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RESEARCH ARTICLE

Resection of liver metastases from breast cancer: a multicentre analysis

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Abstract

Background Surgery is becoming more practical and effective than conservative treatment in improving the poor outcomes of patients with breast cancer liver metastasis (BCLM). However, there is no generally acknowledged set of standards for identifying BCLM candidates who will benefit from surgery.

Methods Between January 2011 and September 2018, 67 female BCLM patients who underwent partial hepatectomy were selected for analysis in the present study. Prognostic factors after hepatectomy were determined. Univariate and multivariate analyses were performed to identify predictors of overall survival (OS) and intrahepatic recurrence-free survival (IHRFS).

Results The 1-, 3- and 5-year OS of patients treated with surgery was 93.5%, 73.7% and 32.2%, respectively, with a median survival time of 57.59 months. The Pringle manoeuvre [hazard radio (HR) = 0.117, 95% CI0.015–0.942, $p = 0.044$] and an increased interval between breast surgery and BCLM diagnosis (HR0.178, 95% CI 0.037–0.869, $p = 0.033$) independently predicted improved overall survival for BCLM patients. The 1-, 2- and 3-year IHRFS of patients who underwent surgery was 62.8, 32.6% and 10.9%, respectively, with a median intrahepatic recurrence-free survival time of 13.47 months. Moderately differentiated tumours (HR 0.259, 95% CI 0.078–0.857, $p = 0.027$) and the development of liver metastasis more than 2 years after breast surgery (HR 0.270, 95% CI 0.108–0.675, $p = 0.005$) might be predictors of increased IHRFS.

Conclusions An interval of more than 2 years between breast cancer surgery and liver metastasis seems to be an indication of liver surgery in BCLM patients. The Pringle manoeuvre and moderately differentiated tumours are potential predictors associated with OS and IHRFS, respectively, as benefits from liver resection. Studies with increased sample sizes are warranted to validate our results.

Keywords Breast cancer liver metastasis · Liver resection · Survival

Introduction

Breast cancer is the largest contributor to mortality from malignant disease among women worldwide[1]. It is estimated that approximately 2.1 million female breast cancer cases were newly diagnosed in 2018[2]. Approximately,

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25–40% of breast cancers are reported to have remote metastasis, 5% of which are classified as advanced disease at the time of initial diagnosis, leading to poor overall survival[3]. The liver is the third most common distant metastatic site after bone and lung, accounting for 7.3% of all breast cancer metastases[4]. If untreated, patients with breast cancer and liver metastasis (BCLM) have a median survival time of only 4–8 months. Despite significant achievements in systemic treatment, such as chemotherapy, antiangiogenic treatment and targeted therapy (e.g. anti-hormonal therapy for patients with luminal breast cancer and Herceptin for HER-2-positive patients), the prognosis of BCLM treated with systemic methods is still poor, with a median survival time of only 25 months[5].

Considering the poor results achieved by systemic treatment, other types of effective treatment such as surgery are urgently needed. Surgery for stage IV carcinomas such as colorectal liver metastasis has been demonstrated to be a potentially curative treatment[6], but there is no widely accepted consensus on surgical treatment for BCLM. The 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) state that local therapy should be proposed only in very selected cases of good performance status, with limited liver involvement, no extrahepatic lesions, and demonstrated control of the disease after adequate systemic therapy[7], while the NCCN Guidelines do not mention liver resection as an option for BCLM[8]. Criteria for selecting the appropriate surgery candidates for BCLM still need to be defined.

Because isolated liver metastasis is relatively rare in breast cancer, occurring in approximately 10% of BCLM cases, the role of surgery remains controversial, and local treatment for BCLM is rarely proposed[5]. Although no randomized controlled trials have performed to confirm whether BCLM might benefit from resection of limited metastatic disease, prolonged survival was observed and reported in highly selected patients by several retrospective studies[9–15]. However, because of the diverse results and limited sample sizes of these studies, there is still no consensus on the selection of BCLM patients who may benefit from liver resection. Moreover, few studies have been performed with patients from Asia. With patients derived from multiple centres, this study aimed to provide further evidence to explore which patients will benefit from surgery.

