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Survival analysis of breast cancer liver metastasis treated by hepatectomy: A propensity score analysis for Chinese women in Hong Kong

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ABSTRACT

Background: Survival of patients with breast cancer liver metastasis is very poor. This study aimed to analyze the survival outcome of hepatectomy for this patient population.

Methods: From January 1995 to December 2014, 2522 patients with liver cancer received hepatectomy at our hospital. Twenty-one of them, all female, received the operation for breast cancer liver metastasis. Performance was compared with patients with colorectal liver metastasis treated with hepatectomy after propensity score analysis in a ratio of 1:3.

Results: Twenty-one patients received hepatectomy for breast cancer. After propensity score matching, 63 patients who had hepatectomy for colorectal cancer were selected for comparison. There was no significant difference in immediate or short-term outcomes between the two groups of patients in terms of operative time, blood loss and surgical morbidities. All patients with breast cancer had R0 resection. No hospital death occurred. After hepatectomy, the 1-, 3- and 5-year overall survival rates were 100.0%, 58.9% and 58.9% respectively in patients with breast cancer. The 1-, 3- and 5-year overall survival rates were 95.0%, 57.2% and 39.7% respectively in patients with colorectal cancer ($P=0.572$). On multivariate analysis, triple negative status was the only independent poor prognostic factor in breast cancer liver metastasis (OR = 6.411; 95% CI: 1.351–30.435; $P=0.019$).

Conclusions: Hepatectomy is a safe and effective way of treating breast cancer liver metastasis at experienced centers where multidisciplinary adjuvant treatments are available. It can be considered more frequently as part of the multidisciplinary care for this patient population.

Introduction

The incidence of breast cancer has been increasing. There are around 200000 new cases per year in the USA [1]. The incidence in Asia is also rising [2,3]. The rate of breast cancer peaks at an age between 45 and 55 years in the Caucasian population in the USA but at an age of 40 years in Chinese women [4]. It is the most common cancer in women and the second most common cause of cancer-related deaths. Approximately 15% of breast cancer patients will develop liver metastasis [5–7]. Despite the development of more effective chemotherapeutic agents (e.g. anthracyclines and taxanes) and antihormonal therapies (e.g. aromatase inhibitors and directed biologic agents like trastuzumab), the overall survival of patients with stage IV breast cancer remains very poor [8–10]. The reported survival durations of patients with stage IV breast cancer after multimodality treatment range from 3 to 20 months [2,11,12].

Hepatectomy for breast cancer liver metastasis (BCLM) has not been advocated, and only several small-scale studies have shown that a survival benefit was gained with surgical treatment [13,14]. Patients with BCLM are seldom referred for surgery evaluation since stage IV breast cancer is generally perceived as a systemic disease with very poor prognosis, but in fact, hepatectomy performed by experienced hepatobiliary surgeons entails low rates of morbidity and mortality in patients without cirrhosis [15]. However, the issue remains controversial amid hepatobiliary surgeons and oncologists.

Currently there has not been a lot of evidence on hepatectomy for BCLM. On the contrary, hepatectomy for colorectal liver metastasis (CRLM) has become a well-established treatment proven to

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Table 1
Baseline demographic data of patients with CRLM and BCLM.

