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The impact of primary tumour location in patients undergoing hepatic resection for colorectal liver metastasis

Kun Wang [a, 1], Da Xu [a, 1], Xiao-Luan Yan [a], Graeme Poston [b, c, **], Bao-Cai Xing [a, *]

[a] Hepatopancreatobiliary Surgery Department I, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing 100142, China
[b] Department of Surgery, School of Translational Studies, University of Liverpool, Liverpool, L9 7AL, UK
[c] Department of Surgery, Aintree University Hospital, Liverpool, L9 7AL, UK

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ABSTRACT

Background: Primary tumour location has long been debated as a prognostic factor in colorectal cancer patients with liver metastases (CRLM) undergoing liver resection. This retrospective study was conducted to clarify the prognostic value of tumour location after radical hepatectomy for CRLM and its underlying causes.

Methods: We retrospectively analysed clinical data from 420 patients with CRLM whom underwent liver resection between January 2002 and December 2015. Right-sided (RS) tumours include tumours located in the cecum, ascending colon, and transverse colon, and left-sided (LS) tumours include those located in the splenic flexure, descending colon, sigmoid colon, and rectum.

Results: Both overall survival (OS) and disease-free survival (DFS) were similar between patients with RS and LS primary tumours (5-year OS: 46.5% vs 38.3%, $P = 0.699$; 5-year DFS: 29.1% vs 22.4%, $P = 0.536$). Specifically, RAS mutation rate was significantly higher in patients with RS tumours ($P = 0.007$). Subgroup analysis showed that the RAS mutation on the LS and RS tumours have different prognostic impact for CRLM patients on long-term survival after hepatic resection (RS, OS: $P = 0.437$, DFS: $P = 0.471$; LS, OS: $P < 0.001$, DFS: $P = 0.002$). The multivariable analysis showed that RAS mutant is an independent factor influencing OS in patients with LS primary tumour only.

Conclusions: The site of the primary tumour has no significant impact on the long-term survival in patients with CRLM undergoing radical surgery. However, prognostic value of RAS status differs depending on the site of the primary tumour.

Introduction

Surgical resection is currently the only curative treatment for patients with colorectal liver metastases (CRLM), with a 5-year overall survival (OS) rates of 35%–60% [1–3]. However, the high recurrence rate remains a big challenge for these patients. Many prognostic factors have been demonstrated to play a key role in predicting prognosis of CRLM patients following hepatectomy, such as clinicopathologic factors [4], and gene status, especially RAS and BRAF mutations [5–7]. Recently, primary colorectal cancer (CRC) of the left and right sides has been identified to have prognostic significance in unresectable metastatic colorectal cancer (mCRC) [8,9]. The proximal colon from the cecum to approximately half to two-thirds of the way along the transverse colon (right-sided, RS) is derived from the embryonic midgut, while the distal third of the transverse colon to the rectum (left-sided, LS) is derived from the embryonic hindgut [10]. Due to the difference in embryonic origin, primary tumours arising from the left and right sides of the colon have distinct clinical and molecular characteristics. Recent data from the AIO KRK-0306 (FIRE-3) and CALGB 80405 studies have showed that long-term survival of patients with mCRC was significantly better in patients with LS primary tumours who received chemotherapy [11,12]. However, controversy remains as to whether the primary tumour location is associated with prognosis

* Corresponding author. Hepato-pancreato-biliary Surgery Department I, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, 52 Fucheng Road, Haidian District, Beijing 100142, China.
** Corresponding author. Department of Surgery, School of Translational Studies, University of Liverpool, Liverpool, L9 7AL, UK.
E-mail addresses: graeme.poston@aintree.nhs.uk (G. Poston), xingbaocai88@sina.com (B.-C. Xing).
[1] Kun Wang and Da Xu contributed equally to this work.