Patients and methods

Study population and ethics

Between January 2011 and September 2018, we included consecutive female patients with pathologically confirmed BCLM who underwent partial radical hepatectomy at Fudan University Shanghai Cancer Center, Zhongshan Hospital or Eastern Hepatobiliary Surgery Hospital. The patients were derived from our retrospectively maintained institutional database, and each medical record was reviewed by two investigators independently to update clinical and pathological data. Before surgery, all patients signed informed consent to have their clinical information used for research purposes. The present study was approved by the Institutional Ethics Review Board of each centre.

Preoperative workup

We retrieved demographic information, tumour-specific variables, clinical outcomes, and imaging characteristics for review. All of these patients were discussed by a multidisciplinary team (MDT) and considered to be suitable for hepatectomy. Patients who met the following criteria received hepatectomy: (1) good general condition and enough liver function (Child–Pugh Score level A), (2) resectable liver metastasis and (3) no extrahepatic metastases or extrahepatic metastasis has been stabilized using radiotherapy or local resection. Hormone receptor positivity was defined as ER (estrogen receptor) and/or PR (progesterone receptor) positivity. HER2-positive results were defined as IHC $\geq 3+$ or FISH-based HER2 gene amplification.

Hepatic resection

Liver resection was performed according to the standard guidelines, with the aim of achieving R0 resection using a liver-sparing technique involving an ultrasonic scalpel and bipolar coagulation. Intra-operative ultrasound was carried out to define foci missed by the imaging data. The major hepatic resections were defined as those in which 3 or more Couinaud segments were removed[16, 17]. Intermittent selective vascular clamping or the Pringle manoeuvre was used, if necessary, to control intra-operative blood loss. Resected tumours were sent to the pathology department for further examination.

Postoperative outcome and follow-up

Postoperative mortality was defined as death within the first 30 days after surgery. Postoperative complication scoring was evaluated according to the Clavien–Dindo classification of surgical complications. Severe complications were defined as those $\geq$ grade III. Routine laboratory tests, tumour markers, and imaging evaluations (CT scan and/or MRI) were conducted one month after surgery and every 3 months thereafter.

Statistical analyses

Statistical analyses were performed using the IBM SPSS 22.0 software. Overall survival (OS) time was defined as the time between liver surgery and death, while intrahepatic recurrence-free survival (IHRFS) time was defined as the time between liver surgery and recurrence in the liver. Kaplan–Meier analysis and the Cox proportional hazards regression model were used to perform survival analysis. Multivariate analysis was performed to adjust the influence of clinical factors on outcome using the Cox model. A two-tailed p value less than 0.05 was considered statistically significant.

Results

The demographic characteristics and clinical features of the patients are shown in Table 1. A total of 73 female patients who underwent hepatic resection for BCLM between January 2011 and September 2018 were initially selected according to our defined criterion. Due to the missing information on OS ($n=6$) and IHRFS ($n=16$), a total of 67 and 57 patients were finally included for OS and IHRFS analysis, respectively. Only one patient had synchronous liver metastasis of breast cancer. None of the patients died within 30 days or 90 days after the surgery, and no in-hospital deaths occurred.

Overall survival after hepatic resection

Factors associated with OS by univariate and multivariate Cox analyses are listed in Table 2. The 1-, 3- and 5-year OS for BCLM patients treated with surgery was 93.5%, 73.7% and 32.2%, with a median survival time of 57.59 months (Fig. 1a). Patients with hormone receptor-positive primary tumours had a median OS of 57.59 months, while patients with primary tumours negative for both ER and PR had a median OS of only 35.15 months ($p=0.001$, Fig. 1b). Compared with a longer interval (> 2 years), a shorter interval (≦2 years) between the breast surgery and diagnosis of BCLM was associated with poor OS (for interval ≦2 *vs.* > 2 years, median OS = 42.81 *vs.* 57.59 months, $p=0.017$, Fig. 1c). Furthermore, patients who received the Pringle manoeuvre during surgery had a longer OS than those who did not, with a median OS increase from 42.81 to 57.59 months ($p=0.016$, Fig. 1d).

