Cohort Study

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Colorectal cancer hepatic metastases resection margins outcomes: a single-centre retrospective cohort study

Samuel Marion, MD[a], Sabrina Facchino, MD[a,b], Sonia Cheng-Oviedo, MD, MSc[a,b], Yves Collin, MD[a,b,*]

Background: Surgical resection is the most efficient treatment for isolated colorectal cancer hepatic metastases. Among the known prognostic factors of this procedure, the impact of the resection margin width is still a controversial matter in the literature.
Methods: A retrospective cohort study was performed including 170 patients who underwent surgical resection of colorectal cancer liver metastases (CRLMs) between 2006 and 2016 in our hepatobiliary unit. Resection margin width was determined histologically by measuring the distance from the tumour in millimetres or centimetres. Patients' clinical characteristics were also collected. Patients were then stratified in two tumour margin groups: below 5 mm (group A) and equal to or above 5 mm (group B). Overall survival (OS) and disease-free survival (DFS) were the primary outcomes.
Results: Kaplan–Meier curves showed significantly better outcomes for cases having resection margins above 5 mm for both DFS with 1508.7 days (range 1151.2–1866.2) in group A, compared to 2463.9 days (range 2021.3–2906.5) in group B ($P=0.049$), and OS with 1557.8 days (range 1276.3–1839.3) for group A and 2303.8 days (range 1921.2–-2686.4) for group B ($P=0.020$). This survival benefit was not significant for patients presenting with stage IV CRC at diagnosis or cases where extended (7 + segments) resections were performed.
Conclusion: Five-millimetre margins provide a significant survival advantage and should be aimed for in the treatment of CRLMs. Further research on the cause for this finding, including tumour biology's impact on survival, is required.

Keywords: colorectal cancer, hepatic resection, liver metastases, resection margin

Introduction

Colorectal cancer (CRC) represents the fourth most common cancer diagnosis in the world and the third most common cause of cancer-associated deaths in North America[1]. More than 50% of patients suffering from CRC will develop distant metastases during their disease. The liver being the preferred metastatic site, 15–25% of patients have hepatic metastases upon presentation, whereas eventually more than 50% of all cases end up developing liver metastases throughout their disease progression[2].

Surgical resection continues to be the most efficient treatment for isolated colorectal cancer hepatic metastases[3]. While a third of patients attain 5-year survival, close to 60% of patients will experience local recurrence within the 5 years following resection, with most relapses occurring within the first 2 years[4]. Local recurrence is found within 1 cm of the margin in 95% of cases, with 70% of these within the first 2 mm[5,6]. Multiple factors influence recurrence risk. Preoperative carcinoembryonic antigen (CEA) levels, number and size of hepatic metastases and primary disease stage at diagnosis are the clearest risk factors[4,7]. Surgical margins have also been studied as a potential prognostic factor[7].

The '*1 cm rule*' stipulates that 1 cm, macroscopically cancer-free margins must be obtained to limit the relapse rate and maximise 5-year survival[3,8–10]. In the last decade, however, many studies have reached conflicting conclusions about this rule[7,11–14]. Often, the 1 cm margin is not achievable and might prevent patients from having surgery. To this day, no consensus has been reached on the topic of preferred resection margins width.

This study presents a cohort of colorectal cancer liver metastases (CRLMs) resections and the impact of surgical margins on patients' survival and hepatic metastasis recurrences after surgery.

HIGHLIGHTS

- Resection margins width for colorectal cancer liver metastasis is still controversial.
- A resection margin of 5 mm or more is associated with prolonged disease-free survival and overall survival.
- Further association with tumor biology could refine these results.

[a]Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke (CIUSSE – CHUS) and [b]Department of Surgery, Université de Sherbrooke, Sherbrooke, Quebec, Canada

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*Corresponding author. Address: Department of Surgery, Sherbrooke University, 580 Rue Bowen S, Sherbrooke, Quebec, Canada J1G 2E8. Tel.: + 18 198 218 000; fax: +18 198 206 877. E-mail: Yves.Collin@usherbrooke.ca (Y. Collin).

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Methods

The study protocol was approved by the CIUSSSE-CHUS ethics board, number 2017-1611 and was registered at the Research Registry (clinicaltrials.gov) [NCT05164419].