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of CRLM patients after radical liver resection. A study by Price et al. found that the location of the primary tumour has no impact on the survival of CRLM patients after radical hepatectomy [8], while another study by Sasaki et al. reported that patients with primary tumours on the left side had a superior OS but a worse DFS than patients with primary tumours on the right [13]. The underlying differences seen in these studies have not been discussed broadly. However, studies have shown that RAS status do play different roles in pathogenesis and oncologic outcomes depending on the site of the primary tumour [14–16]. With this, we designed this study to investigate the prognostic value of primary tumour locations, and to determine whether RAS status is a prognostic variable to the site of the primary CRC among patients who underwent hepatectomy for CRLM.

Materials and methods

Patients selection

Pathologically confirmed CRLM patients who underwent liver resection between January 2002 and December 2015 in the Hepato-pancreato-biliary Surgery Department I at the Beijing Cancer Hospital and Institute (Beijing, China) were identified from our patient database. Patient exclusion criteria included those who: (1) underwent palliative surgery, (2) underwent repeat hepatectomy due to intrahepatic recurrences, (3) were lost in follow-up, (4) had double primary malignancies. All study participants provided written consent. The study design was approved by the Ethical Review Board committee of the Beijing Cancer Hospital and Institute (Beijing, China).

Study design

This study is based on the definition according to previous studies, primary tumours located in the cecum, ascending colon, and transverse colon were defined as RS tumours, and those located in the splenic flexure, descending colon, sigmoid colon, and rectum were defined as LS tumours [17,18]. All hematoxylin and eosin (H&E) stained slides of every tumour resection block were reviewed to identify the appropriate tissue block for molecular studies. DNA was extracted from formalin-fixed paraffin-embedded tumours. Once a block was selected for RAS and BRAF V600E mutation analysis, 10 consecutive sections were then made from the block. The quality of whole-genome amplified DNA was verified by polymerase chain reactions (PCR) using 2 control amplicons [19]. All known RAS and BRAF mutation site, including KRAS (codons 12, 13 and 61), NRAS (codons 12, 13 and 61), BRAF (codon V600E) were detected.

Pre-operative management

A multidisciplinary team meet weekly in our center to discuss the treatment strategy for every patent with CRLM. Gadoxetic acid/contrast-enhanced MRI combined with diffusion-weighted MRI were routinely performed in CRLMs patients to prevent small lesions going undetected. Radiologists assisted surgeons in identifying and measuring each tumour before and after chemotherapy with chest and pelvic CT scans, and PET-CTs were used when patients were suspected to have extrahepatic disease.

Patient selection for liver resection and operative technique

For some patients, the primary tumour resection was conducted at another institute, however all LMs surgical treatments were conducted at our center. Liver metastases were considered resectable provided the following criteria were met: (1) the possibility of R0 resection with a liver remnant of $\geq$30.0% and sufficient hepatic blood inflow and outflow and (2) no evidence of unresectable extrahepatic metastases [20,21]. Prior to hepatectomy, intra-operative ultrasound was routinely performed to detect the presence of any new lesions. An ablation technique was performed in combination with surgery for tumours that were too deep and technically difficult to resect [22,23].

Post-operative outcome evaluation and follow-up

Contrast-enhanced CT scans or MRI, liver function tests, and carcinoembryonic antigen levels were performed 4 weeks after surgery and every 3 months thereafter. For those patients with recurrence limited to the liver, surgery or ablation, were the treatment option of choice.

Statistical analyses

Continuous variables were presented as the mean and standard deviation, or the median and interquartile range. Discreet variables were presented as numbers and percentages. Categorical variables were compared using the Chi-squared test and continuous variables were compared using a student's *t*-test or non-parametric test, as appropriate. Disease-free survival (DFS) and OS were calculated from the date of hepatectomy until the date of radiographic detection of recurrence, death, or the latest follow-up date. Follow-up time was calculated from the day of liver resection to death or the last follow-up date using reverse Kaplan-Meier (KM) method. Survival curves were plotted using the Kaplan-Meier method and compared by the log-rank test. Variables that were statistically significant in the univariate analysis ($p < 0.05$) were included in the multivariate analysis using a Cox proportional hazards model. All statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, software version 21.0 (IBM Corp., Armonk, NY, USA). A $p < 0.05$ was considered statistically significant.