Variables	CRLM ($n=63$)	BCLM ($n=21$)	P value
Age (yr)	59 (27–83)	45 (35–65)	0.080
Female	63 (100%)	21 (100%)	–
Hepatitis B virus infection	1 (1.6%)	2 (9.5%)	0.055
Hepatitis C virus infection	6 (9.5%)	5 (23.8%)	0.191
Comorbidity	22 (34.9%)	5 (23.8%)	0.345
Cardiovascular	19 (30.2%)	2 (9.5%)	0.059
Pulmonary	3 (4.8%)	2 (9.5%)	0.790
Diabetes mellitus	7 (11.1%)	1 (4.8%)	0.668
Gastrointestinal	5 (7.9%)	2 (9.5%)	1.000
Child-pugh class A	63 (100%)	21 (100%)	–
Carcinoembryonic antigen (ng/mL)	12 (0.7–680)	5.1 (1.2–321)	**0.041**
Total bilirubin (μmol/L)	8 (3–19)	6 (3–13)	**<0.001**
Albumin (g/L)	42 (31–49)	43 (38–48)	0.133
Platelet ($\times10^9$/L)	234 (117–479)	209 (132–413)	0.077
International normalized ratio	1 (0.9–1.3)	1 (0.8–1.0)	0.091
Creatinine (mmol/L)	66 (28–171)	66 (43–92)	0.355
Hemoglobin (g/dL)	12.5 (8.5–15.2)	12.5 (9.5–14.4)	0.402
AST (U/L)	24 (10–94)	25 (11–45)	0.463
ALT (U/L)	17 (8–69)	19 (9–45)	0.453
Prothrombin time (s)	11.3 (1.8–17.3)	10.8 (9.3–12.6)	**0.016**

provide a survival benefit. The aim of this study is to evaluate whether hepatectomy for BCLM provides any survival benefit as in the case of CRLM. To our knowledge, this is the first study on the outcome of hepatectomy for BCLM in the Chinese population.

Methods

This is a retrospective study using prospectively collected perioperative data of patients. The use of data and the study were approved by the institutional review committee of our hospital.

From January 1995 to December 2014, 773 out of 2252 patients with liver cancer had liver metastasis and received hepatectomy at our hospital. Twenty-one of them, all female, received the operation for BCLM. They all had pathologically confirmed invasive breast cancer and received modified radical mastectomy as the primary treatment. Patients with CRLM were compared with propensity score matching in a ratio of 1:3.

The propensity score analysis model was used to eliminate potential bias of case-match election. Variables with potential influence on the outcomes were assigned propensity scores after logistic regression analysis. Based on the generated propensity scores, the nearest neighbors in each of the two groups were matched one on one, and the survival outcomes in the two groups were then compared.

All the patients were managed by the same multidisciplinary team of oncologists and surgeons. Diagnosis of liver metastasis was made by tumor marker CA15-3 level check in addition to contrast computed tomography (CT) scan or contrast magnetic resonance imaging (MRI). Patients were assessed by anesthesiologists for operative fitness and preoperative morbidities were recorded. Only patients with isolated liver metastasis were included in this study. Patients were selected for hepatectomy if they had (i) no extrahepatic disease, (ii) lesions that could be resected technically, and (iii) good functional reserve with a potential minimum residual liver volume >30% of their estimated standard liver mass.

The extent of hepatectomies was defined according to the Brisbane 2000 terminology [16]. A gross margin of 1 cm was aimed for if possible. Immediate operative outcomes including blood loss, operative time, hospital stay, hospital mortality and complications were recorded.

All the patients were followed up by the same multidisciplinary team of surgeons and oncologists. Systemic chemotherapies, hormonal therapies and biological agents were administered according to individual receptor status. CT scan was performed at one month after the operation, quarterly in the first year, and half-yearly subsequently. Recurrence was defined as the appearance of typical CT/MRI features on follow-up assessments or as proven by cytology, if necessary. Overall survival and disease-free survival after hepatectomy were recorded. The outcomes were compared with reference to the receptor status of the liver lesions. Factors affecting the survival of patients with stage IV breast cancer were analyzed.

Table 2
Surgical characteristics in the two groups of patients.

