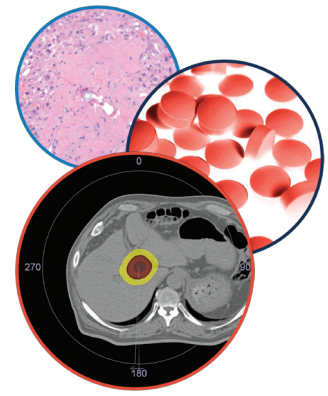
REVIEW

A role for hepatic surgery in patients with liver metastatic breast cancer: review of literature



Hepatic Oncology

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Practice points

- Liver resection could improve overall survival in selected patients with breast cancer liver metastases. The selection of these patients should be based on a multidisciplinary team decision.
- Hepatectomy should be recommended mainly in patients presenting:
- Completely resectable liver metastases.
- Disease-free interval between primary tumor resection and liver metastases development longer than 1 year.
- Liver metastases stable or responsive to preoperative chemotherapy.
- Absence of extrahepatic disease (or limited extrahepatic disease, either resectable or stable during a treatment interval of minimum 6 months).
- Hormonal receptor status of the primary tumor represents an important predictor of overall survival after resection of breast cancer liver metastases; negative status of hormone receptors could not represent definitive criteria to preclude liver resection.

SUMMARY Traditionally, patients with metastatic breast cancer were seen as carrying a grim prognosis and therapy was based mainly on palliative chemotherapy and hormonal therapy, with surgery being considered as ineffective. However, in the last 20 years different centers worldwide published series of metastatic breast cancer patients who underwent resection for different metastatic sites (liver, brain, lung), reporting favorable results. Most of these papers addressed to the role of liver surgery in patients with breast cancer liver metastases, mainly due to the favorable results achieved by liver resection in patients with metastatic colorectal cancer. In this review are presented the results achieved by liver surgery in patients with breast cancer liver metastases.

KEYWORDS: • breast cancer • hepatic resection • liver metastasis • survival

Breast cancer is the most common malignancy in women around the world, with a higher incidence in economically developed countries. About 11% of all women in the western world will develop breast cancer during their lifetime [1]. Approximately 50% of breast cancer patients will develop

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metastases [2], with a propensity to metastasize to liver, lung and bone. More than half of the metastatic patients present liver involvement at some point [3]. Although most of the liver metastatic group patients have evidence of other systemic disseminations, about 5% of them present liver only metastatic disease [2].

Traditionally, the median survival rates of the untreated patients with metastatic breast cancer range between 3 and 6 months [4,5], while in patients receiving the modern oncologic treatment the median survival rates did not exceed 15 months [4,6,7].

Due to these low survival expectancies of the patients with breast cancer liver metastases (BCLM) managed by nonsurgical therapy and to the higher survival rates achieved by hepatic resections for colorectal cancer liver metastasis (CLMs), some authors raised the question of the benefit of liver resection in patients with BCLM. However, conceptually there is an important difference when comparing metastatic colorectal cancer to the liver with metastatic breast cancer. In the first situation, the spread from the primary tumor to the liver is by portal flow or abdominal lymphatic channel; it is therefore theoretically possible that the tumor burden be confined only to the abdomen/liver. In the case of MBC, liver becomes involved via systemic circulation, other sites thus having equal probability of involvement [4].

Anyway, in the last years, few centers reported the results achieved by liver surgery in BCLM, in an attempt to disclose the benefit of this treatment and to identify a selected group of BCLM patients who can achieve long-term survival rates following liver resection.

To better understand the present situation in surgical management of BCLM, in this paper we addressed some issues regarding the rationale, the place of hepatectomy in the multimodal treatment of BCLM, the results of liver resection and the prognostic factors associated with survival following surgical treatment of these patients.

• What is the rationale of liver resection in BCLM?

