





Recurrence patterns predict survival after resection of colorectal liver metastases

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Key words

colorectal liver metastases, hepatectomy, liver resection, recurrence, survival.

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Introduction

Liver resection is the mainstay of curative-intent treatment for colorectal liver metastases (CRLM) with five-year overall survival rates of up to 58% and actual 10-year recurrence-free survival rates of

Abstract

Background: Effective treatment of colorectal liver metastases (CRLM) is challenging because recurrence occurs in many patients after curative-intent resection. This study evaluates the recurrence patterns after resection of CRLM and its association with survival.

Methods: A retrospective review of prospectively collected data of patients with CRLM managed with curative-intent resection from January 2007 to December 2017 was performed. The main outcomes and measures were the timing of recurrence, initial sites of recurrence, overall survival and recurrence-free survival. Early recurrence was defined as the detection of any organ recurrence ≤ 6 months from resection of CRLM.

Results: A cohort of 194 patients was included for analysis. After a median follow-up of 85.3 months, 145 patients (74.7%) were diagnosed with recurrence. The median overall survival was 67.6 months (95% CI 50.4–80.2) and the 5-year overall survival was 54.1%. After initial recurrence was detected, the median survival was 28.9 months (95% CI 23.6–37.8) months and the 5-year overall survival was 28.8%. Early recurrence occurred in 58 patients (29.9%). Initial recurrence patterns included: liver only in 53 patients (36.5%), multiple sites in 48 patients (33.1%), lung only in 30 patients (20.7%), and other single extrahepatic sites in 14 patients (9.6%). Early recurrence and initial multi-site recurrence were independent predictors of worse overall survival for patients who develop recurrence after resection of CLRM.

Conclusion: The timing and initial sites of recurrence are prognostic factors in determining survival after curative-intent resection of CRLM.

20% reported.^{1,2} However, the effective treatment of CRLM is challenging because recurrence occurs in up to 75% within the first 2 years after liver resection, and many patients eventually die from recurrent disease.^{3,4} Numerous studies have attempted to define

preoperative clinicopathologic factors associated with prognosis and consolidate significant predictors of poor long-term outcomes into prediction models. However, these models have only demonstrated modest concordance with survival outcomes and do not retain their prognostic significance over time.^{5,6} Furthermore, the significance of these preoperative prognostic factors on overall survival after recurrence has occurred is uncertain.

The timing and initial sites of recurrence of CRLM are potential surrogates of tumour biology.⁷ Patients with resected CRLM are free of clinical disease at a defined time point and present an opportunity to study the disease course of metastatic colorectal cancer. Early recurrence is associated with worse survival than patients who developed late recurrence following resection of CRLM.^{8,9} Despite the negative prognosis, rescue treatment has been shown to improve survival. Repeat hepatic resection is feasible in approximately a third of patients with early intrahepatic recurrence, with comparable 5-year survival (47.2%) to patients with repeat liver resection for late recurrence (48.7%).⁸ Perioperative systemic chemotherapy has also been shown to modify recurrence patterns in high-risk patients and is associated with lower extrahepatic disease.¹⁰ Understanding the patterns of recurrence is important to inform surveillance and treatment strategies that can potentially impact the disease course of patients with CRLM. The current study evaluates the timing and initial site of recurrence in a cohort of patients undergoing curative-intent resection of CRLM and examines the effects of these factors on survival outcomes.

Methods

Data sources and patient population

This retrospective cohort study used prospectively collected data from the Northern Upper Gastrointestinal Surgical Unit Liver Resection Database with ethical approval provided by the Human Research Ethics Committee of the Northern Sydney Local Health District (Reference: ETH12205, addendum 14.1). Patients were included if they had undergone their first curative-intent liver resection between January 2007 and December 2017 and had a minimum follow-up of 6 months. Patients with an initial hepatectomy before 2007, unresectable residual tumour (R2 resection), follow-up of fewer than 6 months, or death within 30 days of liver resection were excluded.