Characteristics	CRLM ($n=63$)	BCLM ($n=21$)	P value
Types of resection			0.630
Right hepatectomy	20 (31.7%)	8 (38.1%)	
Extended right hepatectomy	4 (6.3%)	1 (4.8%)	
Left hepatectomy	7 (11.1%)	3 (14.3%)	
Left lateral sectionectomy	9 (14.3%)	2 (9.5%)	
Left trisectionectomy	0	1 (4.8%)	
Segmentectomy	7 (11.1%)	1 (4.8%)	
Wedge	16 (25.4%)	5 (23.8%)	
Blood loss (mL)	500 (50–2780)	360 (50–1400)	0.253
Blood transfusion	6 (9.5%)	1 (4.8%)	0.820
Blood replacement (mL)	0 (0–1200)	0 (0–600)	0.477
Operative time (min)	300 (130–795)	271 (135–562)	0.492
Invasion of major branch of portal or hepatic vein	1 (1.6%)	1 (4.8%)	1.000
Invasion of adjacent organ other than gallbladder	2 (3.2%)	0	1.000
Microvascular invasion	12 (19.0%)	7 (33.3%)	0.292

The baseline characteristics of patients were expressed as median and range. The Mann-Whitney U test was used to compare continuous variables, and Pearson's Chi-square test was used to compare discrete variables. Survival curves were computed by the Kaplan–Meier method and compared between groups by the log-rank test. The Cox regression model was used in univariate and multivariate analyses for intragroup comparison of factors that might affect overall survival. Factors that might affect the survival of BCLM patients after hepatectomy were identified by discriminating analysis. Statistical significance was defined as $P < 0.05$. The computer software SPSS/PC+ (SPSS, Chicago, IL, USA) was used for all statistical calculations.

Results

Twenty-one breast cancer patients who developed liver metastasis received hepatectomy. The median age at diagnosis of the primary tumor was 42 (range 28–61) years. The median age at diagnosis of liver metastasis was 45 (range 35–65) years. The median time from mastectomy to hepatectomy was 41.7 (range 13–107) months. All the patients had good liver function in terms of serum total bilirubin level, carcinoembryonic antigen level and prothrombin time. Two patients were hepatitis B virus carriers. Five patients had comorbidities. They had no significant difference in resection type, tumor number and tumor size when compared to patients with CRLM after propensity matching. The patients' characteristics are shown in Table 1.

Table 2 compares surgical characteristics between the CRLM and BCLM groups. As shown, no significant difference between groups was found. The immediate and short-term surgical outcomes were comparable between the two groups. In the BCLM group, one patient received the Pringle maneuver, and the group had a median hospital stay of 6 (range 3–27) days. No hospital death occurred in either group. Details of postoperative complications in the two groups are shown in Table 3 and pathological details are shown in Table 4. Again, no significant difference between groups was found.

In the BCLM group after hepatectomy, the median survival was 134.5 months and the 5-year survival rate was 58.9%. The median

Table 3
Postoperative complications in the two groups of patients.

Complications	CRLM ($n=63$)	BCLM ($n=21$)	P value
Total complications	12 (19.0%)	5 (23.8%)	0.875
Major complications (Clavien-Dindo 3a or above)	3 (4.8%)	2 (9.5%)	0.790
Pleural effusion			0.692
Tapping not required	4 (6.3%)	1 (4.8%)	
Tapping required	1 (1.6%)	1 (4.8%)	
Wound infection	3 (4.8%)	1 (4.8%)	1.000
Wound dehiscence	1 (1.6%)	0	1.000
Subphrenic abscess	1 (1.6%)	1 (4.8%)	1.000
Intraabdominal bleeding	0	0	
Peptic ulcer bleeding	0	0	
Urinary tract infection	2 (3.2%)	1 (4.8%)	1.000
Cardiac arrhythmia	1 (1.6%)	0	1.000
Heart failure	0	0	–
Biliary fistula/leakage	0	2 (9.5%)	0.098
Infected ascites	0	0	–
Intestinal obstruction	0	0	–
Pulmonary embolism	0	0	–
Pneumothorax	1 (1.6%)	0	1.000
Liver failure	0	0	–
Renal failure	0	0	–
Subphrenic collection	1 (1.6%)	0	1.000
Perforation of small bowel	1 (1.6%)	0	1.000
Pseudo-obstruction	1 (1.6%)	0	1.000

Table 4
Pathological examination of patients with CRLM and BCLM.