Results

Patient characteristics of study group

A total of 463 patients underwent curative intent hepatectomy between January 2002 and December 2015 in the Hepato-pancreato-biliary Surgery Department I at the Beijing Cancer Hospital and Institute. Forty-three patients were excluded from the study, including 7 patients who underwent palliative surgery, 30 patients who underwent repeated liver surgery, 2 patients were lost to follow-up, and 4 patients had a double primary tumour. A total of 420 patients were included in the study, RAS and BRAF status were available in 332 patients (71.7%). More patients had LS primary tumours (n = 334, 79.5%) than RS (n = 86, 20.5%). The clinicopathologic characteristics of the cohort, stratified by primary CRC tumour location are summarised in Table 1. A higher proportion of female patients were seen with CRLM of the right side. Particularly, the proportion of patients with RAS mutation were much higher in RS tumours than patients with LS tumours (43.3% in right vs. 25.9% in left, P = 0.007). Since only one patient was detected with BRAF V600E mutation in RS tumour, the data was not concluded in the table. Other clinicopathologic characteristics were comparable between the two groups (Table 1).

Survival analysis

The median follow-up duration was 26 months. A total of 299 patients (71.2%) suffered tumour recurrence and 148 patients (35.4%) are still alive. The median OS was 43 (95% CI: 36.7–49.3)

Table 1
Patient clinicopathological characteristics.

Characteristic	Right-sided (n = 86)	Left-sided (n = 334)	P
Age, years, Median (IQR)	58.5 (49.7–65.0)	57.0 (49.7–64.0)	0.950
Sex, n (%)			**0.003**
Male	40 (46.5)	217 (65.0)	
Female	46 (53.5)	117 (35.0)	
T stage (n = 370)[a], n (%)			0.079
T1~2	3 (4.0)	33 (11.2)	
T3~4	72 (96.0)	262 (88.8)	
Primary nodal metastases (n = 372)[a], n (%)			0.328
Positive	47 (63.5)	208 (69.8)	
Negative	27 (36.5)	90 (30.2)	
Presentation of liver metastases, n (%)			0.808
Synchronous	46 (52.9)	169 (50.8)	
Metachronous	41 (47.1)	164 (49.2)	
Preoperative CEA, Median (IQR)	9.12 (4.6–34.2)	8.85 (3.9–30.4)	0.457
No. of CRLM, Median (IQR)	2 (1–3.5)	2 (1–4)	0.467
Size of largest CRLM, Median (IQR)	30 (20–40)	30 (20–40)	0.611
Bilobar disease, n (%)	36 (41.8)	149 (44.6)	
Extrahepatic disease, n (%)	11 (12.7)	39 (11.6)	0.255
RAS status (n = 332)[a], n (%)			**0.007**
Wild-type	38 (56.7)	195 (74.1)	
Mutated	29 (43.3)	68 (25.9)	
Purpose of chemotherapy (n = 238)[a], n (%)			0.059
Neoadjuvant	30 (76.9)	159 (79.9)	
Conversion	9 (23.1)	40 (20.1)	
Tumour response (n = 229)[a], n (%)			1.000
Response	30 (78.9)	149 (78.4)	
No response	8 (21.1)	41 (21.6)	

CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; IQR, interquartile range; Response, tumour shrinkage after chemotherapy; No response, tumour size increased after chemotherapy.
Bold values indicate statistically significant differences.
[a] The number of patients that data was available. A total of 238 patients (238/420, 56.7%) received postoperative chemotherapy for liver metastases among the whole cohort. Tumour response refers to the response to the last line chemotherapy. The tumour response of nine patients was not available.