Although during the last period were recorded important improvements in the treatment of patients with breast cancer (by the advent of anthracyclines and taxanes to chemotherapy regimens, aromatase inhibitors to antihormonal treatment and trastuzumab for Her2-neu-positive tumors), these progresses improved survival mainly in patients with early stage disease (without distant metastases). In patients presenting with metastatic disease, the survival rates were fairly constant over the time, suggesting that new therapeutic methods are needed to improve their life expectancies [4]. In a study of Saad E *et al.* on advanced breast cancer trials the average median overall survival was 20.7 months in trials assessing first-line chemotherapy and 31.1 months with first-line hormone therapy [8].

In spite of the differences in spreading (to the liver) of colorectal cancer and breast cancer, taking into account the results achieved by liver resection in patients with CLMs, few centers considered that similar favorable results could be achieved by adding liver resection to the multimodal treatment of some patients with BCLM. At least theoretically, in patients with liver only MBC, complete resection by hepatectomy and oncologic therapy could improve survival.

In patients with hepatic and extrahepatic metastases, the argument for liver resection could be supported by the fact that most of these patients decease due to the liver metastases. Thus, when comparing overall survival of different subgroups of patients with MBC by metastatic site, one may observe that liver metastases group has a much worse prognosis than lung and especially bone groups, which have a more indolent course of evolution. Therefore, resection of liver metastases could, at least in theory, increase survival for this category of patients

• Is liver resection for BCLM a safe procedure?

Liver resection in general is increasingly employed and becoming a safer procedure. A study by Dynick *et al.* [5] on hepatic resections in the United States over a period of 13 years (1988–2000) showed a nearly twofold increase in number of procedures over this time span with decrease in overall mortality from 10.4% (1988–1989) to 5.3% (1999–2000). Moreover, in high-volume centers, the mortality rates after liver resections decreased from more than 10% (in the first period) to less than 4% in the last period.

Even though there is an obvious increase in the number of studies concerning BCLM resections, the number of patients referred to surgery is still rather small. The number of patients analyzed ranges from 9 (11) to 86 (24), except for the French multicenter (41 hospitals) study conducted by Adam *et al.* [9] which presented a

Table 1. Safety, morbidity and mortality of major and minor hepatectomy for breast cancer liver metastases.

Study	Number of patients	Median age (years)	Period	Type of resection	Postoperative morbidity	Management of postoperative complications	Postoperative mortality	Ref.
Raab *et al.*	34	47	1983–1996	-	-	-	3%	[28]
Selzner *et al.*	17	48†	1987–1999	wr+segmentectomy – 10 Hemihepatectomy – 5	NR	NR	ARDS syndrome following BCNU chemo	[6]
Yashimoto *et al.*	25	51.3	1985–1998	RH-4 LH – 3 Extended LH– 4 Left segmentectomy – 1 SR– 13	NR	NR	0	[7]
Pocard *et al.*	52	47.07‡	1988–1997	RH – 15 LH – 5 Extended LH – 4 SR – 18	11.5% (6 patients) Four pleural effusions one ascites one postoperative hemorrhagic syndrome	One surgical reintervention for hemorrhagic syndrome	0	[15]
Maksan *et al.*	9	44	1984–1998	RH -1 LH –1 Segmental resection -7	No major complication		0	[26]
Elias *et al.*	54	49 years ± 5.2	1986–2001	RH – 20 Extended RH – 7 LH – 3 Extended LH – 2 SR – 12 WR– 12 Two patients underwent repeat hepatectomy	12.9% BL hematoma	Conservative management	0	[19]
Ercolani *et al.*	21 (out of 142 patients with NCNNM)	54.6 ± 11.4	1990–2003	83 curative resections for the lot of 142 patients MH >3 segments 41%	17 patients (20,5%)	2 patients/83 – relaparotomy for hemoperitoneum	0	[14]

†At the time of breast surgery.
‡At the time of primary breast diagnosis.
Major hepatectomies (>3 segments).
ARDS: Acute respiratory distress syndrome; BCNU: Carmustine ; BL: Bile leaks; LH: Left hepatectomy; MiH: Minor hepatectomies; PH: Postoperative haemorrhage; PO: Postoperatively; RH: Right hepatectomy; SR: Segmental resection; WI: Wound infections; WR: Wedge resection.