Characteristics	CRLM ($n=63$)	BCLM ($n=21$)	P value
Tumor number			0.143
1	32 (50.8%)	12 (57.1%)	
2	10 (15.9%)	3 (14.3%)	
≥3	21 (33.3%)	6 (28.6%)	
Tumor size (cm)	2.5 (0.4–8.0)	2.1 (1.2–10.0)	0.880
Margin size (cm)	1.0 (0–3.5)	0.6 (0.1–5)	0.228
R0 resection	21 (100%)	21 (100%)	1.000
ER positive	–	11 (52.4%)	
PR positive	–	8 (38.1%)	
HER2 positive	–	5 (23.8%)	
Triple negative	–	7 (33.3%)	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

disease-free survival was 13.7 months and the 5-year disease-free survival rate was 25.3%. On discriminating analysis, 14 factors that might affect the survival of BCLM patients after hepatectomy were identified (Table 5). In univariate analysis, Cox regression was used. Progesterone receptor (PR) might affect overall survival [odds ratio (OR) = 0.135; 95% CI: 0.016–1.135; $P=0.067$]. Estrogen receptor (ER) was a protective factor for overall survival (OR = 0.159; 95% CI: 0.030–0.848; $P=0.031$). When it comes to human epidermal growth factor receptor 2 (HER2), one patient had an equivocal status, and since the number of patient was too small, the OR was too small to estimate. As to negative status (the reference group) versus positive status, HER2 was not associated with overall survival (OR = 0.337; 95% CI: 0.040–2.809; $P=0.315$). Triple negative status was a risk factor for overall survival (OR = 5.580; 95% CI: 1.210–25.731; $P=0.027$). On univariate analysis, only the following factors were significant: age >49.1 years at the development of liver metastasis, age >45.2 years at mastectomy, ER status, and triple negative status. On multivariate analysis with the forward method, triple negative status was the only independent poor prognostic factor in BCLM (OR = 6.411; 95% CI: 1.351–30.435; $P=0.019$). After hepatectomy, the 1-, 3- and 5-year overall survival rates were 100.0%, 58.9% and 58.9% in BCLM and 95.0%, 57.2% and 39.7% in CRLM, respectively ($P=0.572$). The survival patterns are depicted in Figs. 1 and 2.

Discussion

The 5-year survival of BCLM patients remains low from 19% to 23% despite the presence of many new drugs [2,17]. Surgery was once considered too invasive for BCLM patients, but reports of successful hepatectomy for these patients have made many clinicians reconsider this treatment option [18].

In the treatment model for CRLM, hepatectomy has proved to have an absolute survival benefit over systemic chemotherapy alone, with a post-resection 5-year survival of 37%–58% and 10-year survival of 20%–25%. On the other hand, <1% of the patients who cannot receive hepatectomy survive 5 years [19]. Adam et al. studied hepatectomy for BCLM patients and in their study the rates of overall survival and disease-free survival were 37% and 21% respectively at 5 years after resection [17]. At high-volume centers where hepatectomies are carried out by experienced hepatobiliary surgeons, the mortality rate can be lower than 1% [14,17,20].

In our present study, hepatectomy was safe for BCLM patients. No hospital death occurred despite the majority of patients underwent major hepatectomy. At our hospital, a significant number of major hepatectomies are conducted for various conditions including diseases with underlying liver cirrhosis. Our substantial experience was definitely a reason for the low mortality rate and little blood loss. Meticulous and slow application of ultrasonic dissector and reduction of the central venous pressure by restriction of intravenous fluid infusion also contributed to the minimal blood loss [15].

The complication rate in the study was 23.8% but a vast majority of the patients had minor complications. Two patients had complications of Clavien–Dindo grade 3a, while no patients had complications more serious. The 5-year survival rate after hepatectomy was 58.9%, which is better than the historic 19.3% for patients with stage IV breast cancer [2]. Nine patients who were older than 49 years showed a poorer survival pattern on discriminating analysis, which contradicts the fact that younger patients generally have more advanced disease with more aggressive tumor characteristics [4]. These patients were either HER2 negative or triple negative.