Patients were retrospectively selected for the cohort using the CIRESS (Centre Informatisé de Recherche Évaluative en Services et Soins de Santé) healthcare data system, and the CIUSSSE-CHUS, Sherbrooke Academic Hospital Centre, database. This study used a non-probabilistic convenience sampling method. Patients included were (1) over 18 years old, (2) diagnosed with hepatic metastasis from CRC, (3) having undergone surgical resection of CRLMs between 2006 and 2016, (4) having histologic specimens available for reanalysis or pathology reports detailing hepatic margins and (5) having follow-up imagery available. Exclusion criteria were the following: patients with (1) repeated hepatic resections, (2) macroscopically positive resection margins (R2) and (3) absent details on resection margins and no histologic specimen available. Collected patients' data included preoperative liver function, primary CRC site, initial AJCC (American Joint Committee on Cancer) cancer stage, total number of liver metastases, extrahepatic metastases, total number of resected segments and resection margins from the pathological report measured in millimetres or centimetres.

Patients were treated according to the existing standard of care, including surgical criteria and methods. Surgical technique always favoured parenchymal sparing liver resection over anatomical resection, when feasible. For intra-operative margin assessment, intra-operative ultrasound is always used (both for diagnosis of new lesions and for surgical guidance). Ultrasonic shears are used for parenchymal transection. Argon beam cauterisation is routinely used on the transection margin for haemostasis. During the span of the study, FOLFOX was the routine chemotherapy regimen at our institution. In chemotherapy-naïve patients undergoing liver resection, it was administered in a neoadjuvant setting including 4–6 cycles preoperatively and 6–8 postoperatively, according to patient tolerance. Patients undergoing liver resection who had previous exposure to FOLFOX (adjuvant treatment after primary resection) went to upfront surgery.

Since 2012, every CRLM histological specimen from patients receiving neoadjuvant chemotherapy is analysed according to a standardised protocol. This protocol includes a precise assessment of the distance between healthy tissue and metastatic tissue in millimetres or centimetres. If more than one metastasis is present, the one closer to the margin is evaluated. This assessment of margin width is achieved using a millimetre ruler incorporated in the $3\times$ objective of the microscope.

Overall survival (OS) and disease-free survival (DFS) were the primary outcomes. Other outcomes were loco-regional disease recurrence and distant recurrence. The follow-up protocol included assessment of patient history and clinical examination, serum CEA level and computed tomography scans every 3–6 months in the first 2 years following surgical intervention, then every 6–12 months for the subsequent 3 years (5 years total). The follow-up was done during scheduled outpatient visits.

To analyse the impact of resected hepatic segments number on survival, each time a segment was at least partially resected, it was considered. Also, segments IVa and IVb were considered as separate, which explains why up to nine segments could be counted as resected while preserving adequate remaining liver.

Statistical analysis was performed using IBM SPSS V26. Descriptive statistics according to variable distribution were obtained. Kaplan–Meier survival curves and log-rank (Mantel–Cox) analyses were performed to assess the impact of resection margins on OS and DFS. Results showing a *P*-value inferior or equal to 0.05 were considered statistically significant. All that work was reported in line using the STROCSS criteria[15].

Table 1

Patients' characteristics and disease status.

Patients' characteristics		*N*	%
Gender	Female	58	34.1
	Male	112	65.9
	Median	SD	Range
Age	65.22	9.23	32.1–87.0
Preoperative CEA	59.824	216.32	0.4–2166.0
	Disease status		
AJCC stage at diagnosis	I	6	3.5
	II	10	5.9
	III	34	20.0
	IV	96	56.5
	ND	24	14.1
Preoperative liver function	Normal	148	87.1
	Abnormal	6	3.5
	ND	16	9.4
Primary CRC site	Caecum	2	1.2
	Right colon	35	20.6
	Transverse colon	3	1.8
	Left colon	20	11.8
	Sigmoid/rectum	110	64.7
Synchronous liver metastases	Yes	104	61.2
	No	66	38.8
Extrahepatic metastases	Yes	24	14.1
	No	146	85.9
	Median	SD	Range
Total number of liver metastases	2.34	2.076	1–15

AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CRC, colorectal cancer.

Results

One hundred and seventy patients meeting inclusion criteria underwent primary resection of a CRLM at the Sherbrooke

Table 2

Interventions and outcomes.