Clinicopathologic and treatment that were recorded include age, sex, primary colorectal tumour location (right colon, left colon, and rectum), primary colorectal tumour regional lymph node status, time interval between the primary CRC and diagnosis of CRLM, preoperative carcinoembryonic antigen (CEA) level, KRAS mutation status, size of the largest hepatic tumour, the number of hepatic lesions, tumour burden score (TBS), distribution of CRLM (unilobar versus bilobar), the extent of liver resection (major versus minor), resection margin status, and use of perioperative chemotherapy. The TBS was calculated using the following formula: $[TBS^2 = (\text{maximum tumour diameter})^2 \times \text{number of liver lesions}]^2$.¹¹ Major hepatectomy was defined as resection of at least 3 Couinaud segments.¹² An R0 margin was defined as a tumour-

free margin ≥ 1 mm, and an R1 margin was defined as microscopic tumour within 1 mm of the resection margin.

After liver resection, patients were monitored for recurrence with 3–6-monthly physical examination, serum CEA and computed tomography. In addition, 18-fluorodeoxyglucose positron emission tomography and magnetic resonance imaging of the liver was performed as indicated. Patients were generally followed up every 3–6 months for the first year and then annually. The treatment of tumour recurrence was decided following consensus among the multidisciplinary team.

Study outcomes and measures

The timing and site of recurrence were determined based on a review of serial digital cross-sectional imaging or documentation of histologic recurrence. The primary author (GYMW) and senior author (TJH) jointly reviewed the cases with indeterminate findings for recurrence on imaging and correlated these findings with clinical documentation to understand how the treating clinicians had interpreted this information. Recurrence was considered present if these findings led to a management decision such as administration of systemic therapy or if initially indeterminate lesions progressed on subsequent follow-up imaging. Early recurrence was defined as cancer recurrence detected ≤ 6 months after resection of CRLM based on prior studies that have demonstrated this cut-off to be of prognostic significance.^{8,9} Overall survival was defined as the time from the date of the first liver resection to the date of last follow-up or death from all causes. Recurrence-free survival was defined as the time from the first liver resection to the detection of recurrence or death from all causes.

Statistical analysis

Summary statistics were reported as frequencies with percentages or median values with interquartile ranges (IQR). Differences in categorical values were estimated using the chi-square test or Fisher's exact test, as appropriate. Differences in continuous values were assessed with the Mann–Whitney *U* test. Median follow-up time for survivors was estimated using the reverse Kaplan–Meier method. Overall survival and recurrence-free survival were estimated using the Kaplan–Meier method, and differences in survival were evaluated with the log-rank test. The Cox proportional-hazards model was used to assess the association of clinicopathological factors with prognosis. Multivariable analysis was performed for factors with a *P* value of ≤ 0.20 on univariable analysis. All statistical testing was two-sided, with significance defined as *P* < 0.05 . Data management and statistical analyses were performed using Stata[®] SE for Windows[®] version 15.1 (StataCorp, College Station, TX, USA).

Results

Cohort description

A total of 245 resections for CRLM were performed or supervised by the senior author (single surgeon, TJH) between 2007 and 2017.

Fifty-one (20.8%) hepatectomies were excluded from analysis: 35 patients with repeat hepatectomies, four patients with disease progression before completion of two-stage hepatectomy, four patients with disease progression before resection of the primary CRC, three patients with unresectable residual disease, two patient deaths within 30 days of hepatectomy, and three patients with a follow-up of fewer than 6 months. A total of 194 patients who underwent their first liver resection were included for analysis. The median follow-up as measured from the time of hepatectomy was 85.3 months, during which 104 patients (53.6%) had died, and 145 patients (74.7%) had developed recurrence. Forty-nine patients (25.3%) had no evidence of recurrence up to their last review. The demographic and clinicopathologic characteristics of the cohort of 194 patients are summarized in Table 1.

Overall survival and recurrence-free survival

The estimated median, 1-year, 3-year and 5-year overall survival were 67.6 (95% CI 50.4–80.2) months, 94.3%, 67.0%, and 54.1%, respectively. Figures 1 and 2 demonstrate the Kaplan–Meier survival curves for recurrence-free survival and overall survival from the initial diagnosis of recurrence, respectively. The estimated median, 1-year, 3-year and 5-year recurrence-free survival were 13.4 months (95% CI 10.6–19.0), 53.0%, 29.0%, and 23.5%, respectively. The median and 5-year overall survival after recurrence was detected was 28.9 months (95% CI 23.6–37.8) months and 28.8%, respectively.