In the study, patients with different receptor status fared differently. Patients who were ER positive fared better than their ER negative counterparts, and patients who were HER2 positive were similar to their HER2 negative counterparts. Our patients had much better survival than the benchmark reference of 19.3% at 5 years [2]. Patients who were triple negative had the worst survival, with a 5-year survival rate of 33.3% only.

It is well-known that patients who are triple negative have very poor survival due to aggressive tumor behavior [21,22]. Newer drug agents like trastuzumab have been shown to be ineffective for them, and different opinions exist among oncologists and surgeons as to whether hepatectomy is beneficial to them. However, with improved understanding of survival analysis, patients can be well informed once the diagnosis of liver metastasis is made and the choice of surgery can be decided by a multidisciplinary team.

In the present study, all of the patients had R0 resection. Apart from the meticulous technique and the use of intraoperative ultrasonography to search for additional tumors, careful patient selection allowed a 100% achievement of R0 resection. Better survival comes with R0 resection rather than R1 or R2 resection [17,23,24].

In the present study, disease-free interval between hepatectomy and primary mastectomy had no statistically significant association with overall survival. Different results in Western series have been reported [14,23,24]. A couple of studies found that circulating tumor cells and micrometastases were detected in 95% of patients with stage I or II breast cancer [25,26]. Development of liver metastasis early after primary mastectomy is not uncommon. More aggressive biological behavior of the primary tumor often entails a

Table 5
Univariate and multivariate analyses for poor prognostic factors in BCLM.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at liver metastasis				
≤49.1 yr (*n* = 12)	Reference group			
>49.1 yr (*n* = 9)	5.152 (1.033–25.689)	**0.046**		
Age at mastectomy				
≤45.2 yr (*n* = 12)	Reference group			
>45.2 yr (*n* = 9)	5.152 (1.033–25.689)	**0.046**		
Total bilirubin				
≤6.6 μmol/L (*n* = 14)	Reference group			
>6.6 μmol/L (*n* = 7)	1.605 (0.400–6.437)	0.504		
International normalized ratio[a]				
≤0.96 (*n* = 7)	Reference group			
>0.96 (*n* = 13)	1.759 (0.339–9.120)	0.501		
Albumin				
≤42.9 g/L (*n* = 9)	Reference group			
>42.9 g/L (*n* = 12)	2.978 (0.596–14.873)	0.184		
PR[a]				
Negative (*n* = 12)	Reference group			
Positive (*n* = 8)	0.135 (0.016–1.153)	0.067		
ER[a]				
Negative (*n* = 9)	Reference group			
Positive (*n* = 11)	0.159 (0.030–0.848)	**0.031**		
HER2[a]				
Negative (*n* = 14)	Reference group			
Positive (*n* = 5)	0.337 (0.040–2.809)	0.315		
Equivocal (*n* = 1)	0.000 (Unavailable)	0.992		
Triple negative[a]				
No (*n* = 13)	Reference group		Reference group	
Yes (*n* = 7)	6.411 (1.351–30.435)	**0.019**	6.411 (1.351–30.435)	**0.019**
Surgical complication				
No (*n* = 16)	Reference group			
Yes (*n* = 5)	1.485 (0.353–6.244)	0.589		
Microvascular invasion				
No (*n* = 14)	Reference group			
Yes (*n* = 7)	1.267 (0.300–5.348)	0.748		
Number of tumor nodule				
1 (*n* = 12)	Reference group			
>1 (*n* = 9)	1.696 (0.423–6.797)	0.456		
Tumor size				
≤3.2 cm (*n* = 13)	Reference group			
>3.2 cm (*n* = 8)	3.288 (0.779–13.882)	0.105		
Mastectomy to liver metastasis				
≤49.1 mon (*n* = 13)	Reference group			
>49.1 mon (*n* = 8)	0.323 (0.064–1.626)	0.170		

OR: odds ratio; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.
[a] One patient's data unavailable. Categorical grouping was used as cut-off value by discriminant analysis.