months. When considering OS rates for tumours of the left and right sides, the 1-, 3-, and 5-year OS rates were 91.2%, 53.7% and 38.3% for patients with LS tumours and 91.9%, 50.8%, 46.5% for patients with RS tumours, respectively. There was no significant difference between the 2 groups (P = 0.699; Fig. 1A). The 1-, 3-, and 5-year DFS rates were 55.5%, 29.1% and 22.4% for patients with LS tumours and 58.1%, 33.6% and 29.1% for patients with RS tumours, respectively. There was also no significant difference between the 2 groups (P = 0.536; Fig. 1B). In the uni/multivariate analysis, primary tumour location was not an independent factor affecting patients' long-term survival [hazard ratio (HR) 1.082; 95% confidence interval (CI): 0.764–1.533, P = 0.655]. On the other hand, RAS mutation is shown to be associated with worse OS (HR 1.740; 95% CI: 1.076–2.815, P = 0.024). In addition, liver metastases tumour size (HR 2.202; 95% CI: 1.337–3.627, P = 0.002), number of tumours (HR 1.716; 95% CI: 1.014–2.903, P = 0.044) and primary N stage (HR 1.694; 95% CI: 1.036–2.770, P = 0.036) were also shown to be independent prognostic factors contributing to OS in patients with CRLMs (Table 2).

Although patients with RAS mutation were associated with worse prognosis and appeared more frequently in patients with RS tumours, the long-term survival was comparable among patients with tumours on both sides. Thus we further explored the prognostic role of RAS status in different tumour sides. Among patients with RS primary tumours, RAS status did not impact OS among patients with wild type-RAS (1-, 3-, and 5-year OS rates: 94.7%,

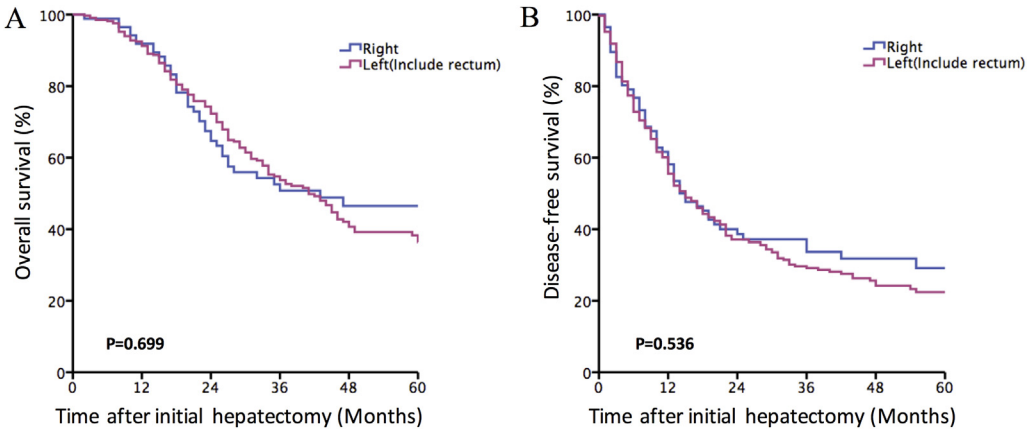

Fig. 1. (**A**) Overall survival and (**B**) disease-free survival in patients with CRLM stratified by LS and RS primary tumour after liver resection (OS: P = 0.699, DFS: P = 0.536; log-rank test).

Table 2
Uni/multivariate analyses of factors associated with overall survival.

Prognostic factor		Univariable P	Multivariable analysis HR (95% CI)	P
Sex	Male/Female	0.223		
Age (years)	<60/≥60	0.815		
Primary tumour location	Left/Right	0.655		
Primary T stage	T1-2/T3-4	0.134		
Primary N stage	N0/N+	**<0.001**	1.694 (1.036–2.770)	**0.036**
Liver metastases number	Single/Multiple	**0.023**	1.716 (1.014–2.903)	**0.044**
Liver metastases size	<50 mm/≥50 mm	**0.005**	2.202 (1.337–3.627)	**0.002**
Liver metastases distribution	Unilateral/Bilobar	0.129		
Presentation of liver metastases	Synchronous/Metachronous	0.214		
CEA before hepatectomy	<200 ng/mL/≥200 ng/mL	0.064		
Tumour response*	No/Yes	**0.003**	1.672 (0.973–2.874)	0.063
RAS status	Wild/Mutant	**<0.001**	1.740 (1.076–2.815)	**0.024**
Extrahepatic metastases	No/Yes	0.097		

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio.* Means the last line chemotherapy.
Bold values indicate statistically significant differences.