Kaplan–Meier survival curves for patients undergoing resection of CRLM showing; Figure 1, Recurrence-free survival; Figure 2, Overall survival from time of recurrence.

Table 1 Demographic and clinicopathologic characteristics of patients undergoing resection of colorectal liver metastases

Characteristic	Total (n = 194)	Early recurrence (n = 58)	Delayed recurrence (n = 87)	No recurrence (n = 49)
Demographic data				
Age, years, median (IQR)	66.1 (58.7–73.10)	66.6 (57.4–65.2)	65.7 (59.0–73.4)	66.0 (60.1–77.1)
Sex, n (%)				
Male	117 (60.3)	29 (50.0)	62 (71.3)	26 (53.0)
Female	77 (39.7)	29 (50.0)	25 (28.7)	23 (47.0)
Preoperative factors				
Primary colon tumour, n (%)				
Right	52 (26.8)	18 (31.0)	20 (23.0)	14 (28.6)
Left	78 (40.2)	22 (38.0)	39 (44.8)	17 (34.7)
Rectum	64 (33.0)	18 (31.0)	28 (32.2)	18 (36.7)
Lymph node metastasis, n (%)				
Absent	63 (32.5)	15 (25.9)	31 (35.6)	17 (34.7)
Present	131 (67.5)	43(74.1)	56 (64.3)	32 (65.3)
CRLM Presentation, n (%)				
Metachronous	92 (47.4)	17 (29.3)	44 (50.6)	31 (63.3)
Synchronous	102 (52.6)	41(70.6)	43 (49.4)	18 (36.7)
Preoperative chemotherapy, n (%)				
No	39 (20.1)	8 (13.8)	21 (24.1)	10 (20.4)
Yes	155 (79.9)	50 (86.2)	66 (75.9)	39 (79.5)
Preoperative CEA, n (%)				
Not elevated	42 (21.6)	10 (18.9)	18 (20.7)	14 (29.2)
Elevated	146 (75.3)	43 (81.1)	69 (79.3)	34 (70.8)
Missing	6 (3.1)			
Size of largest CRLM, cm [median (IQR)]	3.0 (2.0–5.0)	3.1 (2.2–6.0)	3.5 (2.0–5.0)	2.5 (1.7–3.7)
Number of CRLM [median (IQR)]	2 (1–3)	2 (1–4)	2 (1–3)	1 (1–2)
Tumour burden score [median (IQR)]	4.1 (3.0–5.8)	5.1 (3.6–6.6)	4.1 (3.0–5.4)	3.2 (2.1–4.0)
Distribution of CRLM, n (%)				
Unilateral	124 (63.9)	32 (55.2)	59 (67.8)	33
Bilateral	70 (36.0)	26 (44.8)	28 (32.2)	16
KRAS mutation status, n (%)				
Wild-type	63 (63.0)	18 (58.1)	30 (63.8)	15 (68.2)
Mutated	37 (37.0)	13 (41.9)	17 (36.2)	7 (31.8)
Not performed	94 (48.5)			
Operative factors				
Liver resection, n (%)				
Minor	128 (66.0)	35 (60.3)	53 (60.9)	40 (81.6)
Major	66 (34.0)	23 (39.7)	34 (39.1)	9 (18.4)
Resection margin, n (%)				
R0	128 (66.0)	38 (65.5)	54 (62.1)	36 (73.5)
R1	66 (34.0)	20 (34.5)	33 (37.9)	13 (26.5)
Postoperative factors				
Postoperative chemotherapy, n (%)				
No	62 (32.0)	15 (25.9)	23 (26.4)	24 (49.0)
Yes	132 (68.0)	43 (74.1)	64 (73.6)	25 (51.0)