Multivariate analysis showed a significant trend towards better survival for patients with > 2-year intervals between breast surgery and BCLM diagnosis [hazard ratio (HR) 0.178; 95% CI 0.037–0.869, $p=0.033$], which was consistent with the Kaplan–Meier analysis. In line with Kaplan–Meier analysis, hepatic portal triad clamping during surgery was an independent predictor for decreased death risk for BCLM patients (HR 0.117; 95% CI 0.015–0.942,

Table 1 Characteristics of patients

Characteristics	Mean ± SD/No	%
Epidemiology		
Age at liver metastasis diagnosis (y)	51.2 ± 10.7	
Hepatitis B carrier (Yes/ No)	4/63	6.0/94.0
Cirrhosis (Yes/ No)	2/65	3.0/97.0
Steatohepatitis (Yes/ No)	35/32	52.2/47.8
Characteristics of breast cancer		
Histology		
Ductal carcinoma	43	64.1
Lobular carcinoma	19	28.4
Neuroendocrine carcinoma	3	4.5
Mucinous adenocarcinoma	2	3.0
Hormone receptor status (Positive/ Negative)	44/15	74.6/25.4
HER2 status (Positive/ Negative)	14/40	26.0/74.0
TNM stage of breast cancer		
Ⅰ	8	11.9
Ⅱ	46	68.7
Ⅲ	12	17.9
Ⅳ	1	1.5
Characteristics of breast cancer liver metastases		
Interval between breast surgery and liver metastasis diagnosis (m)	51.21 ± 10.74	
Maximum diameter (cm)	4.20 ± 2.17	
Number of metastases (solitary/multiple)	43/24	64.2/35.8
Tumour distribution (unilobar/bilobar)	52/15	77.6/22.4
Extrahepatic metastases(yes/no)	14/53	20.9/79.1
Differentiation (moderate/low)	16/17	48.5/51.5
Treatments of liver metastases		
Neoadjuvant treatments (Yes/ No)	26/41	38.8/61.2
Laparoscopic (Yes/ No)	21/46	31.3/68.7
Major/minor hepatectomy	32/35	47.8/52.2
Anatomical/non-anatomical hepatectomy	42/25	62.7/37.3
Hepatic portal triad clamping (Yes/ No)	35/32	52.2/47.8
Surgical margin (R0/ R1)	64/3	95.5/4.5
Clavien–Dindo grades		
Ⅰ	53	79.1
Ⅱ	7	10.4
Ⅲ	4	6.0
Ⅳ	3	4.5

There were 59 patients with hormone receptor data, 54 patients with HER2 data, and 33 patients with tumour differentiation data

Table 2 Univariate and multivariate analysis of overall survival in patients who underwent a partial hepatectomy for BCLM

Variables	No.	Median OS (m)	Univariate analysis	Multivariate analysis		
			P value	*P* value	HR	95% CI
Epidemiology						
Age at liver metastasis diagnosis (y)			0.410			
≦50	29	NS				
>50	38	57.59				
Hepatitis B carrier			0.346			
Positive	4	23.43				
Negative	63	57.59				
Cirrhosis			0.625			
Positive	2	NS				
Negative	65	NS				
Steatohepatitis			0.669			
Positive	35	57.59				
Negative	32	NS				
Characteristics of breast cancer						
Hormone receptor status (Positive/Negative)			0.001*			
Positive	44	57.59		0.171	0.006	0.000–9.347
Negative	15	35.15			1.000	
HER2 status (Positive/ Negative)			0.552			
Positive	14	57.59				
Negative	40	42.81				
T stage of breast cancer			0.506			
T1–T2	60	57.59				
T3–T4	7	NS				
Axillary lymph node metastasis			0.550			
Positive	41	NS				
Negative	26	57.59				
Characteristics of breast cancer liver metastasis						
Interval between breast surgery and BCLM diagnosis (m)			0.017*			
≦24	30	42.81			1.000	
>24	37	57.59		0.033*	0.178	0.037–0.869
Maximum diameter (cm)			0.477			
≦3	24	NS				
>3	43	57.59				
Number of metastasis			0.667			
Solitary	43	NS				
Multiple	24	57.59				
Tumour distribution			0.273			
Unilobar	52	NS				
Bilobar	15	57.59				
Extrahepatic metastasis			0.492			
Yes	14	35.15				
No	53	57.59				
Tumour differentiation			0.875			
Moderate	16	57.59				
Poor	17	NS				
Treatments of liver metastasis						
Neoadjuvant treatments			0.119			
Present	26	NS				

Table 2 (continued)

