within 30 days of surgery were considered perioperative mortality.

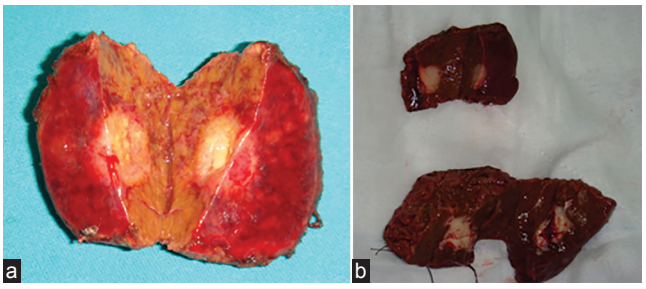
Data were analyzed using Student's *t*-test. All data were presented as mean ± SD. Statistical analyses were performed with SPSS, version 17 for Windows computer software (IBM, Armonk, New York, USA).

Results

Patient and tumor characteristics

Nine patients diagnosed with breast cancer metastatic to the liver were considered for surgical management. The mean age at the time of referral was 52.5 years (range, 36–63 years), and all patients were female.

Figure 3



(a) Tumorectomy resection with 1 cm safety margins. (b) Tumorectomy resection with 1 cm safety margins.

Eight patients had metastatic disease confined to the liver; one patient had concurrent metastases to the bone that was managed preoperatively with radiotherapy alone (disease-free interval 6 months).

All patients underwent a resection of their primary breast cancer (three lumpectomy and six modified radical mastectomies) before the diagnosis of liver metastases. Four patients had positive axillary nodes at the time of the resection for primary cancer. The mean interval between diagnosis of primary breast cancer and subsequent liver metastases was 29 months (range, 10–44 months). CA 15-3 and CEA were evaluated at the initial evaluation and during the follow-up; they were elevated in 88 and 66% of patients, respectively. During follow-up the levels returned to normal in all patients and remained in a plateau, except for two patients who had recurrence, in whom both markers started to rise again to the preoperative levels.

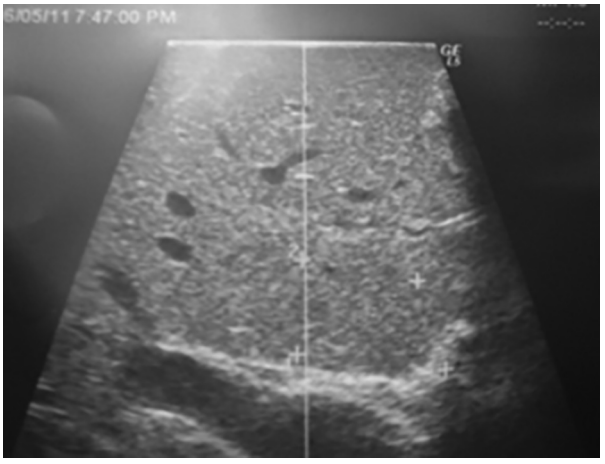
The number of liver metastases were identified intraoperatively with either visual, manual, or intraoperative ultrasound (performed routinely in all patients) (Fig. 4) and was confirmed to be solitary in one patient in the left lobe (Fig. 5) and multiple in the remaining eight cases (range, 1–4). Two cases had more than one lesion confined to one lobe of the liver, and six cases had bilateral metastases and the tumor size was more than 4 cm in only two cases.

Preoperative patient demographics and tumor characteristics are summarized in Table 1.

Surgical results

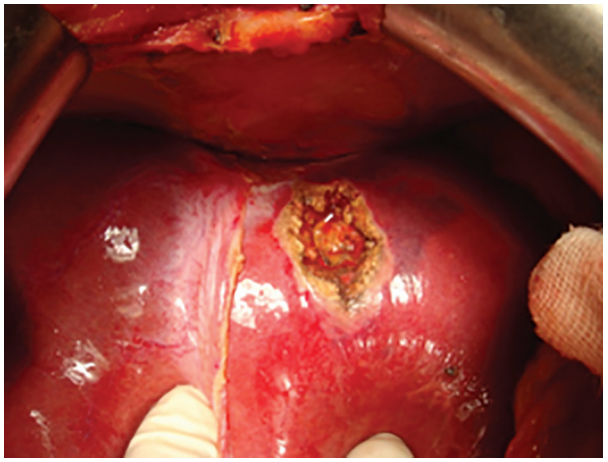
All patients underwent tumorectomy with safety margins (Fig. 6) except for two cases for which