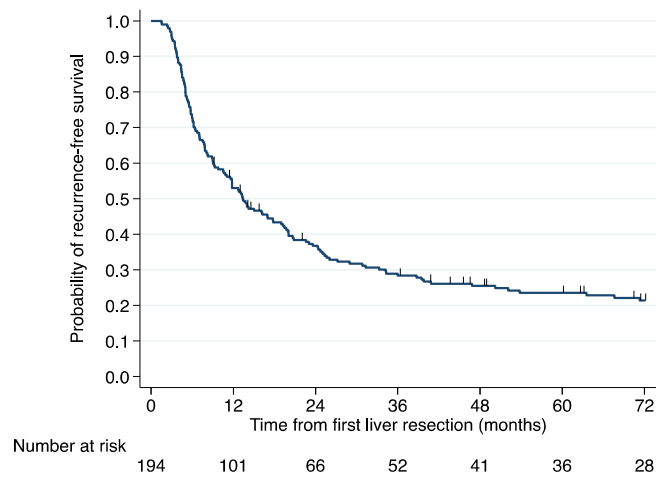


Fig. 1. Recurrence-free survival after resection of colorectal liver metastases.

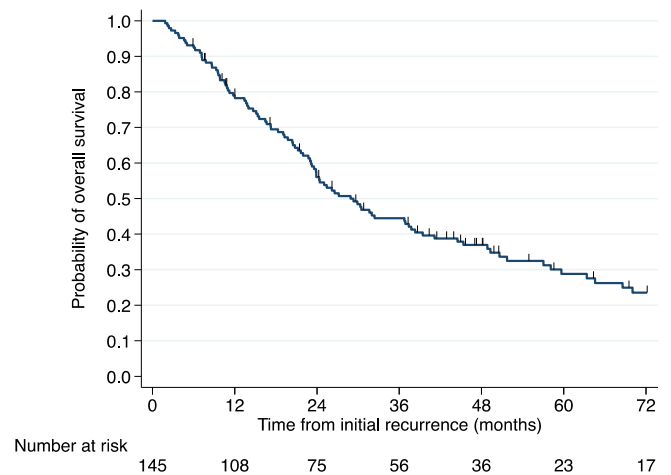


Fig. 2. Overall survival from time of first recurrence after resection of colorectal liver metastases.

Timing of recurrence

The features of patients with early and late recurrence were comparable except for the distribution of the number of liver metastases and the tumour burden score. Among the 145 patients who developed recurrence, 58 patients (40.0%) had early recurrences, and 87 patients (60.0%) had late recurrences. Figure 3 shows the Kaplan–Meier survival curves for patients stratified by timing of recurrence. The median survival was 27.5 months (95% CI 43.5–75.4) for patients with early recurrence and 64.9 months (95% CI 43.5–75.4) for patients with late recurrence. The 5-year overall survival was 25.9% for patients with early recurrence and 53.1% for patients with late recurrence. Early recurrence was associated with a significantly lower overall survival (log-rank $P < 0.001$) compared to patients with late recurrence.

Kaplan–Meier survival curves for patients undergoing resection of CRLM showing; Figure 3, Overall survival stratified by timing of recurrence; Figure 4, Overall survival stratified by initial sites of recurrence.

Initial site of recurrence

Table 2 demonstrates the initial sites of recurrence after resection of CRLM according to the timing of recurrence. The liver was the most common initial site of recurrence, with isolated intrahepatic recurrence occurring in 53 patients (36.6%) and as part of multi-site recurrence in 36 patients (24.8%). Among 66 patients (36.6%) with an R1 resection margin, isolated resection margin recurrence was detected as the initial site of recurrence in three patients (4.5%), and recurrence distant to the resection margin was detected as the initial site of recurrence in 51 patients (77.3%). Isolated recurrence of disappearing CRLM after neoadjuvant chemotherapy was detected in two of 53 patients (3.8%) with intrahepatic recurrence. The lungs were the most common initial site of extrahepatic recurrence, with isolated lung recurrence occurring in 30 patients (20.7%) and as part of initial multi-site recurrence in 36 patients (24.8%). Fourteen patients (9.6%) with recurrence at single sites other than the lungs made up a relatively small proportion of the

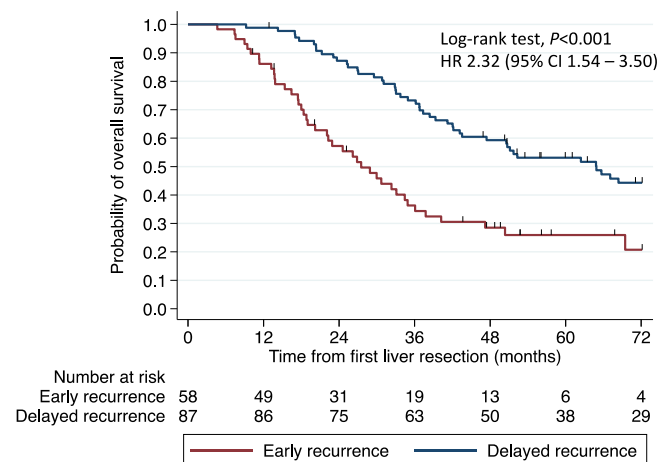


Fig. 3. Overall survival stratified by timing of recurrence.

