ORIGINAL ARTICLE

Retrospective Study

Resection margin influences the outcome of patients with bilobar colorectal liver metastases

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Abstract

AIM

To evaluate the outcome of patients with bilobar colorectal liver metastases (CRLM) and identify clinico-pathological variables that influenced survival.

METHODS

Patients with bilobar CRLM were identified from a prospectively maintained hepatobiliary database during the study period (January 2010-June 2014). Collated data included demographics, primary tumour treatment, surgical data, histopathology analysis and clinical outcome. Down-staging therapy included Oxaliplatin- or Irinotecan- based regimens, and Cetuximab was also used in patients that were *K-RAS* wild-type. Response

to neo-adjuvant therapy was assessed at the multi-disciplinary team meeting and considered for surgery if all macroscopic CRLM were resectable with a clear margin while preserving sufficient liver parenchyma.

RESULTS
Of the 136 patients included, thirty-two (23.5%) patients were considered inoperable and referred for palliative chemotherapy, and thirty-four (25%) patients underwent liver resection. Seventy (51.4%) patients underwent down-staging therapy, of which 37 (52.8%) patients responded sufficiently to undergo liver resection. Patients that failed to respond to down-staging therapy ($n = 33$, 47.1%) were referred for palliative therapy. There was a significant difference in overall survival between the three groups (surgery *vs* down-staging therapy *vs* inoperable disease, $P < 0.001$). All patients that underwent hepatic resection, including patients that had down-staging therapy, had a significantly better overall survival compared to patients that were inoperable ($P < 0.001$). On univariate analysis, only resection margin significantly influenced disease-free survival ($P = 0.017$). On multi-variate analysis, R0 resection ($P = 0.030$) and female ($P = 0.036$) gender significantly influenced overall survival.

CONCLUSION
Patients undergoing liver resection with bilobar CRLM have a significantly better survival outcome. R0 resection is associated with improved disease-free and overall survival in this patient group.

Key words: Colorectal liver metastases; Chemotherapy; Liver resection

Core tip: The management of colorectal liver metastases (CRLM) has evolved over the last decade. More patients are being subjected to potentially curative liver resection following down-staging therapy and the introduction of specialist multi-disciplinary team meetings. The introduction of biological agents has also increased resection rates. The current study analysed patients with bilobar CRLM referred to our centre. Patients that underwent liver resection had a significantly better survival outcome following our multi-disciplinary approach.

INTRODUCTION
Hepatic resection is the only potentially curative treat-ment for patients with colorectal liver metastases (CRLM) and the 5-year survival rate is up to 50%[1,2]. Patients with extensive, bilateral disease present a surgical challenge in removing all macroscopic disease while preserving sufficient functional liver remnant. Studies have shown that 20%-30% of all patients with CRLM are resectable at the time of diagnosis[3], with bilobar distribution of metastases a major contributing factor for unresectability[4].

More recently, the introduction of biological agents and the improved efficacy of down-staging chemotherapy regimens to treat bilobar CRLM have increased the proportion of patients with initially unresectable disease to subsequently operable disease. In addition, neo-adjuvant chemotherapy can potentially treat systemic disease to lower the risk of distant spread, and allow the identification of patients with biologically aggressive tumours that progress on chemotherapy that would not benefit from liver surgery[5]. Down-staging chemotherapy regimens are more toxic than palliative regimens, and hence, it is essential that there is multi-disciplinary team approach in determining the management plan for these patients[6]. However, long term outcomes for these patients following down-staging therapy and liver resection are indeterminate.

The aim of this study was to evaluate the outcomes of patients with bilobar CRLM following multi-disciplinary therapy. The secondary aim was to identify clinico-pathological variables that influenced disease-free and overall survival in this group of patients.

MATERIALS AND METHODS
Patients
Patients with bilobar CRLM were identified from a pro-spectively maintained hepatobiliary database at Queen's Medical Centre (QMC), Nottingham University Hospitals NHS Trust**,** Nottingham, United Kingdom during a 4-year period from January 2010 to June 2014. QMC is a tertiary referral center for Nottinghamshire and surrounding regions located in the north of East Midlands, United Kingdom. Pre-operative radiological assessment included a computed tomography (CT) scan of the thorax, abdo-men and pelvis and magnetic resonance imaging (MRI) of the liver. Patients with indeterminate lesions, in particular lung nodules, and patients with synchronous presentation underwent a positron emission tomography scan. Synchronous presentation was defined as the presence of liver metastases when colorectal cancer was diagnosed. Prior to any treatment, all patients including patients referred from the surrounding regions were discussed in a specialist multidisciplinary team (MDT) meeting consisting of hepatobiliary surgeons, hepatologists, oncologists, radiologists and pathologists. Patients were selected for liver resection without any prior neo-adjuvant therapy if all macroscopic CRLM were resectable to achieve a clear margin while preserving sufficient liver parenchyma.