Figure 4



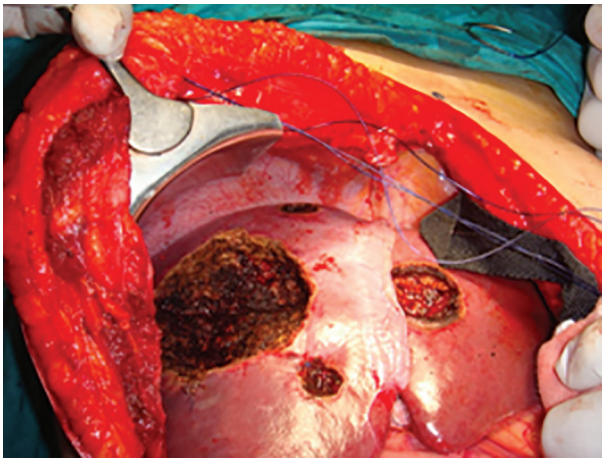
Intraoperative ultrasound revealing hypoechoic HL and its relation to the portal vein.

Figure 5



A case with solitary lesion in the left lobe.

Figure 6



Tumorectomy with safety margins for three bilobar lesions.

Table 1 Demographic and characteristics of liver metastases from breast cancer

Characteristics	*N*=9
Sex (number of patients)	
Female	9
Age (years)	
Mean ± SD	52.5 ± 2.6
Range	36–63
Primary breast surgery	
Lumpectomy	3
Modified radical mastectomy	6
Axillary LN	
Positive	4
Negative	5
Tumor markers CEA (ng/ml)	
>5	6
<5	3
Tumor markers CA 15-3 (IU/ml)	
>25	8
<25	1
Interval between primary and diagnosis of liver metastases (months)	
Mean ± SD	29 ± 13.3
Range	10–44
Tumor size (cm)	
≤4	7
>4	2
Number of lesions	
Solitary	1
2	4
3	2
4	2
Lesion site [nodule (*n*)]	
Left lobe	8
Right lobe	15
Tumor distribution	
Unilobar	3
Bilobar	6

CEA, carcinoembryonic antigen; LN, lymph node.

combined segmentectomy and tumorectomy with safety margins (Fig. 7) was performed (Table 2). One patient was found to have a tumor adjacent to the central biliary structures that was near to the pedicle and was resected after lowering of the pedicle and freeing the biliary structures (Fig. 8). All patients underwent R0-resections.

The mean operating time for hepatic resection was 150 min (range, 85–195 min), and blood loss was around 360 ± 95 ml (range, 200–970 ml). Six patients were admitted to the ICU for 1 day and the main hospital stay was 5 ± 2 fifth day (range, 3–17) (Table 3).

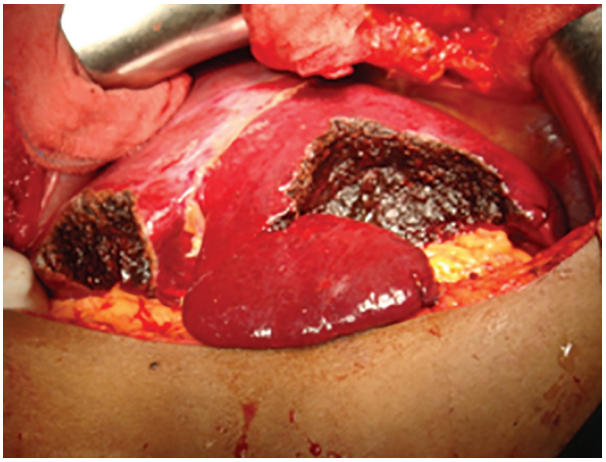
Morbidity and mortality

There was an overall morbidity rate of 33%, with grade 1 complication in one patient (wound infection opened at the bed side) (11%) and grade 2 (22%) in two patients; one patient had urinary tract infection and received antibiotics and the other had bile leak and pleural effusion, which was managed conservatively (Table 4).