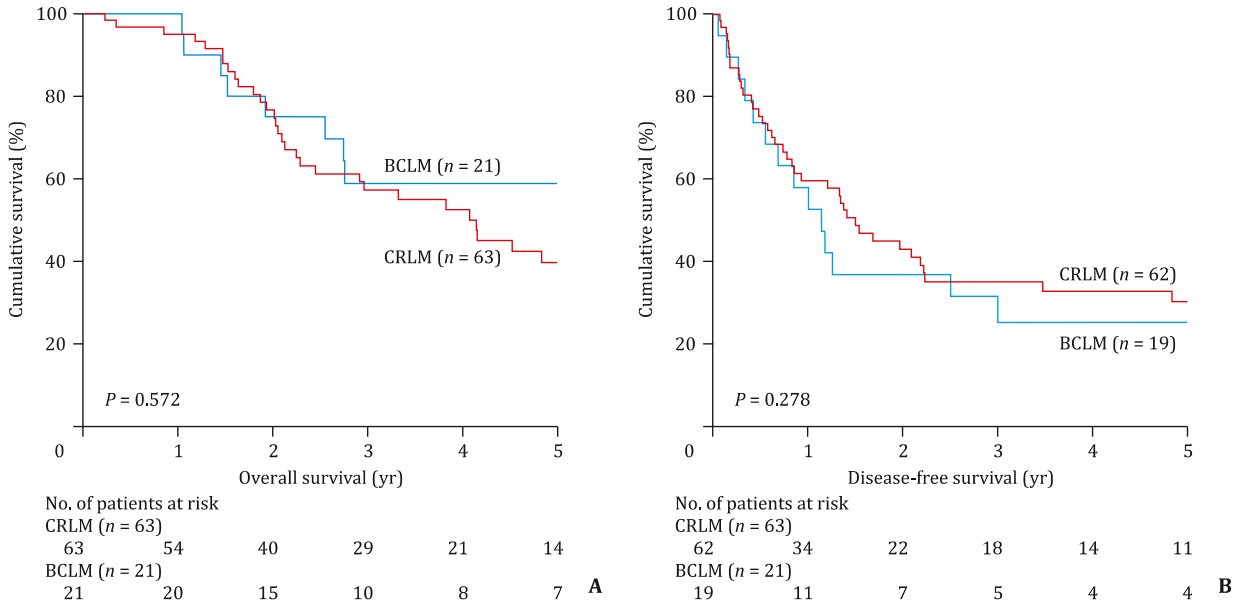

Fig. 1. Overall survival (**A**) and disease-free survival (**B**) of CRLM versus BCLM. CRLM: colorectal liver metastasis; BCLM: breast cancer liver metastasis.