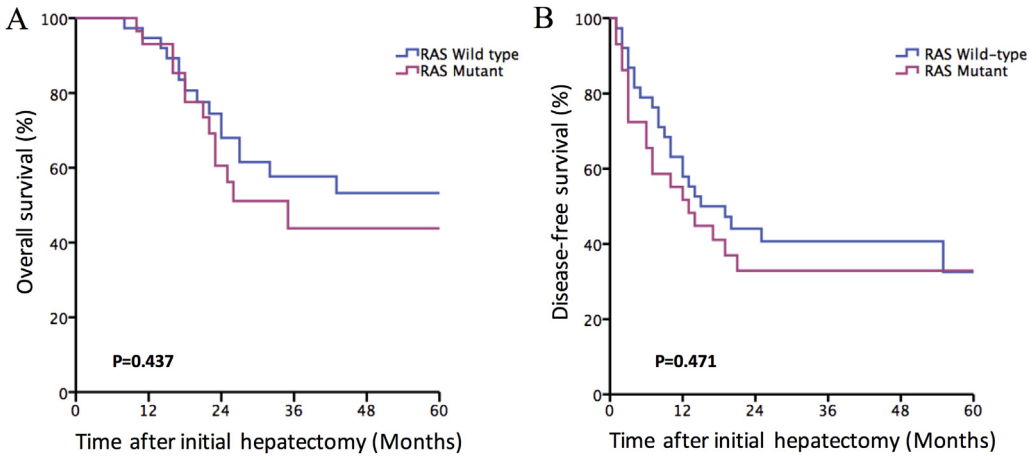

Fig. 2. (**A**) Overall survival and (**B**) disease-free survival for patients stratified by RAS status with RS primary tumour (OS: P = 0.437; DFS: P = 0.471, log-rank test).

57.7%, 53.2%) versus mutant-RAS (1-, 3-, and 5-year OS rates: 93.1%, 43.8%, 43.8%) (Fig. 2A, P = 0.437). Similarly, DFS did not differ among patients with wild type-RAS (1-, 3-, and 5-year DFS rates:57.9%, 40.7%, 32.5%) versus mutant-RAS (1-, 3-, and 5-year DFS rates: 51.7%, 32.9%, 32.9%) (Fig. 2B, P = 0.471). However, among patients with LS primary tumours who underwent surgical resection, OS was significantly worse in patients with mutant-RAS (1-, 3-, and 5-year OS rates: 87.6%, 35.3%, 27.5%) than wild type-RAS (1-, 3-, and 5-year OS rates: 95.3%, 63.7%, 44.6%) (P < 0.001) (Fig. 3A). Similarly, DFS was also significantly worse in patients with mutant-RAS (1-, 3-, and 5-year DFS rates: 46.3%, 21.1%, 21.1%) than wild type-RAS (1-, 3-, and 5-year DFS rates: 61.1%, 36.6%, 23.9%) (P = 0.002) (Fig. 3B). In the uni/multivariate analysis, RAS mutation was not associated with OS among patients with a RS primary tumour even in univariate analysis (HR 1.272; 95% CI: 0.064–2.679, P = 0.526), but was significantly affecting OS among patients with a