Table 1. Safety, morbidity and mortality of major and minor hepatectomy for breast cancer liver metastases (cont.).

Study	Number of patients	Median age (years)	Period	Type of resection	Postoperative morbidity	Management of postoperative complications	Postoperative mortality	Ref.
				WR – 13.3%				
				SR – 45.8%				
Vlastos *et al.*	31 patients	46	1991–2002	MH >3 segments – 14 patients MiH – 17 pts	NR	NR	0	[20]
Adam *et al.*	85 patients single center	47	1984–2004	MH >3 segments – 54 patients (64%)	22% (19 pts)	Percutaneous drainage for 10 patients infected intraabdominal collections	0	[4]
				MiH – 41 patients (36%)	- BL 7% Intra-abdominal infected fluid collections 2 patients (2%) Noninfected perihepatic collections 11 pts (13%) Postoperative hemorrhage 1 patient transient hepatic insufficiency – 1 pt 20 patients (24% general complications)	Urgent reoperation for postoperative hemorrhage		
Adam *et al.*	460 patients/1452 (32%)	53 range 10–87	1983–2004	MH (>2 segments)-55% - for the whole lot	Local morbidity – 14% General morbidity – 15%		Perioperative mortality (during the 2 months period following hepatectomy – 2.3%	[9]
Sakamoto *et al.*	34	51	1985–2003	Hemihepatectomies -15 patients Segmentectomies- 4 patients NA – 15	NR	NR	0	[24]
Lubrano *et al.*	16	54	1989–2004	MH 9 (>3 seg) MiH (<3 seg) - 7	6/16 BL-1 Subphrenic abscess -2 Urinary tract infection - 3	NR	0	[23]
Thelen *et al.*	39	NR	1988–2006	MH 20 patients (51%)	13% (5 patients) biliomas most frequently	NR	0	[25]

†At the time of breast surgery.

‡At the time of primary breast diagnosis.

Major hepatectomies (>3 segments).

ARDS: Acute respiratory distress syndrome; BCNU: Carmustine ; BL: Bile leaks; LH: Left hepatectomy; MiH: Minor hepatectomies; PH: Postoperative haemorrhage; PO: Postoperatively; RH: Right hepatectomy; SR: Segmental resection; WI: Wound infections; WR: Wedge resection.

Table 1. Safety, morbidity and mortality of major and minor hepatectomy for breast cancer liver metastases (cont.).

Study	Number of patients	Median age (years)	Period	Type of resection	Postoperative morbidity	Management of postoperative complications	Postoperative mortality	Ref.
				MiH19 patients (49%)				
Bockhorn *et al.*	26	55.2	1998–2007	RH – 6 patients LH– 1 patient Left trisegmentectomy - 4 Left lateral resection – 4 Sectorectomy - 11	30% four pleural effusion one WI one deep venous thrombosis one subphrenic abscess	2 patients (8%) required reoperation	8% (2 patients) within 30 days PO	
Caralt *et al.*	12	58.4	1988–2006	MH (>3 segments) 6 (50%)	2 patients (16.6%) – BL Bile duct stenosis	Hepatico-jejunostomy for the bile duct stenosis at 7 months after LR	0	[16]
Belda *et al.*	12 patients resected/21	48	1998–2008	58.3% MH	0	-	0	[29]
Hofmann *et al.*	41 resected/50	NR	1999–2008	54% MH	21%: -noninfected perihepatic fluid collection – 1 - wound complication -2 - BL -3 - transient liver insufficiency	- percutaneous drainage for BL	0	[10]
Van Walsum multicenter study	32	50	1991–2011	13 patients/32 MH	Intraoperative complications:	- one ileus	0	[12]
					-two iatrogenic lesions of the spleen – splenectomy - one patient – iatrogenic lesion of the left duct - stenting	- one pneumonia - two patients – pleural effusion - one patient – abdominal abscess - one patient – stenosis of the bile duct – ERC drainage		