Patient outcome

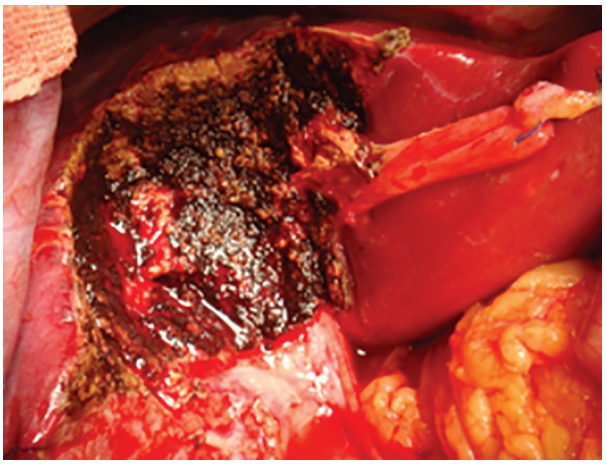
The mean follow-up period was 21 ± 2.7 months. Of the patients who underwent hepatic resection, one patient presented with liver and brain disease recurrence at 8 months, and died at 10 months postoperatively. Previously, this patient had four bilobar lesions, all less than 4 cm (1-year survival, 88%). The second patient had local breast recurrence and died at 19 months postoperatively. Previously, this patient had a lumpectomy for the primary breast disease and three lesions in the right lobe. The patient received chemotherapy, and died from fungal pneumonia associated with leukopenia (2-year survival, 77%) (Table 5).

Figure 7



Combined segmentectomy and tumorectomy with safety margins for a lesion in the left lobe and tumorectomy for a second lesion in the right lobe.

Figure 8



A tumor adjacent to the central biliary structures near to the pedicle that was resected after lowering of the pedicle and freeing the biliary structures.

Table 2 Type of operative procedure adopted

Type of operation	Patients (*N* = 9)	Nodules (*N* = 23)
Major resection	0	0
Segmentectomy	0	2
Limited resection	7	21
Combined resection	2	—

Table 3 Mean operative blood loss and transfusion and mean operative time

Operative finding	Value
Mean blood loss (ml)	
Mean ± SD	360 ± 95
Range	200–970
Blood transfusion (number of patients)	1
Blood transfusion (number of bags)	1
Mean operating time (min)	
Mean ± SD	150 ± 17
Range	85–195

Table 4 Length of stay and surgical morbidity

Length of stay	*N* = 9
ICU stay	
Number of patients	6
Mean days ± SD	1 ± 0
Hospital stay	
Mean days ± SD	5 ± 2
Range	3–17
Type of complication	
Bile leak	1
Pleural effusion	1
Wound infection	1
Urinary tract infection	1
Mortality	0

Table 5 Follow-up period, survival, and recurrence

Postoperative finding	Value
Follow-up period (months)	
Mean ± SD	21 ± 2.7
Range	17–29
1-year survival (%)	88
2-year survival (%)	77
Local recurrence (*N*)	1
Liver recurrence (*N*)	1

Discussion

There are limited data in the published literature evaluating the use of local surgical therapies for the treatment of breast cancer liver metastases [12]. A prospective randomized-controlled study on this aspect is not available [13,14].

A general problem in all studies dealing with that topic is the inhomogeneous and small study groups. Different tumor biologies of the underlying cancers, differing medical histories and time intervals between primary breast cancer and liver metastases including variation in preceding endocrine treatment as well as chemotherapy, and different surgical approaches lead to an inevitable inhomogeneity [15,16].

The reasons for the small study groups in the literature may be due to the reluctance in referring these patients to surgical evaluation. First, most patients with breast cancer liver metastases also have extrahepatic metastases [17], a finding that has traditionally been considered a contraindication to hepatic resection. Secondly, breast cancer has been considered a systemic disease since its onset. Therefore, this concept seems to contraindicate any surgical therapy, and treatments with a minimal profile have been preferred over aggressive treatments such as resection [8].

Data on the primary tumor stages are contradictory in the literature [18–21]. A good histopathological grading of the primary cancer proved to be statistically the most favorable prognostic factor. In contrast, there are references in which the grading of the primary breast cancer was stated to be irrelevant in liver metastases [18,19]. Our limited data at this point result from the treatment of primary breast cancer at different institutions and an interval between primary surgery and liver surgery of up to 4 years.

The receptor status of the primary breast cancer is not necessarily the same in the metastases [22]. The receptor status of breast cancer patients developing liver metastases is therefore not a good indicator to select candidates for liver resection. The hormone receptor status of the primary breast cancer seems to be relevant in some studies, whereas other authors disagree with it [15,16]. Moreover, the expression of Herb-2 did not show influence on survival but was described as a prognostic factor in a former study [2]. Unfortunately, we cannot answer this question for our study group.

The mean disease-free interval between the primary breast disease and the appearance of the liver metastases in our study (29 ± 13.3 months) appears to be too short when compared with the median time interval (55 months) in the study conducted by Weinrich *et al.* [23]. Pocard *et al.* [24] found that a short disease-free interval between treatment of the primary tumor and onset of liver metastases significantly correlated with poor survival and reported that survival at 36 months was 55% when liver metastases occurred before 48 months, versus 85% when liver metastases occurred after 48 months ($P = 0.01$); they found that it was the only parameter statistically correlated with survival. The poorer outcome of patients with a short disease-free interval might be explained by the more aggressive behavior of these tumors. This may explain the overall survival in this study (77%), but the small study group limits the generalization of our results.