Interventions and outcomes		*N*	%
Resection margins	≥ 5 mm (A)	92	54.1
	< 5 mm (B)	77	45.3
Hepatic disease recurrence	Yes	81	47.6
	No	89	52.4
Disease recurrence elsewhere	Yes	77	45.3
	No	93	54.7
	Median	SD	Range
Resection margins (mm)	8.155	8.8	0–50
Total number of resected segments	3.83	1.552	1–8
DFS (days)	920.11	887.63	0–4249
OS (days)	1244.42	836.74	146–4249

DFS, disease-free survival; OS, overall survival.

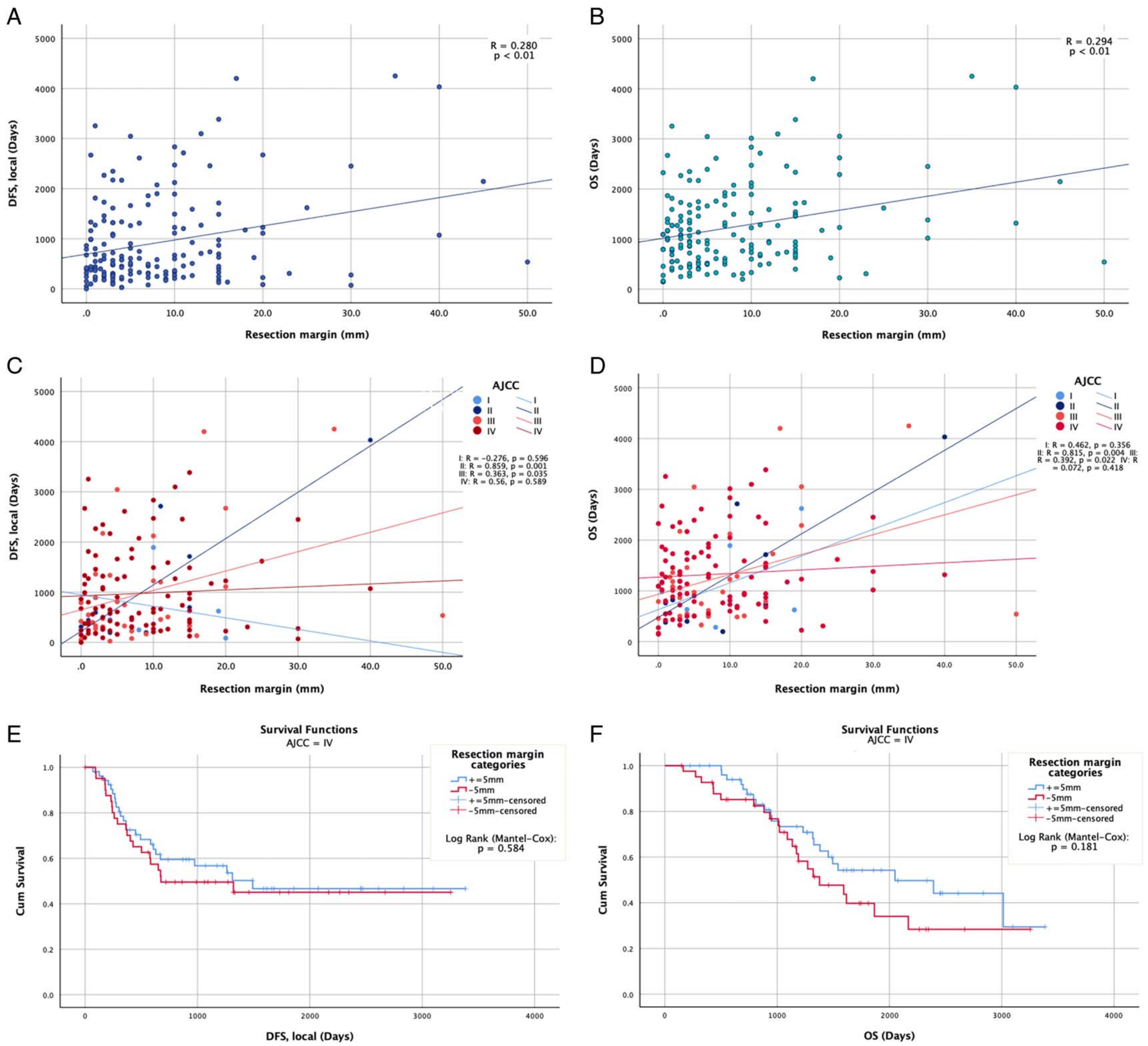

Figure 1. Local DFS and OS according to resection margins and AJCC stage. (A) Local DFS and (B) OS show a significant, positive mild correlation to resection margins. When comparing AJCC stages (C) and (D), this correlation is significant, positive and strong for stage II and moderate for stage III. Kaplan–Meier curves showing (E) local DFS and (F) OS according to margin group and cancer stage at diagnosis for AJCC stage IV. AJCC, American Joint Committee on Cancer; DFS, disease-free survival; OS, overall survival.

University Hospital Centre between 2006 and 2016. The median age was 65 years (range 32–87); there were 112 men (65.9%) and 58 women (34.1%). Resection margins were classified as below 5 mm (group A) and 5 mm and above (B). The 5 mm cut-off was chosen after initial evaluation of the distribution curve and finding an approximate inflection point at 5 mm.

Table 1 shows patients' characteristics and disease status at diagnosis. The median number of hepatic metastases was 2 (range 1–15); 96 (56.5%) patients' cancer was stage IV at presentation with eight more becoming metastatic within 1 year of diagnosis [synchronous disease in 104 (61.2%) patients].

Interventions and outcomes are depicted in Table 2. The median resection margin length was 8.155 mm (range 0–50). Margins higher or equal to 5 mm were obtained for 92 (54.1%) patients, and 77 (45.3%) patients had margins of less than 5 mm. Hepatic disease recurrence was seen in 81 patients (47.6%) and extrahepatic disease recurrence happened in 77 patients (45.3%). Median DFS and OS for all patients were 920.11 days (range 0–4249) and 1244.42 days (range 146–4249), respectively.