†At the time of breast surgery.
‡At the time of primary breast diagnosis.
Major hepatectomies (>3 segments).
ARDS: Acute respiratory distress syndrome; BCNU: Carmustine ; BL: Bile leaks; LH: Left hepatectomy; MiH: Minor hepatectomies; PH: Postoperative haemorrhage; PO: Postoperatively; RH: Right hepatectomy; SR: Segmental resection; WI: Wound infections; WR: Wedge resection.

Table 1. Safety, morbidity and mortality of major and minor hepatectomy for breast cancer liver metastases (cont.).

Study	Number of patients	Median age (years)	Period	Type of resection	Postoperative morbidity	Management of postoperative complications	Postoperative mortality	Ref.
						-1 patient – BLERC drainage		
Abbott *et al.*	86	50% > 50†	1997–2010	MH (>3 segments) in 62% of patients	NR	-	0	[27]
Dittmar *et al.*	34/50	53	1997–2010	MH 23/34 patients	12 patients (24%) BL-3 pleural effusion-6 PH-1 wound dehiscence-2	NR	0	[22]
Kostov *et al.*	42	58.2	2001–2007	RH – 54.8%	15 patients (35.9%)	- laparotomy for intra-abdominal bleeding – one patient	one patient died within a month -MSOF	[11]
				Extended	inal bleeding -1	- biliary stenting and percutaneous drainage for BL 1 pt	- 60- and 90-day mortality were two patients (4.8%) each	
				RH - 2.4%	- BL – 1	- drainage for WI – two patients		
				Extended LH – 2.4	- WI-2	- percutaneous drainage for intra-abdominal collection – two patients		
				Lateral hepatectomy – 9.5%	- intra-abdominal collections – two patients	- renal dyalsis for renal failure – two patients		
				The rest of the patients underwent multiple segmentectomies	- hepatic insufficiency – two patients - renal failure – two patients - pulmonary infection – five patients			
Ehrl *et al.*	30	52‡	2002–2011	MH 37.9%	four patients (13.3%)	NR	one patient (3.3%)	[12]

†At the time of breast surgery.
‡At the time of primary breast diagnosis.
Major hepatectomies (>3 segments).
ARDS: Acute respiratory distress syndrome; BCNU: Carmustine ; BL: Bile leaks; LH: Left hepatectomy; MiH: Minor hepatectomies; PH: Postoperative haemorrhage; PO: Postoperatively; RH: Right hepatectomy; SR: Segmental resection; WI: Wound infections; WR: Wedge resection.

Table 1. Safety, morbidity and mortality of major and minor hepatectomy for breast cancer liver metastases (cont.).

Study	Number of patients	Median age (years)	Period	Type of resection	Postoperative morbidity	Management of postoperative complications	Postoperative mortality	Ref.
				MiH 62.1%	-PH – two patients - WI – one patient - urinary tract infection – one patient		- pulmonary embolism	
Bacalbasa *et al.*	43 resected/52	52	2002–2013	MiH 67% MH 33%	-BL – three patients - intra-abdominal abscess – two patients, -urinary tract infection – one patient WI – one patient	Conservative	0	[30]

†At the time of breast surgery.
‡At the time of primary breast diagnosis.
Major hepatectomies (>3 segments).
ARDS: Acute respiratory distress syndrome; BCNU: Carmustine ; BL: Bile leaks; LH: Left hepatectomy; MiH: Minor hepatectomies; PH: Postoperative haemorrhage; PO: Postoperatively; RH: Right hepatectomy; SR: Segmental resection; WI: Wound infections; WR: Wedge resection.

Table 2. Overall, 3- and 5-year survival after hepatectomy for breast cancer liver metastases.