The operation adopted in our study was tumorectomy in all nine patients, a principle adapted from the management of colorectal liver metastases; this type of resection did not increase recurrence in the liver remnant and more importantly improved 5-year survival in case of recurrence (salvageability); it was thus recommended to be the standard approach for salvage surgery in case of liver recurrence [25].

The number, and not the size, of the liver metastases was reflected in our patient outcome, as the two patients who suffered from recurrence had multiple nodules and in both of them the tumor size was less than 4 cm. Reports on the influence of the number and size of metastases are controversial [2,26,27]. The extent of resection and the intraoperatively deviating metastasis distribution had no prognostic relevance if resection was possible. In contrast, Weinrich *et al.* [23] reported that the number of metastases proved to be a prognostically relevant factor.

It is fundamental to underline that in none of these series neither the extent of the liver disease (the number and the maximal size of the liver metastases) nor the presence of positive hilar lymph nodes had a significant prognostic impact on overall survival [28]. This suggests that hepatectomy for liver metastases is only a cytoreductive surgery and cannot be considered as a definitive and isolated treatment.

The curative resection rate (100%) in the present study is relatively higher than that reported in the references. It was stated to be 66% in a study; this series was obtained without preoperative selection of suitable patients [29] and this reflects the importance of selection of patients suitable for liver resection. Curative resection significantly correlates with superior survival and is considered as an independent prognostic factor [8].

A recent review of the literature has shown a benefit of resection in breast cancer liver metastases, with a median survival of 38 months compared with 18 months in patients with chemotherapy alone [30]. Overall, this is not surprising due to decrease in the tumor burden after resection.

In general, the prognosis of patients with breast cancer liver metastases is poor, with a median survival of 6–14 months [13,14]. Systemic chemotherapy and/or hormone therapy are still considered the treatment option of choice in these patients. Although these therapies achieved response rates between 40 and 70%, the median survival time has been reported to be no more than 5–12 months [31].

In accordance with our results, the 1- and 2-year survival in the present study was 88 and 77%, respectively. These survival rates correlate well with those published on surgically treated liver metastases in breast cancer for 1-, 2-, and 5-year survival rates of 86, 81, and 33%, respectively [23].

Selzner *et al.* [3] and Elias *et al.* [32] reported 5-year overall survival rates of 22 and 34%, respectively, in patients who underwent resection. Adam *et al.* [8] recently published the largest series so far, with 84 resected patients and a 5-year overall survival of 34%. In a study by Maximilian *et al.* [33], the 5-year overall survival was 44% after resection.

Moreover, the response to chemotherapy was found to correlate significantly with survival after liver resection [8], which documents the important role of systemic therapy in the multimodal treatment of patients with metastatic breast cancer.

The low morbidity and mortality rate indicates the safety of this procedure in these circumstances. Therefore, liver resection represents a therapeutic tool with low risk in these patients, and the results of the recently published series, as well as our study, indicate that liver resection should be considered in the multimodal treatment approach of patients with breast cancer liver metastases.

The recurrence rate among our patients (18%) was lower compared with that reported in other studies (65%) within the first 2 years, and this may be due to small sample size. Nevertheless, the 3- and 5-year survival rates of patients with local recurrence were 67 and 42%, respectively, and 57% of these patients developed metastases [3].

The two patients with recurrence in our study expressed an elevation in the CA 15-3 and CEA serum level after a period of initial decrease. Coveney *et al*. [26] proved a significant correlation between CA 15-3 value at locoregional recurrence and time to subsequent metastasis ($P = 0.0133$). Use of CEA in conjunction with CA 15-3 improves the detection of systemic disease.

Conclusion

Definitive conclusions cannot be drawn because of the limited and selected number of cases of these series; however, this approach represents a valid cytoreductive procedure for many patients with isolated liver metastases and may be curative for some of them.

The results of this study show that a selected group of patients with isolated breast cancer liver metastases benefit from complete surgical resection. This benefit was obtained with a low morbidity rate and no mortality.

Only a prospective randomized study with larger number of patients and longer follow-up period will demonstrate definitively whether surgical resection can really improve long-term survival rates in patients with isolated liver metastases with or without systemic chemotherapy, compared with other methods of treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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