Collated data included patient demographics, type of surgical resection, histopathology analysis and clinical

outcome. This study has been registered and approved by the Clinical Audit Department, Nottingham University Hospitals NHS Trust. Since this is a retrospective study, individual patient consent was not required, and all local ethical guidelines with respect to retrospective studies in this Trust were adhered to.

Down-staged therapy and adjuvant chemotherapy

Patients scheduled for preoperative systemic chemotherapy had 3-6 mo of neo-adjuvant treatment. The regimens used were either Oxaliplatin based: Two weekly FOLFOX [5-fluorouracil (FU) 400 mg/m^2 bolus, and 2400 mg/m^2 over 46 h, Leucovorin and Oxaliplatin 85 mg/m^2] or three weekly CAPOX (Capecitabine 1000 mg/m^2 BD for 14 d and Oxaliplatin 130 mg/ m^2).

However, in patients tested and found to be *K-RAS* wild-type, two weekly FOLFIRI (Irinotecan 180mg/m^2, 5-FU 400 mg/m^2 bolus, and 2400 mg/m^2 over 46 h) was administered with concurrent Cetuximab (400 mg/m^2 cycle 1, then 250 mg/m^2 cycle 2 onwards).

The response to neo-adjuvant therapy was assessed after 3-6 mo of therapy by CT scan and repeat MRI of the liver if required. Patients were then re-discussed at the MDT and considered for surgery based on absence of new disease, tumour response and extent of disease. Patients deemed to have resectable disease were scheduled for a liver resection, 4-6 wk after their last cycle of chemotherapy. Resectable disease was defined as excision of all macroscopic CRLM to achieve a clear margin while preserving sufficient liver parenchyma based on pre-operative radiological imaging.

Following liver resection, chemotherapy was considered in patients with tumour present at the margin (R1 resection).

Surgery

Liver resection was performed using the Cavi-Pulse Ultrasonic Surgical Aspirator. Intra-operative ultrasound was performed to confirm the findings of pre-operative imaging and to assist in surgical planning. The number of hepatic Couinaud's[7] segments resected was determined by the procedure performed as stated in the Brisbane nomenclature[8]. Type of surgical procedure was dependent on the resection of all macroscopic disease and achieving a clear resection margin, while preserving sufficient remnant liver. The extent of hepatic resection in this study was classified into two groups; less than hemi-hepatectomy and hemi-hepatectomy or more radical resection. Pre-operative PVE was performed if the FRL volume was estimated to be 20% or less of the total liver volume. Liver-first approach was defined when the hepatic resection was performed first prior to colonic or rectal resection[9,10].

In patients where the liver-first approach was adopted, primary tumour resection was usually scheduled 4-8 wk following liver resection, or after completion of chemo-radiotherapy for patients with locally advanced rectal cancer. All patients underwent re-staging with a CT scan and MRI to ensure there was no evidence of liver recurrence or distant metastases. Colorectal resection was performed according to accepted oncological standards, with complete meso-rectal excision for rectal cancers and lymph node dissection for colonic cancers.

Histology

Histopathological data of the resected liver specimen were collated. This included: Tumour size in maximum diameter; tumour number; and status of resection margin. R0 resection was defined as no microscopic evidence of tumour at or within 1 mm of the margin. Lymphatic, peri-neural, biliary and vascular invasion were also determined[11].

Follow-up

Patients were followed up in specialist hepatobiliary clinics. Following initial post-operative review at one month, all patients were examined in the outpatient clinic at 3, 6, 12, 18 and 24 mo and annually thereafter. At each clinical review, carcino-embryonic antigen levels were measured. All patients in this study had a minimum follow-up of 6 mo following hepatic resection for CRLM.

Surveillance imaging included CT scan of the thorax, abdomen and pelvis. Patients underwent 6-monthly CT scan during the first two post-operative years, followed by annual CT scans thereafter. Liver MRI was used to characterise suspicious hepatic lesions demonstrated on CT. Development of symptoms of recurrence at any time-point prompted earlier review than scheduled.