cohort and were heterogeneous in terms of the initial sites of recurrence. Figure 4 shows the Kaplan–Meier survival curves for patients stratified by initial sites of recurrence. The median survival in descending order is isolated lung recurrence (75.4 months, 95% CI 40.2–109.5), other single site recurrences (64.9 months, 95% CI 18.4–80.2), isolated liver recurrence (43.5 months, 95% CI 32.9–81.6), and multi-site recurrence (31.1 months, 95% CI 22.9–41.2).

Factors associated with overall survival

Univariable and multivariable analyses for overall survival following recurrence are presented in Table 3. On univariable analysis, eight factors were significant predictors of overall survival: timing of recurrence, initial site recurrence, age, primary tumour sidedness, TBS, KRAS mutation status, preoperative chemotherapy and the extent of liver resection. On multivariable analysis, early recurrence (HR 3.15, 95% CI 1.62–6.11, $P = 0.001$), initial multi-site of recurrence (HR 3.39, 95% CI 1.53–7.53, $P = 0.008$) and KRAS

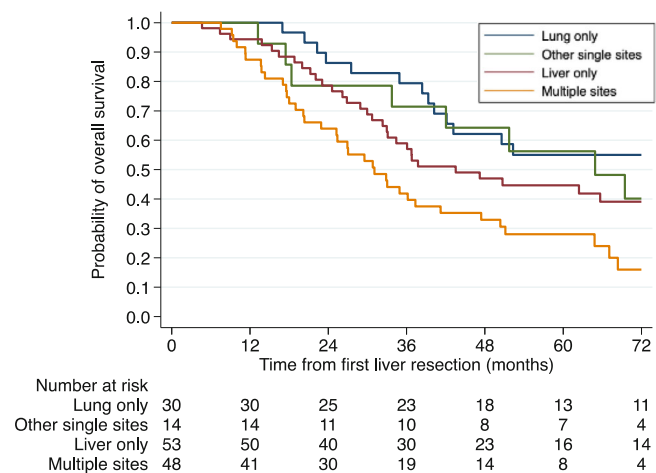


Fig. 4. Overall survival stratified by initial site of recurrence.

mutation (HR 2.03, 95% CI 1.04–3.96, $P = 0.039$) were independent predictors of poor overall survival.

Discussion

The current study examines the timing and initial sites of recurrence after resection of colorectal cancer on long-term survival. The 5-year overall survival of 52.0% and overall recurrence of 74.5% following curative-intent liver resection for CRLM are consistent with published survival outcomes.^{1–4} The high overall recurrence over different study populations and time may reflect the expanding criteria of resectability and selection of patients with more

aggressive disease.¹³ The timing, initial sites of recurrence, and KRAS mutation status were significant predictors of long-term outcome. All these factors are potential surrogates of tumour biology. None of the other examined preoperative clinicopathologic outcomes or perioperative chemotherapy retained prognostic significance in patients who developed recurrence after resection of CRLM. These findings reinforce the contribution of biologic selection, which is often underestimated.

Early recurrence is the single most useful clinical feature in estimating worse conditional disease-free survival after resection of CRLM.⁶ In our cohort, 56 patients (28.6%) had an early recurrence, consistent with the reported literature (10–40%).^{8,9} The findings in the current study agree with ≤ 6 months as a clinically important cut-off time for early recurrence based on differences in overall survival.^{8,9} The primary aim of surveillance after resection of CRLM is to enable early detection of further recurrences that may be amenable to definitive treatment. Current guidelines do not provide definitive surveillance recommendations, and significant variation exists because of the lack of evidence.¹⁴ However, the therapeutic opportunity for further potentially curative surgery and survival benefit with multimodal treatment for unresectable disease supports the implementation of surveillance within 6 months after resection of CRLM.^{4,9}