Variables	No.	Median OS (m)	Univariate analysis	Multivariate analysis		
			P value	*P* value	HR	95% CI
Absent	41	57.59				
Laparoscopic			0.466			
Yes	21	35.15				
No	46	57.59				
Hepatectomy			0.467			
Major	32	57.59				
Minor	35	42.81				
Hepatectomy			0.149			
Anatomical	42	57.59				
Non-anatomical	25	NS				
Hepatic portal triad clamping			0.016*			
Yes	35	57.59		0.044*	0.117	0.015–0.942
No	32	42.81			1.000	
Surgical margin			NS			
R0	64	NS				
R1	3	NS				

$n=67$, there were 59 patients with hormone receptor data, 54 patients with HER2 data, and 33 patients with tumour differentiation data

NS no specified

*$p<0.05$

$p=0.044$). Multivariate analysis was completed with a Cox proportional hazards model with adjustment for cirrhosis status, steatohepatitis status, age at liver metastasis diagnosis, tumour distribution, extrahepatic metastasis and status of axillary lymph nodes.

Intrahepatic recurrence-free survival after hepatic resection

Factors associated with IHRFS by univariate and multivariate Cox analyses are listed in Table 3. The 1-, 2- and 3-year IHRFS for BCLM patients treated with surgery was 62.8%, 32.6% and 10.9%, respectively, with median IHRFS time of 13.47 months (Fig. 2a). The median IHRFS was 7.20 versus 13.50 months in the comparison of laparoscopic liver resection versus open surgery group ($p=0.045$, Fig. 2b). Similar to the OS analysis, the interval between breast surgery and liver metastasis diagnosis was also predictive of IHRFS, with 7.20 months versus 20.83 months in the comparison of BCLM patients with ≦2-year intervals versus those with > 2-year intervals ($p=0.032$, Fig. 2c). We also concluded that BCLM patients with moderately differentiated tumours tended to have better IHRFS than those with poorly differentiated tumours (20.83 versus 8.97 months, $p=0.040$, Fig. 2d), as indicated by the Kaplan–Meier analysis.

Multivariate Cox analysis showed that a longer interval (> 2 years) between the breast surgery and diagnosis of BCLM was associated with a decreased recurrence risk (HR 0.270; 95% CI 0.108–0.675, $p=0.005$). Interestingly, multivariate Cox analysis indicated that moderately differentiated tumours were associated with decreased recurrence risk (HR 0.259, 95% CI 0.078–0.857, $p=0.027$) after liver resection. BCLM patients with open surgery had a boundary trend towards decreased recurrence risk (HR 0.410, 95% CI 0.167–1.009, $p=0.052$) when compared with laparoscopic surgery, but the results with borderline significance need to be validated in an increased sample size.

Discussion

Metastatic breast cancer is characterized by a systemic disease with a poor prognosis. Traditionally, surgery was considered to have limited utility in the treatment of these patients[18]. Although advanced achievement was acquired in systemic treatment (e.g. chemotherapy, hormonal therapy, and biological therapy), the survival of breast cancer patients with liver metastasis remains poor[19]. Considering the poor results achieved by systemic treatment, other types of effective treatment such as surgery need to be identified. Given the lack of consensus on liver resection for BCLM patients to date, our retrospective multicentre analysis might provide useful evidence for clinical decisions. Moreover, consistent with previous investigations[9], our data demonstrated that the 5-year OS for the BCLM patient cohort was as high as