Overall and disease-free survival was recorded, with disease-free survival being defined as the time from primary hepatic resection to the first documented disease recurrence on imaging. Overall survival was defined as the time interval between the date of commencement of neo-adjuvant/induction therapy and the date of death or most recent date of follow-up if the patient was still alive. Following detection of recurrent disease on surveillance imaging, all patients were discussed at the MDT meeting. Patients who had non-resectable disease were referred to the oncologists for consideration of palliative chemotherapy.

Statistical analysis

Categorical data was presented as frequency and percentage. The Kaplan-Meier method was used to assess the actuarial survival and disease-free survival, and presented as median (range). Univariate analysis was performed to assess for a significant difference in clinico-pathological characteristics that influenced disease recurrence and survival. A multivariate analysis was performed by Cox regression (Step-wise forward model) for variables significant on univariate analysis. Statistical analyses were performed using the SPSS for Windows™ version 16.0 (SPSS Inc, Chicago, Ill, United States), and statistical significance was taken at the 5% level. The statistical methods of this study were reviewed and performed by Gomez D, QMC, Nottingham, United Kingdom.

Table 1 Clinical data of patients with bilobar colorectal liver metastases in this study

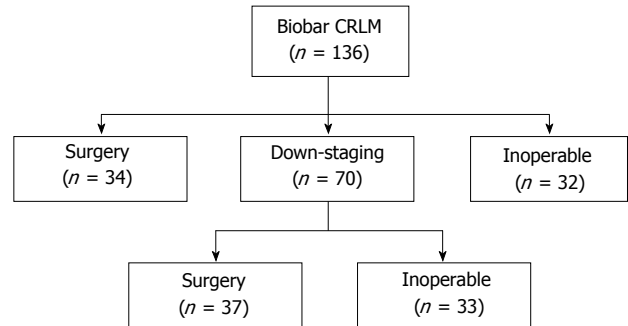| Demographic, clinical and pathological factors	Total (*n*)
All patients (*n* = 136)	
All surgery patients (*n* = 71)	
Demographic factors	
Age > 65 yr	68
Male gender	99
Synchronous presentation	80
Down-staging therapy	70
Oxaliplatin-based regimen	60
Irinotecan-based regimen	10
Addition of biological agent	30
Surgical factors (*n* = 71)	
Hemi-hepatectomy or more	22
Histo-pathological factor (*n* = 71)	
Largest tumour size ⩾ 5 cm	11
Number of metastases < 4	44
Lymphatic invasion present	15
Vascular invasion present	28
Peri-neural invasion present	9
Biliary invasion present	25
Resection margin (R0)	40

RESULTS

Patients
During the study period, a total of 136 patients (Table 1) with bilobar CRLM were discussed in the unit's MDT, of which 34 (25.0%) patients underwent surgery with curative intent as their primary treatment (Figure 1). There were 32 (23.5%) patients that had extensive disease and were referred for palliative therapy.

Seventy (51.4%) patients were considered for down-staging therapy, in view to consider liver resection depending on response to therapy. Besides receiving either an Oxaliplatin-based (*n* = 60) or Irinotecan-based (*n* = 10) regimen, 30 (42.8%) patients also had biological agents as part of their down-staging treatment. Within the group of patients that received down-staging therapy, 37 (52.8%) patients had a response to their down-staging therapy and underwent hepatic resection, while the remaining patients [*n* = 33 (47.2%)] did not undergo surgical resection. These patients did not respond to their down-staging therapy, which included: (1) having new metastases; (2) disease progression; and (3) inability to remove all macroscopic liver disease whilst leaving sufficient remnant liver. This decision was based on MDT review of up to date radiological imaging following down-staging therapy.

Liver resection
Overall, there were 71 (52.2%) patients that underwent liver resection, of which twenty-two patients had a hemi-hepatectomy or more. The most common surgical procedures performed was multiple non-anatomical resections (*n* = 40, 56.3%). Twenty-one patients were female and the median age at the diagnosis was 65 (range: 44-84) years. Seven (9.8%) patients had portal vein embolization prior to liver resection. There were 35

Figure 1 Outcome of patients with bilobar colorectal liver metastases in this study. CRLM: Colorectal liver metastases.

patients with synchronous disease, of which 17 patients had a liver-first approach. There was no post-operative mortality.