The initial site of recurrence in this study was time-dependent and had different effects on overall survival. The liver was the most common site of recurrence after resection of CRLM and occurred in approximately 60% of patients. Isolated recurrence at the hepatic resection margin was relatively low in patients with an R1 resection, defined as microscopic tumour within 1 mm of the resection margin in the current study. Submillimeter pathological margins likely underestimate the actual distance between the

Table 2 Initial sites of recurrence after resection of colorectal liver metastases ($n = 145$)

Recurrence ≤ 6 months from liver resection ($n = 58$)		Recurrence > 6 months from liver resection ($n = 87$)	
Recurrence in a single organ		Recurrence in a single organ	
Intrahepatic only	27 (18.6%)	Intrahepatic only	26 (17.9%)
Resection margin recurrence	2	Resection margin recurrence	1
Resection margin and new intrahepatic recurrence	3	Resection margin and new intrahepatic recurrence	4
New intrahepatic recurrence	22	New intrahepatic recurrence	21
Extrahepatic only	12 (8.3%)	Extrahepatic only	32 (22.1%)
Lung only	8	Lung only	22
Locoregional primary	1	Locoregional primary	2
Peritoneum	–	Peritoneum	3
Adrenal	2	Adrenal	1
Retroperitoneal lymph nodes	1	Retroperitoneal lymph nodes	–
Bone	–	Bone	2
Brain	–	Brain	1
Other single sites	–	Other single sites	1
Abdominal wall	–	Abdominal wall	–
Recurrence in multiple organs	19 (13.1%)	Recurrence in multiple organs	29 (20.0%)
Liver/lung	8	Liver/lung	9
Liver/intra-abdominal	3	Liver/intra-abdominal	9
Lung/intra-abdominal	2	Lung/intra-abdominal	8
Lung/bone	–	Lung/bone	1
Liver/lung/other	5	Liver/lung/other	2
Other multi-site	1	Other multi-site	–
Lung/bone/retroperitoneal lymph nodes	–	Lung/bone/retroperitoneal lymph nodes	–

Table 3 Univariable and multivariable analyses of the association between recurrence patterns and clinicopathologic factors and overall survival for patients with recurrence (*n* = 145)

Predictors	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	<i>P</i> value	Hazard ratio	95% CI	<i>P</i> value
Age	1.02	1.01–1.05	0.012	–	–	–
Primary CRC lymph node status			0.870			
Negative	Ref					
Positive	1.03	0.68–1.57				
Site of primary CRC			0.001	–	–	–
Right	Ref					
Left	0.50	0.33–0.76				
Timing of CRLM—synchronous			0.228			
Metachronous	Ref					
Synchronous	1.28	0.86–1.92				
Tumour burden score			0.145	–	–	–
<3	Ref					
≥3–9	0.94	0.57–1.53				
>9	2.52	1.18–5.37				
Carcinoembryonic antigen level			0.369			
Not elevated	Ref					
Elevated	1.26	0.76–2.11				
Preoperative chemotherapy			0.125	–	–	–
No	Ref					
Yes	1.48	0.90–2.45				
KRAS mutation status			0.090			0.039
Wild type	Ref			Ref		
Mutated	1.65	0.92–2.94		2.02	1.04–3.96	
Distribution of CRLM						
Unilateral	Ref					
Bilateral	1.02	0.67–1.54	0.932			
Extent of resection						
Minor	Ref					
Major	1.32	0.89–1.96	0.171	–	–	–
Resection margin						
R0	Ref					
R1	1.20	0.80–1.80	0.370			
Postoperative chemotherapy						
No	Ref					
Yes	1.14	0.73–1.80	0.562			
Timing of recurrence						0.001
>6 months (delayed)	Ref		<0.001	Ref		
≤6 months (early)	2.33	1.55–3.51		3.15	1.62–6.11	
Initial site of recurrence						0.008
Liver only	Ref		0.005	Ref		
Lung only	0.76	0.43–1.34		1.01	0.38–2.67	
Other extrahepatic sites—single	1.02	0.50–2.08		1.16	0.34–3.91	
Multiple sites	1.91	1.19–3.05		3.39	1.53–7.53	