Correlations between OS and DFS with resection margin width are shown in Figure 1. DFS and OS show a significant and positive mild correlation with resection margins (Fig. 1A, B). AJCC cancer stage stratification shows this correlation is significant, positive and strong for stage II and moderate for stage III (Fig. 1C, D). There is no significant difference between margin groups and DFS or OS for initial stage IV disease (Fig. 1E, F).

Table 3

Survival according to margins and AJCC at presentation.

	Resection margin category		
	Group A <5 mm, mean (CI 95%)	Group B ≥5 mm, mean (CI 95%)	P
	DFS, local (days)		
Global	1508.7 (1151.2–1866.2)	2463.9 (2021.3–2906.5)	0.049
AJCC			
I	717.0 (265.0–4084.1)	712.0 (589.2–2013.2)	0.808
II	385.0 (200.0–570.0)	1870.6 (51.4–3792.6)	0.009
III	643.0 (319.3–966.7)	1270.8 (624.2–1917.4)	0.436
IV	894.3 (651.2–1137.4)	1040.6 (800.8–1280.4)	0.584
Global	$P=0.419$	$P=0.411$	
	OS (days)		
Global	1557.8 (1276.3–1839.3)	2303.8 (1921.2–2686.4)	0.020
AJCC			
I	807.500 (565.6–1049.3)	2036.250 (635.5–3439.9)	0.808
II	768.7 (489.2–1048.2)	2604.6 (1065.1–4144.0)	0.233
III	1146.956 (795.3–1498.5)	2471.1 (1647.5–3294.7)	0.092
IV	1750.2 (1374.5–215.9)	2136.5 (1782.2–2490.7)	0.181
Global	$P=0.037$	$P=0.954$	

AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; OS, overall survival.

Global DFS for group A (<5 mm) was 1508.7 days (range 1151.2–1866.2) compared to 2463.9 days (range 2021.3–2906.5) for group B ($P=0.049$) (Table 3). The most significant outcome difference was for stage II cases, with a DFS of 385.0 days (range 200.0–570.0) for group A as opposed to 1870.6 days (range 51.4–3792.6) for group B ($P=0.009$). There was no statistically significant difference between margin groups for upfront stage IV disease in OS or DFS ($P=0.181$ and 0.584, respectively). Global OS of groups A and B was 1557.8 days (range 1276.3–1839.3) and 2303.8 days (range 1921.2–2686.4), respectively ($P=0.02$).