Survival outcome
The median overall survival for all patients in this study was 18 (1-48) mo (Figure 2). There was a significant difference in overall survival between the three groups (Surgery *vs* Down-staging therapy *vs* Inoperable disease, *P* < 0.001; Figure 3). All patients that underwent hepatic resection, including patients that had down-staging therapy, had a significantly better overall survival compared to patients that were inoperable [24 (6-48) mo *vs* 17 (1-43) mo; *P* < 0.001; Figure 4]. The disease-free survival for patients that underwent liver resection was 8 (range: 2-36) mo.

Prognostic factors influencing disease-free and overall survival
With respect to disease-free survival, patients with a clear (R0) resection margin following liver resection had a significantly better disease-free survival compared to patients with a R1 resection (*P* = 0.017; Table 2 and Figure 5).

Patients with a R0 resection (*P* = 0.022; Figure 6) and female gender (*P* = 0.024; Figure 7) has a significantly better overall survival compared to patients with a R1 resection and male gender on univariate analysis. On the multi-variate analysis, both R0 resection and female gender were independent predictors of improved overall survival (Table 3).

DISCUSSION

With the improvement in chemotherapy agents and the increased efficacy with the addition of biological agents, many centers have reported an increased number of patients being converted from initially unresectable, to resectable disease[12,13]. However, although there are an increased number of patients undergoing liver resection with curative intent, some authorities may suggest that these patients are unlikely to be cured[14]. Nevertheless, these patients have a better overall survival in comparison to patients treated with palliative systemic

Table 2 Statistical analysis of prognostic factors with respect to disease-free survival

Demographic, clinical and pathological factors	Survival [median (range) mo]	Uni-variate analysis
Demographic factors		
Age		0.099
< 65 yr (*n* = 43)	6 (3-36)	
≥ 65 yr (*n* = 28)	12 (2-36)	
Gender		0.343
Male (*n* = 50)	6 (3-36)	
Female (*n* = 21)	5 (2-36)	
Presentation		0.755
Synchronous (*n* = 35)	6 (2-36)	
Metachronous (*n* = 36)	6 (3-36)	
Surgical factors		
Less than hemi-hepatectomy (*n* = 49)	6 (2-36)	0.760
Hemi-hepatectomy or more (*n* = 22)	6 (2-36)	
Histo-pathological factor		
Largest tumour size		0.813
< 5 cm (*n* = 60)	6 (2-36)	
≥ 5 cm (*n* = 11)	9 (2-36)	
No. of metastases		0.538
< 4 (*n* = 44)	7 (2-36)	
> 5 (*n* = 27)	6 (3-36)	
Lymphatic invasion		0.256
Positive (*n* = 15)	6 (2-24)	
Negative (*n* = 56)	6 (2-36)	
Vascular invasion		0.775
Positive (*n* = 28)	6 (2-36)	
Negative (*n* = 43)	7 (2-36)	
Peri-neural invasion		0.115
Positive (*n* = 9)	6 (2-24)	
Negative (*n* = 62)	6 (2-36)	
Biliary invasion		0.919
Positive (*n* = 25)	6 (2-36)	
Negative (*n* = 46)	6 (2-36)	
Resection margin (R0)		0.017
R0 (*n* = 40)	8 (2-36)	
R1 (*n* = 31)	6 (2-36)	

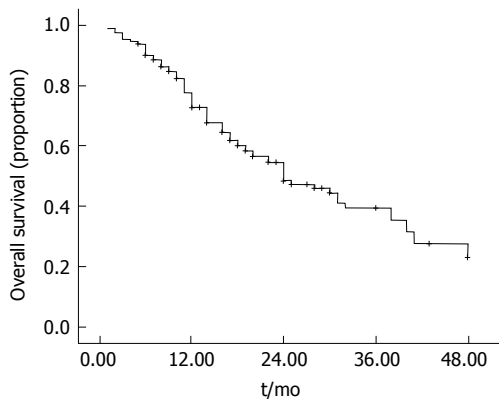**Table 3 Statistical analysis of prognostic factors with respect to overall survival**