Author	Median survival (months)	3-year survival (%)	5-year survival (%)	Ref.
Raab *et al.*	27	50	18.4	[28]
Selzner *et al.*	24	35	22 (17% disease free)	[6]
Yashimoto *et al*	34	71 (2 years survival)	27	[7]
Pocard *et al.*	42	65	NR	[15]
Makson *et al.*	NR	NR	51 (estimated)	[26]
Elias *et al.*	34	50	34	[19]
Ercolani *et al.*	40.3	53.9	24.6	[14]
Vlastos *et al.*	63	86 (2 years survival)	61	[20]
Adam *et al.*	32 (46 from the date of liver metastasis diagnosis)	NR	37% (41% from the date of liver metastases diagnosis)	[4]
Adam *et al.*	45	NR	41	[9]
Sakamoto *et al.*	36	52	21	[24]
Lubrano *et al.*	42	61	33	[23]
Thelen *et al.*	NR	50	42	[25]
Bockhorn *et al.*	NR	53	44	–
Caralt *et al.*	35.9	79	33	[16]
Belda *et al.*	33.8	NR	23	[29]
Hofmann *et al.*	58	68	48	[9]
Van Walsum *et al.*	55	WR	37	[12]
Abbott *et al.*	57	NR	NR	[27]
Dittmar *et al.*	36	NR	28	[22]
Kostov *et al*	43	64.1	38.5	[11]
Ehrl *et al.*	29	31	20,7	[13]
Bacalbasa *et al.*	32.2	74.42	58.14	[30]

NR: Not recorded; WR: Wedge resection.

group of 460 patients undergoing liver resection for BCLM out of a total of 1452 patients undergoing hepatectomies for noncolorectal nonneuroendocrine liver metastases (over 22 years).

However, most studies reported very low mortality rates after liver resection for BCLM, hepatectomy being considered an extremely safe procedure (Table 1).

The postoperative morbidity is reported to be less than 35%, consisting mainly in minor complications (pleural effusion, bile leak, haematoma, intra-abdominal infected or noninfected collections, bile duct stenosis, wound infection) that could be managed either by conservative treatment or mini-invasive methods: percutaneous [4,10,11] or endoscopic [11,12] drainage. Only occasionally reoperation was required, either for postoperative hemorrhage [4,11,13–15] or in a case of bile duct stenosis [16] (hepaticojejunostomy at 7 months after liver resection) (Table 1).

• Does liver resection bring survival benefit?

The median and 5-year survival rates (higher than 30 months and 30%, respectively – Table 2) reported by most authors presenting the results achieved by liver resection in patients liver only breast cancer metastases seem to be higher than those achieved by palliative oncologic treatment. However, there are at least two factors that may induce a bias toward a better survival in patients undergoing hepatectomy: all the studies presented were single-armed, comparing survival of liver resected patients with survival data available in the literature for patients with broader spectrum of metastatic breast cancer undergoing only systemic therapy; patients with metastatic breast cancer who underwent liver resection represent a selected group of patients with more favorable outcome features (limited number of liver metastases, absent or controlled extrahepatic metastatic disease). To better understand

the impact of these drawbacks on the interpretation of the results achieved by liver resection in different series published until now, we reviewed some studies, which (indirectly) addressed these issues.

In a case-control study published by Mariani *et al.* [17], 51 patients undergoing liver resection for BCLM (with or without concomitant bone metastases) were matched (by age, year of breast cancer diagnosis, interval between breast cancer diagnosis and liver metastasis, TNM stage, ER/PR status, breast cancer histology) with 51 unresected patients presenting similar metastatic spread; hepatectomy was not proposed to the patients from the latter group because their physicians were reluctant to accept the usefulness of liver resection. Thus, the study design ensured elimination of a selection bias between the surgically treated patients matched with the cohort of patients treated only by medical therapy. A statistically significant higher survival rate was demonstrated in the surgically resected patients over the group receiving systemic therapy alone (p value < 0.001).