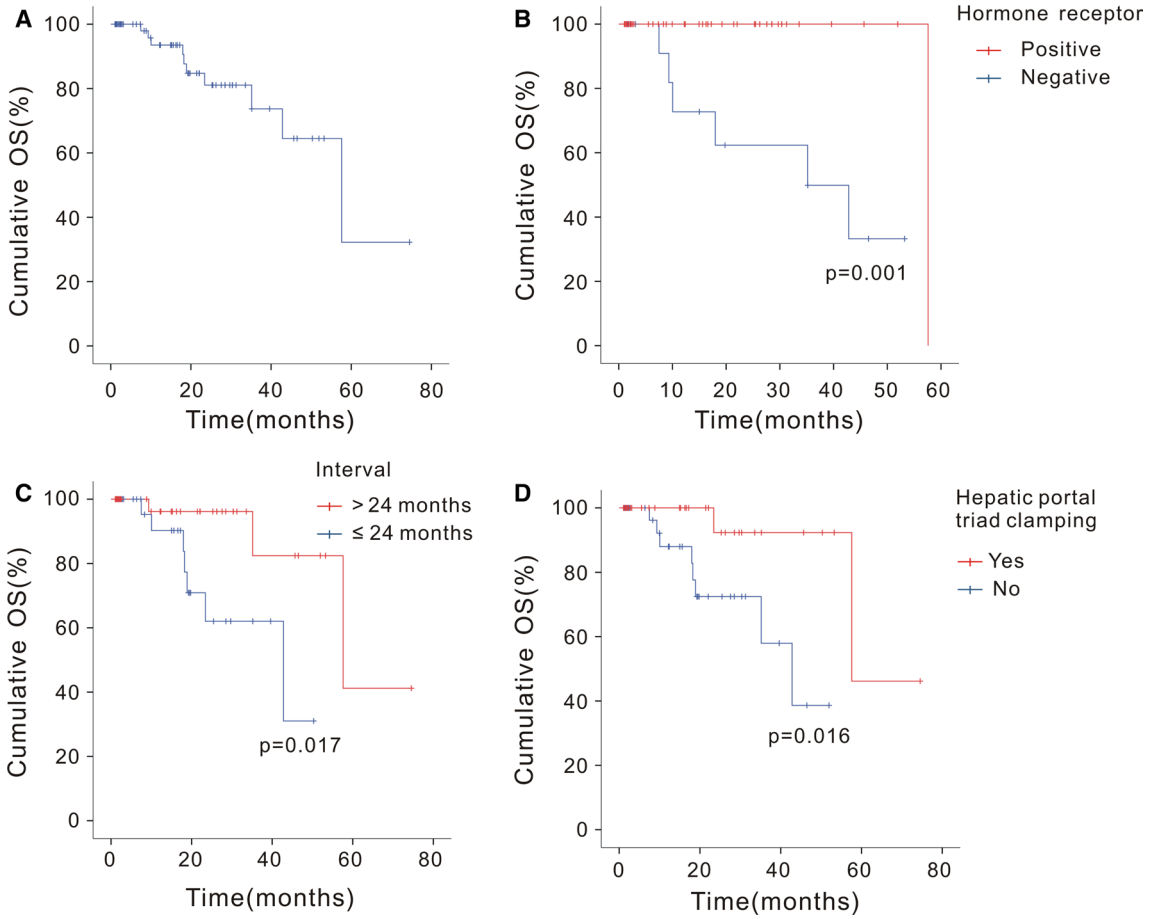

Fig. 1 **a** Overall survival of all patients from the time of hepatic resection. **b** Overall survival based on hormone receptor status. **c** Overall survival based on the interval between breast surgery and liver metastasis diagnosis. **d** Overall survival based on the use of hepatic portal triad clamping

32.2%, with a median survival time of 57.59 months, indicating that surgery was an effective way to improve prognosis for selected patients. Beyond primary sites, distant liver metastasis also presented substantial heterogeneity. Therefore, it is crucial to verify the features of suitable candidates for surgery.

Several studies have been performed on this topic, but the results are inconsistent to some extent. Hoffmann et al. [11] discovered that patients who developed liver metastases within the first 12 months had a shorter OS than those who suffered metastasis disease within a longer interval, while Caralt et al.[10] and Pocard et al.[20] noted that a 2-year interval from diagnosis to liver metastasis was the optimal cutoff discriminating the outcome of the patients well. Meanwhile, Selzner et al.[21] and Treska et al.[22] found that a disease-free interval between the treatment of the breast tumour and the diagnosis of liver metastasis shorter than 1 year or 4 years was a negative independent predictor of both OS and IHRFS, respectively. Our results showed that a relatively long interval (> 2 years) between breast surgery and liver metastases was a predictor of both OS and IHRFS benefits from liver surgery, which was consistent with previous studies. The interval between breast surgery and liver metastases might be a reflection of the metastatic ability of primary tumours, leading to varied IHRFS and OS after liver resection, as indicated by our data. Another important factor affecting the results of surgical treatment of BCLMs is hormone receptor status. Abbott et al.[13], Treska et al. [23], and Kostov et al.[24] noticed relatively poor results in patients whose tumours were both ER and PR negative, but others, such as Adam et al.[9], reported no role of hormone receptor status in predicting postoperative outcomes. In our study, the association of both ER- negative status and PR-negative status in the primary tumour with poor OS were observed only in univariate analysis and were not significant after adjustment for other clinical factors.