Demographic, clinical and pathological factors	Survival [median (range) mo]	Uni-variate analysis	Multi-variate analysis	Risk ratio (confidence interval)
Demographic factors				
Age		0.173		
< 65 yr (*n* = 43)	20 (6-48)			
≥ 65 yr (*n* = 28)	27 (7-48)			
Gender		0.024	0.036	3.172 (1.079-9.327)
Male (*n* = 50)	19 (6-48)			
Female (*n* = 21)	20 (11-48)			
Presentation		0.932		
Synchronous (*n* = 35)	23 (6-48)			
Metachronous (*n* = 36)	24 (6-48)			
Surgical factors				
Less than hemi-hepatectomy (*n* = 49)	22 (6-48)	0.947		
Hemi-hepatectomy or more (*n* = 22)	28 (7-48)			
Histo-pathological factor				
Largest tumour size		0.216		
< 5 cm (n = 60)	24 (6-48)			
≥ 5 cm (n = 11)	28 (12-48)			
Number of metastases		0.674		
< 4 (*n* = 44)	24 (6-48)			
> 5 (*n* = 27)	24 (11-48)			
Lymphatic invasion		0.943		
Positive (*n* = 15)	24 (11-48)			
Negative (*n* = 56)	23 (6-48)			
Vascular invasion		0.367		
Positive (*n* = 28)	25 (6-48)			
Negative (*n* = 43)	23 (6-48)			
Peri-neural invasion		0.220		
Positive (*n* = 9)	12 (11-48)			
Negative (*n* = 62)	24 (6-48)			
Biliary invasion		0.608		
Positive (*n* = 25)	27 (11-48)			
Negative (*n* = 46)	22 (6-48)			
Resection margin (R0)		0.022	0.030	0.403 (0.178-0.917)
R0 (*n* = 40)	24 (6-48)			
R1 (*n* = 31)	22 (6-48)			

chemotherapy, with some authors reporting a median survival up to 45 mo[12,15]. In the present study, patients with bilobar disease who underwent surgery had a significantly better overall survival compared to patients who failed down-staged chemotherapy and/or treated with palliative chemotherapy.

Conversion rate
The addition of biological agents to current Oxaliplatin- and Irinotecan- based regimens has led to further improvements in response rates. In a large randomised control trial, Folprecht *et al*[16] showed an increased response rate up to 68% with the addition of Cetuximab. Similarly, Masi *et al*[17] observed that the addition of Bevacizumab to Oxaliplatin- and Irinotecan- based regimens increased the response rate up to 80%. In the present study, the unit's down-staging therapy protocol had a response rate and a conversion of unresectable to resectable disease of more than 50%. These results were consistent with data reported by the groups of Van Custem *et al*[18] and Bokemeyer *et al*[19] that observed a conversion rate of approximately 60% following down-staging chemotherapy.

Survival data
Adam *et al*[13] recently published their long-term survival results following down-sizing chemotherapy and hepatic resection in patients with CRLM and demonstrated that 24 (16%) of 148 patients were alive and disease-free with a minimum of 5-year follow-up. Several studies have shown the improvements in survival after the addition of anti-VEGF/EGFR[20-22]. Recently, a number of case series describing 10-year actual survivors after liver resection of CRLM have been published[23,24]. The present series demonstrated that hepatic resection for patients with bilobar CRLM had a median disease-free and overall survival of 8 and 24 mo, respectively.
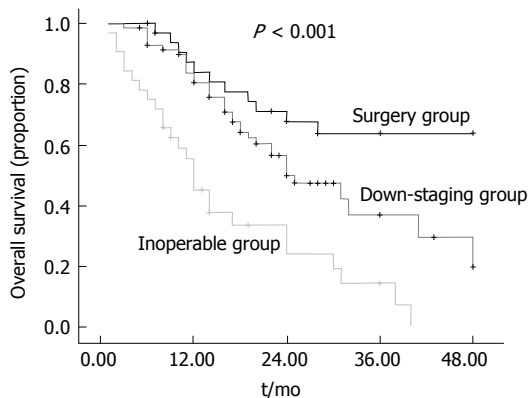
MDT approach
Definitions of resectable disease have evolved over time, with current consensus suggesting that disease should be considered technically resectable as long as complete macroscopic resection is feasible, whilst maintaining