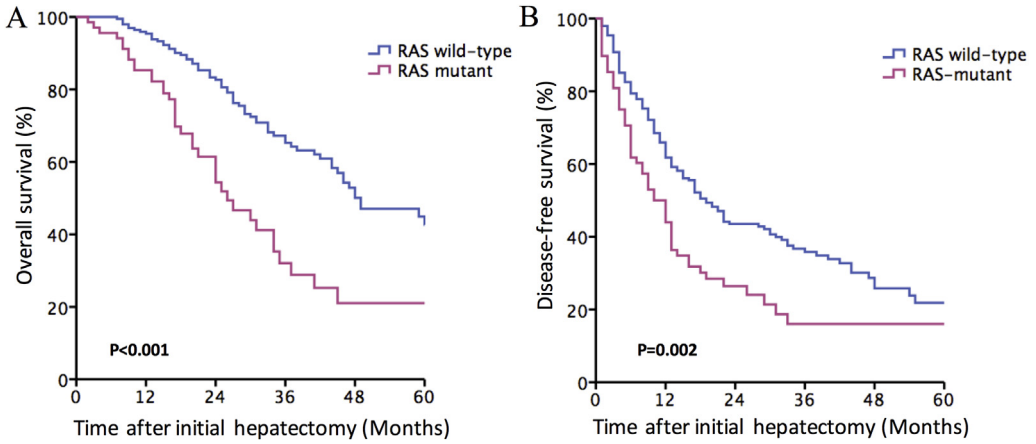

Fig. 3. (**A**) Overall survival and (**B**) disease-free survival for patients stratified by RAS status with LS primary tumour (OS: P < 0.001; DFS: P = 0.002, log-rank test).

Table 3
Uni/multivariate analyses of factors associated with overall survival stratified by primary tumour location.

Prognostic factor		Left-sided			Right-sided		
		Univariable P	Multivariable analysis HR (95% CI)	P	Univariable P	Multivariable analysis HR (95% CI)	P
Sex	Male/Female	0.275			0.527		
Age (years)	<60/≥60	0.611			0.658		
Primary T stage	T1-2/T3-4	0.178			0.430		
Primary N stage	N0/N+	**<0.001**	2.186 (1.238–3.862)	**0.007**	0.443		
Liver metastases number	Single/Multiple	**<0.001**	3.117 (1.561–6.224)	**0.001**	0.065		
Liver metastases size	<50 mm/≥50 mm	**0.028**	1.708 (0.973–2.998)	0.062	0.059		
Liver metastases distribution	Unilateral/Bilobar	**0.044**	0.657 (0.382–1.128)	0.127	0.682		
Presentation of liver metastases	Synchronous/Metachronous	0.341			0.383		
CEA before hepatectomy	<200 ng/mL/≥200 ng/mL	0.073			0.320		
Tumour response*	No/Yes	**0.003**	2.121 (1.179–3.818)	**0.012**	0.512		
RAS status	Wild/Mutant	**<0.001**	2.300 (1.328–3.983)	**0.003**	0.526		
Extrahepatic metastases	No/Yes	0.336			0.089		

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio. * Means the last line chemotherapy.
Bold values indicate statistically significant differences.

LS primary tumour (HR 2.300; 95% CI: 1.328–3.983, P = 0.003) (Table 3).

Discussion

Two recent pooled studies investigated the predictive and prognostic effect of the location of the primary tumour in patients with metastatic and unresectable colorectal cancer included in six randomized trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK and 20050181), and found that OS, PFS and objective response rate (ORR) were significantly worse among patients with RS tumours compared with patients with LS tumours [10,24]. Despite this, whether the primary tumour location was a prognostic factor for CRLM patients after radical liver resection remained controversial. In a multicenter retrospective study of a total of 414 patients with mCRC who underwent liver resection, results showed that the OS was comparable in patients with RS and LS primary tumours [8]. Another recent study found that LS primary tumours were associated with worse DFS, but better OS in resectable CRLM patients after surgical resection [13]. However, patients with rectal tumours were excluded in the study as he authors believed that RS tumours relapse less frequently, but spread more aggressively once they recurred. Another study found that both OS or DFS of the patients with LS primary tumours were superior to those with RS tumours, yet patients with transverse colon and rectal cancer were excluded from the study [25]. In this study, we also found that there was no difference on DFS between CRLM patients with LS and RS primary tumour after liver resection. However, unexpectedly OS was also comparable between the 2 groups. Several reasons might help to explain these findings. Firstly, there are some differences in the incidence, clinicopathological features and pathogenesis between Chinese and North American patients with CRLM from an ethnic and racial perspective, leading to differences in prognostic value of anatomic primary tumour site. Secondly, the FIRE-3 and CALGB 80405 study mainly embodied the close relationship between the therapeutic effect of chemotherapy and the primary tumour location [11,12]. Several genes have been identified to be related to worse response to chemotherapy, such as BRAF mutations, MSI-H, and ERCC1 expression, which were more common in patients with RS tumours, leading to a worse outcome for them receiving palliative chemotherapy [26–30]. However, hepatectomy plays dominant role in improving survival in patients with CRLM who underwent radical resection; while the effect of chemotherapy solely, in comparison, is significantly less. Thirdly, the impact of primary tumour location on survival significantly differs depends on tumour stages. While there is limited association between tumour location and survival in early stage (I and II) CRC patients, it is still controversial in stage III patients. However, for stage IV patients, there is strong evidence that survival is significantly influenced by tumour location for stage IV unresectable patients [31–33]. As for stage IV resectable patients, this remains uncertain. A study has previously shown that the 5-year survival is comparable after radical resection between patients with resectable CRLM and those with stage III colorectal cancer [34]. We observed similarities between patients' oncological features between patients with CRLM post liver resection and those in stage III. Our study confirms this finding, showing that the impact of primary tumour location on long-term survival in CRLM patients undergoing hepatectomy was similar to those in stage III, but different to those in stage IV with unresectable metastases receiving palliative treatment.