It is worth noting that we identified something no previous work has examined: the use of the Pringle manoeuvre increased the survival substantially and laparoscopic procedure could decrease the IHRFS. The Pringle manoeuvre,

Table 3 Univariate and multivariate analysis of intrahepatic recurrence-free survival in patients who underwent a partial hepatectomy for BCLM

Variables	No.	Median IHRFS (m)	Univariate analysis	Multivariate analysis		
			P value	*P* value	HR	95% CI
Epidemiology						
Age at liver metastasis diagnosis (years)			0.804			
≦50	24	13.73				
>50	33	13.18				
Hepatitis B carrier			0.158			
Positive	4	NS				
Negative	53	NS				
Cirrhosis			0.345			
Positive	2	NS				
Negative	55	NS				
Steatohepatitis			0.197			
Positive	31	13.47				
Negative	26	13.50				
Characteristics of breast cancer						
Hormone receptor status (Positive/ negative)			0.354			
Positive	40	13.73				
Negative	10	6.74				
HER2 status (positive/ negative)			0.419			
Positive	13	20.83				
Negative	35	13.27				
T stage of breast cancer			0.845			
T1–T2	50	13.47				
T3–T4	7	6.97				
Axillary lymph node metastasis			0.109			
Positive	34	12.12				
Negative	23	20.83				
Characteristics of breast cancer liver metastasis						
Interval between breast surgery and BCLM diagnosis (m)			0.032*			
≦24	24	7.20			1.000	
>24	33	20.83		0.005*	0.270	0.108–0.675
Maximum diameter (cm)			0.416			
≦3	21	13.73				
>3	36	12.12				
Number of metastasis			0.280			
Solitary	37	13.73				
Multiple	20	13.18				
Tumour distribution			0.996			
Unilobar	44	13.47				
Bilobar	13	20.83				
Extrahepatic metastasis			0.713			
Yes	14	13.18				
No	43	13.50				
Tumour differentiation			0.040*			
Moderate	12	20.83		0.027*	0.259	0.078–0.857
Poor	17	8.97			1.000	
Treatments of liver metastasis						
Neoadjuvant treatments			0.956			
Present	26	13.50				

Table 3 (continued)

Variables	No.	Median IHRFS (m)	Univariate analysis	Multivariate analysis		
			P value	*P* value	HR	95% CI
Absent	31	13.27				
Laparoscopic			0.045*			
Yes	20	7.20			1.000	
No	37	13.50		0.052	0.410	0.167–1.009
Hepatectomy			0.473			
Major	27	12.12				
Minor	30	13.73				
Hepatectomy			0.435			
Anatomical	36	13.18				
Non-anatomical	21	13.50				
Hepatic portal triad clamping			0.282			
Yes	31	20.83				
No	26	13.47				
Surgical margin			0.444			
R0	54	NS				
R1	3	NS				

$n = 57$, there were 50 patients with hormone receptor data, 48 patients with HER2 data, and 29 patients with tumour differentiation data