Figure 2 **Overall survival of patients with bilobar colorectal liver metastases in this study.** All patients (*n* = 136): 18 (1-48) mo.
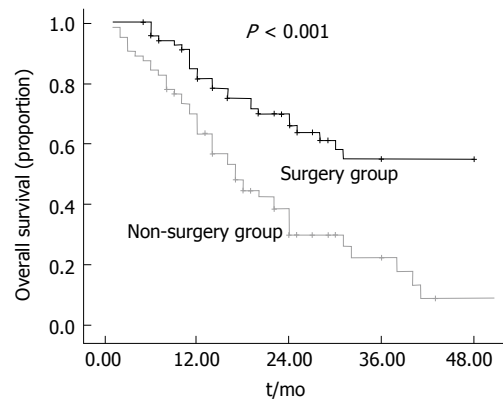
Numbers at risk

Patients	0	12	36	48	60
All (*n* = 136)	136	97	23	6	0

Surgery (*n* = 34): 28 (7-48) mo
Down-staging therapy (*n* = 70): 18 (3-48) mo
Inoperable (*n* = 32): 11 (1-40) mo

Numbers at risk

Patients	0	12	36	48	60
Surgery (*n* = 34)	34	32	14	4	0
Down-staging (*n* = 70)	70	49	6	2	0
Inoperable (*n* = 32)	32	16	3	0	0

Figure 3 **Difference in overall survival in patients that underwent surgery, down-staging therapy followed by surgery or palliative therapy and inoperable patients.**
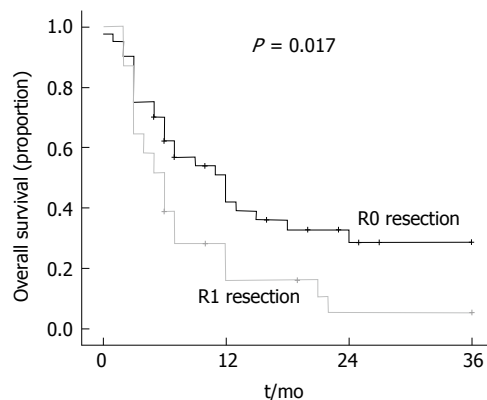

Surgery (*n* = 71): 24 (6-48) mo
No surgery (*n* = 65): 17 (1-43) mo

Numbers at risk

Patients	0	12	36	48
Surgery group (*n* = 71)	71	66	18	6
Non-surgery group (*n* = 65)	65	40	6	0

Figure 4 **Difference in overall survival in patients that underwent surgery following down-staging therapy compared to patients that either failed down-staging therapy or were treated with palliative therapy.**
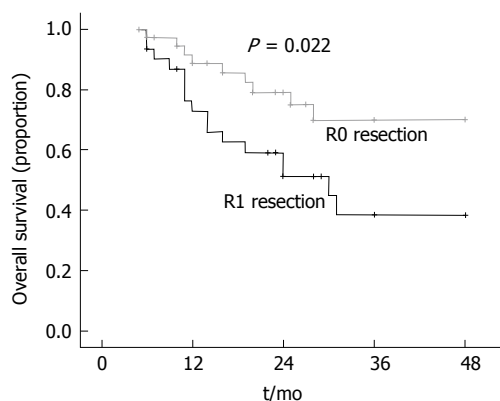

Numbers at risk

Patients	0	12	36
R0 resection (*n* = 40)	40	17	5
R1 resection (*n* = 31)	31	7	1

Figure 5 **Difference in disease-free survival in patients with R0 resection compared to patients with R1 resection.**

sufficient future liver volume[25]. However, there remains concern that not all patients with technically resectable liver-limited metastases benefit from surgery; with approximately half of these patients will develop recurrences within three years of liver resection[26]. Therefore, it is crucial that the decision-making process around treatment strategies for metastatic colorectal cancer are made in a MDT environment that consists of specialist hepato-biliary surgeons, radiologists and oncologists that can define optimal patient management on a case by case basis. A recent study demonstrated that almost two-thirds of patients with tumours deemed unresectable by non-specialists were considered potentially resectable

by a panel of specialist hepato-biliary surgeons based on radiological imaging[27].