Our study found that most of the clinicopathologic characteristics were comparable among LS and RS CRLM, except gender and RAS mutation status. Previous studies have validated that RS tumours are more common in women, and are more likely to be diploid [35,36]. Another important finding is that the proportion of mutant-type RAS tumours is significantly higher in CRLM patients with a RS primary tumour than those with LS tumours. RAS status was widely accepted as an important prognostic factor among patients with CRLM after liver resection [6]. However, in this study we found that the prognostic effect of RAS status seemed quite different depending on the primary tumour location. The OS and DFS were much worse among mutant RAS patients with LS CRLM, but comparable between RAS wild-type and mutant patients with RS CRLM. This finding is consistent with previous study [37]. However, there are also studies that found that the impact of RAS status on survival in CRLM patients who underwent surgical resection was independent of site of embryonic origin. Yet, it should be noted that rectal cancers and transverse colon cancers were excluded in this study, which might also cause the different impact on survival by RAS status [25]. While not completely understood, several studied have found that the effect of RAS in the mechanism of liver metastasis is different between LS and RS primary tumour. For example, aggressive tumour behavior after RAS activation can be explained by tumour hypermethylation [16]. Methylation differs across tumour sites and CpG island methylator phenotype is more common in RS CRLM [15,26]. In contrast, LS CRLMs were shown to be associated with higher levels of epiregulin and amphiregulin, which in turn may confer a more indolent biologic behavior in RAS [14]. Based on the results of this study, RAS status is an independent prognostic factor for survival, but the impact on survival depends on primary tumour location. In patients with LS tumours, RAS

mutation is strongly associated with worse survival, so it should be taken into consideration in decision-making and prognostic evaluation. However, the survival was similar between RAS wild-type and RAS mutant among patients with RS tumours, suggesting that RAS might not played a crucial role in the development of liver metastases of RS tumours. The molecular mechanisms behind it needs further research.

There are some limitations in this study. Firstly, since genetic testing was not regularly performed in CRLM patients in the earlier years (before the year of 2010), genetic testing data of some patients enrolled in this study were not complete. Secondly, since this is a retrospective study, some patients had their primary tumour resected at other institutions, so some of the primary tumour data (primary T and N stage) were missing. Thirdly, although BRAF mutation was also proven to be associated with survival and appeared more common in patients with RS tumours, the mutation rate is much lower than RAS (about 5%). In this study, we only confirmed one patient with BRAF mutation, since patients with BRAF mutation rarely have the chance to receive liver resection due to their more aggressive tumour behavior [5].

In conclusion, primary tumour location has no influence on survival after hepatic resection for CRLM. RAS status does have a variable prognostic impact for CRLM after hepatic resection depending on the site of the primary CRC.

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Conflict of interest

None.

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