However, the patients who underwent liver resection in the study of Adam *et al.* [4] presented a spectrum of disease which was significantly broader than in previously reported series [4,10,16,18–20], Thus, out of 85 patients resected for BCLM, 19 (22.3%) were treated (before hepatectomy) for locoregional recurrence following primary breast cancer operation, 16 (18.8%) presented extraabdominal metastases and 14 (16.4%) presented extrahepatic intraabdominal metastases at the time of hepatic resection. By an aggressive surgical approach, a complete resection of the metastatic burden was performed in about 50 patients. For the entire group of patients, the median and 5-year overall survival rates were 32 months and 37%, respectively, from the time of liver resection, and 46 months and 41%, respectively from the time of liver metastases diagnosis. These results confirm that, even in an eclectic group of patients (including more than 50% cases with extrahepatic disease – prior or concomitant with liver metastases), an aggressive approach (including hepatectomy, resection of extrahepatic disease and systemic treatment) could ensure long-term survival rates, obviously higher than those achieved by systemic therapy alone. Moreover, eight patients were still alive at more than 5 years following the first hepatectomy, and four patients at more than 10 years. Similar to this study, long-term survivors were reported in most series dealing with the liver resection for BCLM in contrast with the anecdotical reports of patients with BCLM treated by medical therapy who survived more than 5 years.

These results clearly depict that in selected patients with BCLM long-term survival rates could be provided especially when liver resection was integrated in the multimodal treatment.

A study published by Momiyama *et al.* has shown that repeated minor metastasectomy are superior to major liver resection regarding the influence of metastatic tumor growth or stromal recruitment. This experimental observation related to effect of liver resection type should be investigated in clinical settings [21].

• Prognostic factors

Size of the breast tumor

No one study revealed any association between primary tumor size (T category) and survival following liver resection for BCLM [4,15,18–20,22–25].

Nodal status at the time of diagnosis

The impact of the axillary nodes involvement (at the time of primary tumor resection) on the prognosis of patients undergoing hepatectomy for BCLM was evaluated in most series published until now. The presence of lymph node metastases has not statistically significant influence on patients' survival following liver resection in any one series. However, in the series presented by Pocard *et al.* [15], liver recurrence rate was statistically significantly higher in N1b-N2 patients (83%) than in N0-N1a patients (41%, p value = 0.021). Based on these observations, the most authors consider that nodal status does not represent a contraindication to liver resection in patients with resectable BCLM.

Disease-free interval between primary tumor resection & liver metastases diagnosis

Many authors considered that a longer disease-free interval from the time of primary tumor treatment to the liver metastases appearance could represent an indirect evidence of low aggressive tumor biology, being associated with a better survival rate following liver resection. These supposition was confirmed in few series who revealed that survival rates achieved by hepatectomy in patients developing BCLM at more than 1 year after primary tumor treatment were statistically significantly higher than in patients whose metastases were diagnosed in the first year

following primary tumor resection [10,13,18,26]. Similar results were reported by Abbott *et al.* [27] in patients developing liver metastases at more than 2 years after breast cancer treatment and Pocard *et al.* [15] for patients with a disease-free interval longer than 48 months.

However, other studies failed to demonstrate that the disease-free interval from the primary tumor diagnosis to the liver metastases development correlates with statistically significant survival benefit after liver resection [4,16,19,20,23,24].

Thus, based on currently available data, the disease-free interval between primary tumor treatment and liver metastases development could be seen as a prognostic factor, but the decision of liver resection could not be reliably based on this factor alone [4].

Number & diameter of liver metastases

Unlike the patients presenting CLMs, whose survival correlates with number of lesions, in patients presenting liver metastases from breast cancer, most studies failed to find any correlation between number (and size) of BCLM and survival rates following hepatectomy. The only paper finding the number of BCLM as a significant independent factor of survival (p value = 0.04) was published in 2008 by Lubrano *et al.* [23] including 16 patients only. Due to the small sample size, the results should be seen with caution, and most authors consider that liver resection should not be ruled out based on the number of metastases only, unless the complete resection of liver metastases could not be technically performed.