Prognostic factors

The role of margin status as a predictor of outcome following resection for CRLM is controversial. Bodingbauer *et al*[28] observed that resection margin and size of margin width did not correlate significantly with survival following resection for CRLM. In a series of 1019 patients, and co-investigators demonstrated that a resection margin > 1 cm was an independent predictor of survival following resection for CRLM[29]. Rees *et al*[1] also demonstrated that positive resection margins were an independent predictor of poorer survival. However,
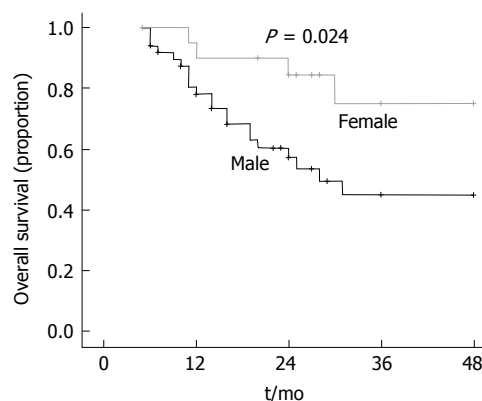
Numbers at risk

Patients	0	12	36	48
R0 resection ($n = 40$)	40	34	12	4
R1 resection ($n = 31$)	31	21	6	2

Figure 6 Difference in overall survival in patients with R0 resection compared to patients with R1 resection.

Numbers at risk

Patients	0	12	36	48
Male ($n = 50$)	50	36	11	4
Female ($n = 21$)	21	20	9	2

Figure 7 Difference in overall survival in female patients compared to male patients following surgery for colorectal liver metastases.

Figueras *et al*[30] showed that a margin width < 1 cm in patients who underwent resection for CRLM did not significantly influence recurrent disease in a cohort of 609 patients. Homayounfar *et al*[31] demonstrated that R0 resection in patients with bilobar CRLM have improved survival rates following multi-modal therapy[32]. In the present series, a clear resection margin, defined as no microscopic evidence of tumour at or within 1 mm of the margin, was an independent predictor of both disease-free and overall survival. Due to the differences in results observed with respect to resection margin between published studies, it may be that only a selected group of patients undergoing resection for CRLM are influenced by a clear margin. In the present series that focused on patients with bilobar CRLM, that would be considered as having a high tumour burden, benefited from a R0 margin. This could be due to the fact that these patients have an aggressive tumour profile and it is crucial that complete tumour clearance is obtained. Hence, for these patients, "down-sizing" chemotherapy should certainly be considered prior to resection to aid in achieving a clear resection margin. Furthermore, many groups advocate a trial of neo-adjuvant chemotherapy in patients with a high tumour burden, as disease progression on chemotherapy would be a contraindication to surgery[33]. Nevertheless, with the increase use of chemotherapy, there is an increase in prevalence of patients undergoing hepatic resection with a background of chemotherapy-related injury, such as steato-hepatitis[34] and sinusoidal obstruction syndrome[35]. In such cases, the quality, rather than quantity of the remnant liver becomes an important issue to consider prior to extensive resection.

The present study also showed that female gender was an independent prognostic factor for improved overall survival. There are currently no other studies that have reported this finding.

There are limitations in this study. This is a retrospective study, and focused on a group of patients with bilobar liver metastases. These are patients with bad tumour biology and in most cases, will require down-staging therapy. Nevertheless, although these group of patients have a higher tumour burden; their prognosis can be improved with a MDT approach that focuses on multi-modal therapy.

Patients with bilobar CRLM treated with liver resection as a primary treatment or following down-staging therapy have a better overall survival compared to patients who failed down-staging therapy and/or treated with palliative chemotherapy. Obtaining a clear resection margin in these cases significantly influences outcome. In this group of patients, multi-modal therapy is crucial to achieve a better survival outcome.

COMMENTS

Background
Hepatic resection is the only potentially curative treatment for patients with colorectal liver metastases (CRLM) and the 5-year survival rate is up to 50%.

Research frontiers
The introduction of biological agents and the improved efficacy of down-staging chemotherapy regimens to treat bilobar CRLM have increased the proportion of patients with initially unresectable disease to subsequently operable disease. In addition, neo-adjuvant chemotherapy can potentially treat systemic disease to lower the risk of distant spread, and allow the identification of patients with biologically aggressive tumours that progress on chemotherapy that would not benefit from liver surgery.

Innovations and breakthroughs
In the present study, patients with bilobar disease who underwent surgery had a significantly better overall survival compared to patients who failed down-staged chemotherapy and/or treated with palliative chemotherapy.

Applications
Patients with bilobar CRLM treated with liver resection as a primary treatment or following down-staging therapy have a better overall survival compared to patients who failed down-staging therapy and/or treated with palliative chemotherapy.

Peer-review
This article is interesting but I think epidemiological data are more interesting

than univariate and multivariate analysis, which is the part highlighted by the authors. Structure of the manuscript is correct.

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