Note: The bold values were used to indicate statistically significant values.

tumour and surgical margin because of the routine use of a cavitron surgical aspirator for parenchymal transection and ablation of the resection margin when the tumour is deemed to be close.¹⁵ Furthermore, positive resection margin after resection of CRLM may be a surrogate of aggressive tumour biology, given that most recurrences occur distant from the surgical margin.¹⁶

Prior critical analysis of recurrence patterns after resection of CLRM have demonstrated distinct prognosis associated with the initial sites of recurrence. Patients with initial lung recurrence were associated with prolonged survival (median survival 36 months), whereas patients with initial multi-site recurrence did not survive beyond 5 years (median survival 13 months).⁴ The survival benefit of resecting lung recurrence has been substantiated through retrospective cohort studies, but a recent randomized controlled trial did not conclusively support pulmonary metastasectomy over continued

active monitoring.¹⁷ As in previous studies, the number of patients with single-site metastasis in our cohort was too small and heterogeneous to draw meaningful inferences.⁴ Current guidelines recommend curative-intent surgery for selected patients with colorectal metastases involving the liver, lungs, and peritoneum only.¹⁸ Metastases beyond these sites should be discussed in a multidisciplinary team to individualize locoregional and systemic treatment options. Although systemic therapy is the accepted standard for patients with multi-site recurrence, this treatment paradigm is being challenged. Emerging evidence supports a survival benefit for resection of CRLM without resection of synchronous low-volume lung metastases.^{19,20}

Clinicopathologic factors and risk scoring systems have been proposed specifically to predict early recurrence and overlap to some degree with established clinical risk scores to predict long-

term outcomes.^{21,22} However, prognostic cut-off values that form the basis of these models lack agreement and external validity. This may reflect differences in the baseline characteristics of the study population and criteria for resectability and selection bias from the retrospective design of these studies. Increasingly, molecular profiling is being used to guide targeted therapy and influences recurrence patterns in colorectal cancer.²³ The findings in this study demonstrated the limitations of preoperative clinicopathologic factors in predicting survival after recurrence has occurred and prompts consideration of molecular profiling, which could provide more specific directions that account for the heterogeneity of cancer recurrence. Thus, future research priorities should attempt to identify and define the prognostic value of molecular biomarkers.

Limitations

Some limitations should be considered when interpreting the findings in this study. Firstly, the study is susceptible to selection bias because of the small sample size, retrospective design and derivation of the cohort from a single institution. Secondly, the complexity of metastatic colorectal cancer introduces a degree of clinical heterogeneity in terms of diagnosis, treatment and follow-up. In particular, the lack of a standardized surveillance protocol and cross-sectional imaging performed for unrelated reasons may contribute to surveillance bias. Thirdly, the correlation between KRAS mutation status and survival in this study needs to consider the low number of patients with known KRAS mutation status and the lack of information on clinically relevant mutations. The low proportion of patients with known KRAS mutation status reflects selective testing for access to anti-epidermal growth factor therapy. Finally, although the direction of effect for TBS on univariable and multivariable analysis indicates that higher TBS is associated with worse survival, the wide confidence interval reflects the small sample size of patients with high TBS (>9), which may have influenced these findings.

Conclusion

Recurrence patterns after resection of colorectal liver metastases are significant time-dependent predictors of long-term outcomes. The heterogeneity of disease behaviour of metastatic recurrence leads to challenges in optimizing treatment and predicting long-term outcomes after potentially curative surgery. The findings in this study support the implementation of standardized surveillance protocols to detect early recurrence. Future research priorities should include defining the role of molecular biomarkers to predict recurrence patterns and guide a personalized treatment approach for patients with metastatic colorectal cancer.

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Author contributions

Geoffrey Yuet Mun Wong: Conceptualization; data curation; formal analysis; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Barend Mol:** Conceptualization; data curation; formal analysis; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Nazim Bhimani:** Data curation; formal analysis; methodology; project administration; visualization; writing – review and editing. **Philip de Reuver:** Supervision; writing – review and editing. **Connie Diakos:** Supervision; writing – review and editing. **Mark P. Molloy:** Supervision; writing – review and editing. **Thomas J. Hugh:** Conceptualization; supervision; writing – review and editing.

Conflict of interest

None declared.

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