NS no specified

*$p < 0.05$

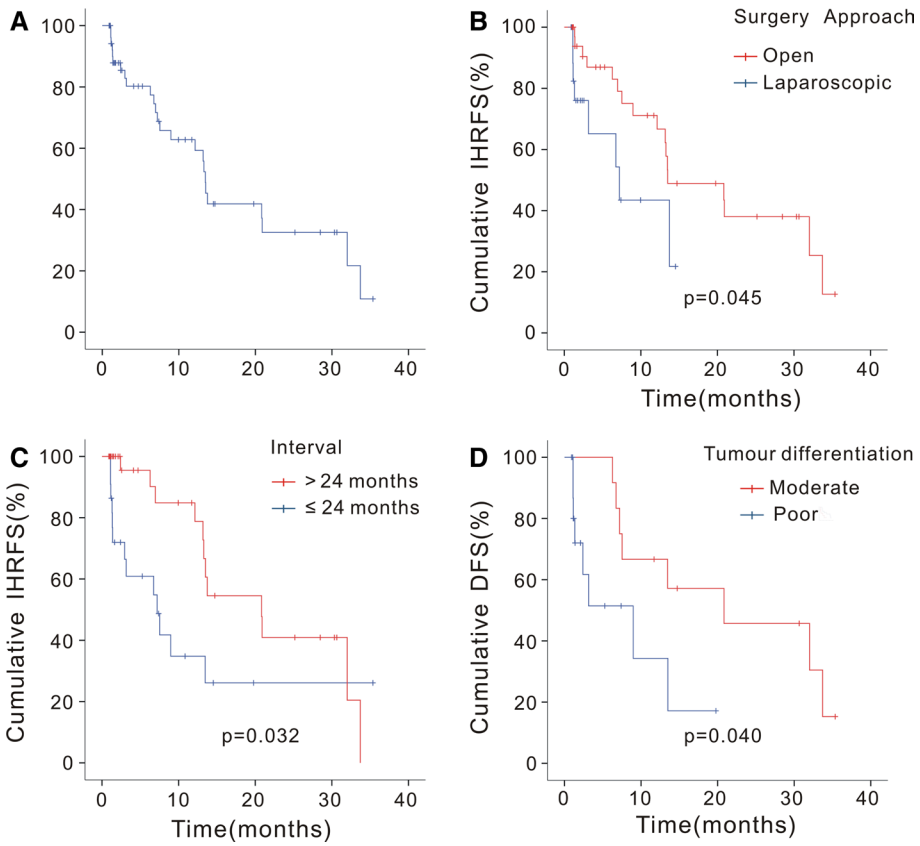

Fig. 2 **a** Intrahepatic recurrence-free survival of all patients from the time of hepatic resection. **b** Intrahepatic recurrence-free survival based on the type of surgical approach (open or laparoscopic). **c** Intrahepatic recurrence-free survival based on the interval between breast surgery and liver metastasis diagnosis. **d** Intrahepatic recurrence-free survival based on tumour differentiation

introduced to help control bleeding during hepatectomy[25, 26], may cause hypoxia in liver tissues but reduces haemorrhage enormously. Our results indicated that patients who received the Pringle manoeuvre during surgery had a longer OS, with a median OS increase from 42.81 to 57.59 months, compared with those without this procedure. The Pringle manoeuvre could simplify the procedure of liver resection, shorten operation time and, most importantly, minimize intra-operative bleeding, allowing the surgeon to remove metastatic lesions with the lowest possible risk of postoperative complications. Moreover, we found no difference in OS between laparoscopic and open surgery. Laparoscopic liver resections are safe and show more favourable outcomes than open liver surgery in selected patients[27], and in our centre, laparoscopic surgery accounted for more than 40% of cases. However, in BCLM patients, especially those with multiple metastases, it is crucial to explore the whole liver during surgery to ensure that no metastasis lesions have been missed. As a result, the more thorough inspection permitted by open surgery might be a reason for the lower recurrence risk in BCLM patients who received hepatectomy. Poorly differentiated malignancies were supposed to have a worse prognosis than well- and moderately differentiated malignancies. There were no well-differentiated tumours among the samples, and we found that patients with moderately differentiated tumours tended to have later recurrence than those with poorly differentiated tumours, while no significant difference was observed in OS between the two groups. It is reasonable to believe that poorly differentiated BCLMs were inclined to relapse early due to the high degree of malignancy. However, in the long run, it did not affect the OS, which means that further efforts will be necessary to investigate the nature of the benefit.

This study has some shortcomings: First, the missing data on IHRFS and OS decreased the sample size and the statistical power in survival analysis; second, the missing information on other clinical variables may limit the clinical applicability of the results; third, bias may have been introduced by the retrospective design of the present study.

Conclusion

Hepatectomy may lead to an improved outcome for a certain type of BCLM patient. Patients with a longer interval (> 2 years) between breast surgery and diagnosis of BCLM seem to be more suitable for surgery. Moderately differentiated tumours were also a predictor of benefit from surgery in terms of prolonged OS and PFS. Hepatic portal triad clamping, if necessary, is recommended to improve the outcome of BCLM patients. Because of the limitations of the present study, studies with increased sample sizes and prospective design are needed to further validate our results.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained for all patients before surgery, and the Fudan University Shanghai Cancer Center, Zhongshan Hospital or Eastern Hepatobiliary Surgery Hospital Ethics Committee gave ethical approval to perform this study.

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