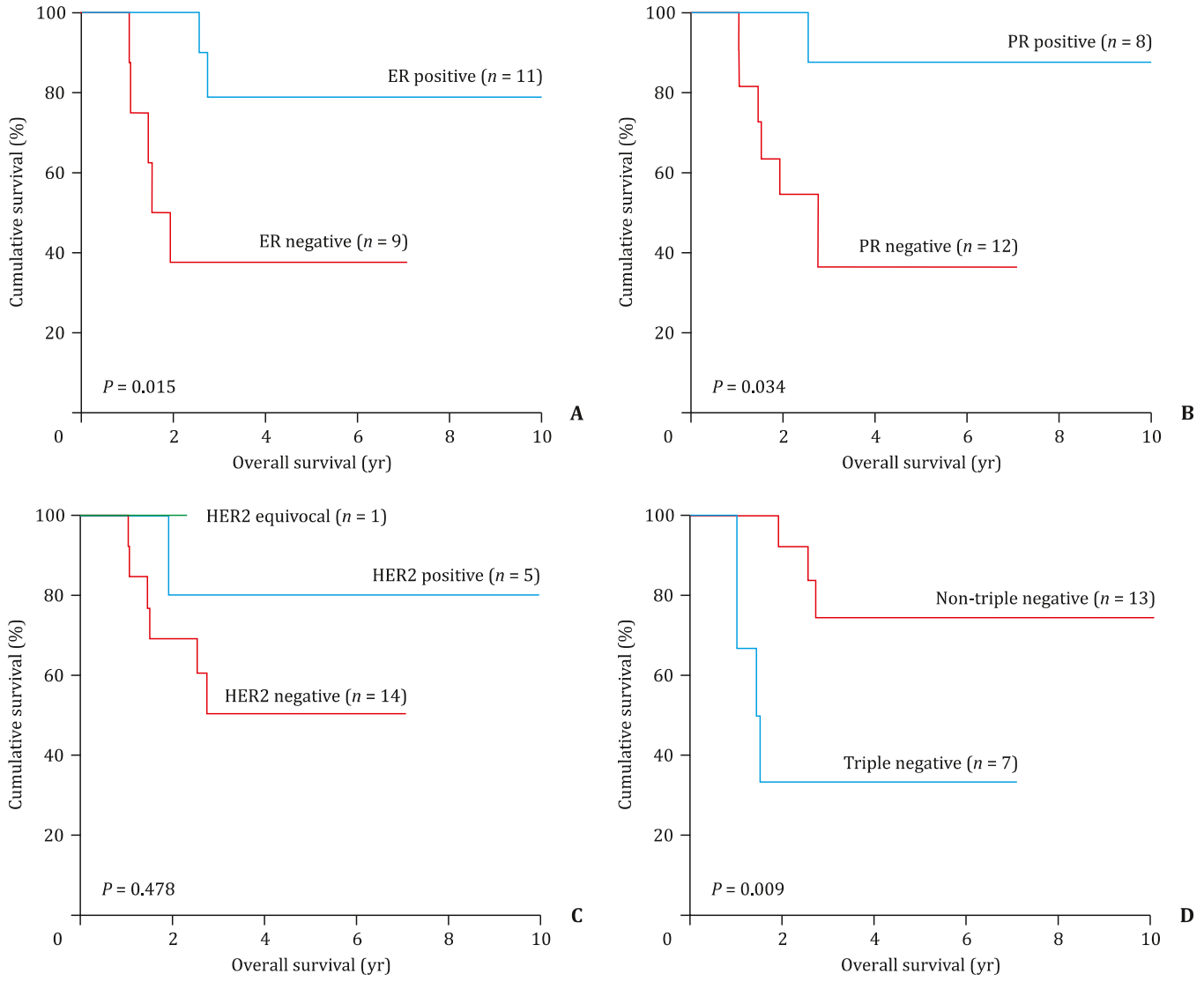

Fig. 2. Survival in the BCLM group, ER negative versus ER positive (**A**), PR negative versus PR positive (**B**), HER2 negative versus HER2 positive versus HER2 equivocal (**C**), and triple negative versus non-triple negative (**D**) (one patient's data unavailable).
BCLM: breast cancer liver metastasis; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

higher chance of disease recurrence as well as a shorter interval between primary breast treatment and the development of liver metastasis. Patients should be alerted to such fact.

This study was limited by its retrospective design and relative small number of patients. Further collection of data from multiple centers is needed for further study.

In conclusion, unlike liver metastases from other origins, there is a unique code of pathological behavior in BCLM which determines subsequent treatments and outcomes. It is important to stage the disease accurately and to document different hormonal receptor statuses. Favorable outcomes can be achieved in patients with isolated liver metastasis by hepatectomy. Hepatectomy is a safe and effective way of treating BCLM at experienced centers where multidisciplinary adjuvant treatments are available. It can be considered more frequently as part of the multidisciplinary care for this patient population.

Contributors

CTT supervised the study and wrote the manuscript. CKSH, CACY, TSHY, DWC, YTCC, KA and LCM collected and analyzed data. All authors approved the final version of the manuscript. CTT is the guarantor.

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Ethical approval

The study was approved by the institutional review committee of Queen Mary Hospital.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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