Resection margins

The best survival results were achieved by R0 resections in most papers presented [4,10,22,25,27] Hoffmann *et al.* [10] revealing that patients undergoing R1/R2 resections were six-times more likely to die than patients with R0 liver resection.

However, in the series of Adam *et al.* [4] the survival difference between patients undergoing R0 versus R1 liver resection was minimal (42 and 41%, respectively, at 5 years following liver metastases diagnosis). In contrast, in patients undergoing R2 liver resections, the 5-year overall survival rate was 10%, suggesting that hepatectomy should be offered only to the patients with macroscopically completely resectable BCLM (based on the preoperative imaging and intraoperative assessment) [4].

Primary breast tumor hormone receptor status & molecular classification

Many studies revealed a favorable correlation between the positive status of hormone receptors (mainly estrogen receptors) and survival following liver resection.

Thus, in the study of Elias *et al.* [19], the relative risk of deaths was 3.5-fold increased when hormone receptors were negative. Van Walsum *et al.* [12] identified estrogen-positive receptors as a significant factor for long-term survival. Abbott *et al.* [27] found that estrogen receptor negative primary tumors are associated with decreased overall survival.

Several other studies [4,15,18,20,24,25] did not find any correlation between hormone receptor status and survival.

These results suggest that, although the negative status of hormone receptors could not represent definitive criteria to preclude liver resection, it represents an important predictor of poor survival after resection of BCLM.

According to the new molecular classification of the breast cancer, it is important to establish which breast tumor are of luminal type, since hormone receptor status is of overwhelming importance in outcome and indications for hepatic resection in BCLM. Thus, molecular subtype-specific predictors may help, in association with other factors to identify preoperatively which patients are more likely to benefit from metastasectomy.

Response to chemotherapy

As it was already revealed in patients with CLMs, the progression of liver disease during preoperative chemotherapy is an important prognostic factor (the 5-year survival rates of patients whose CLMs progressed during preoperative systemic treatment was only 8%, while patients whose metastases were stable or decreased under chemotherapy harbored a statistically significant better prognosis – more than 30% survived at 5 years postoperatively). Adam *et al.* [4] revealed, in their series, that in patients with BCLM, the situation seems to be somehow different: although no one patient with BCLM that progressed under preoperative systemic treatment was alive at 5 years, it was observed a statistically significant lower 5-year survival rate in patients with stable disease than those achieved by hepatectomy in patients who had an objective response to preoperative systemic treatment. Based on these findings, the

authors recommend to assess thoroughly the response to prehepatectomy chemotherapy when selecting patients with BCLM for hepatic resection.

Presence of extrahepatic metastases

In their series, Adam *et al.* [4] and Thelen *et al.* [25] found that presence of extrahepatic disease has a negative impact on survival.

Although few series failed to reveal a survival difference following liver resection in patients presenting liver only BCLM and those with hepatic and extrahepatic metastases [6,7,10,12,22], liver resection in patients with BCLM and extrahepatic disease does not meet unanimous consent. However, some authors consider that among patients with extrahepatic disease may be identified a subset of patients who could enjoy a survival benefit from hepatectomy, the best results being achieved in patients with either extrahepatic disease resected or in remission prior to hepatectomy [4]. Therefore, an aggressive oncosurgical treatment could be considered even in patients with stable extra-abdominal metastases or in patients with low-volume resectable intra-abdominal disease.

Conclusion & future perspective

From the experience gathered in the studies published so far, the best candidate according to the current croquis of indications should have good performance status, solitary or limited number of liver metastases, evaluated as completely resectable without extrahepatic metastatic disease or limited and well-controlled extrahepatic disease, with a primary tumor positive for hormone receptors and a large disease-free interval between surgery for the primary tumor and diagnosis of the liver recurrence.

It must be said, however, that long-term survival in limited number of patients who do not respect these criteria has been observed, so further study in larger series of patients is necessary.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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