Kaplan–Meier DFS and OS curves in relation to surgical margin width are shown in Figure 2. Both DFS and OS show significantly higher survival rates for group B (≥5 mm).

Extended resections (7–9 segments) show earlier local recurrence when compared to discrete (1–3) or moderate (4–6) ones (Fig. 3). This difference is significant for margin groups, with moderate resections (4–6) showing a significantly shorter time for local recurrence in group A as opposed to group B (≥5 mm) (1602 vs. 2825 days, $P=0.042$). This difference between groups is lost for extended resections as shown in Fig. 3C.

Cox regression multivariate analysis including AJCC stage, resection margin value, total number of resected liver segments and total number of liver metastases showed only larger resection margins (≥5 mm) remained statistically significant ($\beta=-0.564$, $P=0.027$).

Discussion

According to Pawlik *et al.*[16], although surgeons strive for the widest possible surgical margins, there has been no definitive evidence regarding the negative margin width necessary to optimise long-term survival in hepatic resection of CRLMs. Numerous authors have shown that a positive margin after liver resection for CRLMs has been associated with a greater incidence of tumour recurrence and a lesser survival rate. Historically, supra-centimetre margins were thought to be the optimal margin width. This 1 cm rule was based on several relatively older studies[8,14,17,18] and has been the subject of significant debate among surgeons for quite some time. Nuzzo *et al.*[19] suggested that the results of these studies were often limited by the lack of a precise assessment of the width of surgical margins less than 1 cm wide. Additionally, Sadot *et al.*[7] stated: '*This cut-off was supported by the observation that, in the absence of preoperative chemotherapy, 95% of microsatellite lesions, when present, were located within 1 cm of the tumour border*'. Many studies have concluded that the development of modern systemic therapy regimens has rendered this rule obsolete[7,20]. For instance, Hamady *et al.*[21] proposed that a 1-mm margin was sufficient to achieve significant survival benefit.

Also, Pawlik *et al.*[16] reported that the width of a negative surgical margin does not in fact affect survival as patients undergoing R0 resection achieve similar OS regardless of the width of the surgical margin. Additional research supports the claim that complete R0 resection seems to be the real factor associated with better outcomes, not margin width[12,16,21,22]. Others have proposed that margin widths of 2 mm are sufficient and lead to outcomes close to those of 1 cm margin resections[23]. However, in these studies, the width of the margin was not an independent prognostic factor regarding survival after hepatectomy for CRLMs. These studies placed margins as an indicator, not a governor, of prognosis. According to Nuzzo *et al.*, the cause of these controversial results may be explained by the studies' inability to stratify patients to the widths of the resection margin, absence of multivariate analysis or lack of distinction of the pattern of local recurrence[19,24].

On the other hand, a meta-analysis by Margonis *et al.*[25] suggested that a 1-cm margin may have an improved survival benefit compared to sub-centimetric margins.

The present study shows that 5 mm margins are associated to better outcomes and should therefore be aimed for in the treatment of CRLMs. A margin of 5 mm proves significantly advantageous in global survival when compared to narrower margins regarding DFS ($P=0.049$) and OS ($P=0.020$). On this subject, in a retrospective study of 185 patients undergoing hepatic resection for CRLMs, Nuzzo *et al.*[19], reached a similar conclusion. A resection margin less than or equal to 5 mm was associated with a greater risk of recurrence on the surgical margin, with reduced OR and DFS. This study therefore opposes the hypothesis that the width of cancer-free resection is not a prognostic factor in CRLMs resection[12,16,21–23]. Furthermore, in a 2005 study, Wray *et al.*[26] demonstrated that the width of the resection margin is indeed a powerful factor affecting prognosis in these patients.

This study provides additional evidence to the literature on this subject. It sets the scene in our single-centre population to investigate other factors like molecular markers. Surgical intervention was carried out by a limited number of surgeons (two) ensuring a homogeneous surgical technique.

This study's limits lie in our inability to recruit a larger sample size, limiting the power of some of our conclusions. Additionally, the small sample size prevented multivariate analysis which could effectively minimise confounding factors and allow better assessment of the independent effects of margin width (for instance, chemotherapy type, duration between induction of chemotherapy and surgery and other potential confounding factors). Furthermore, the number of resected segments is most likely

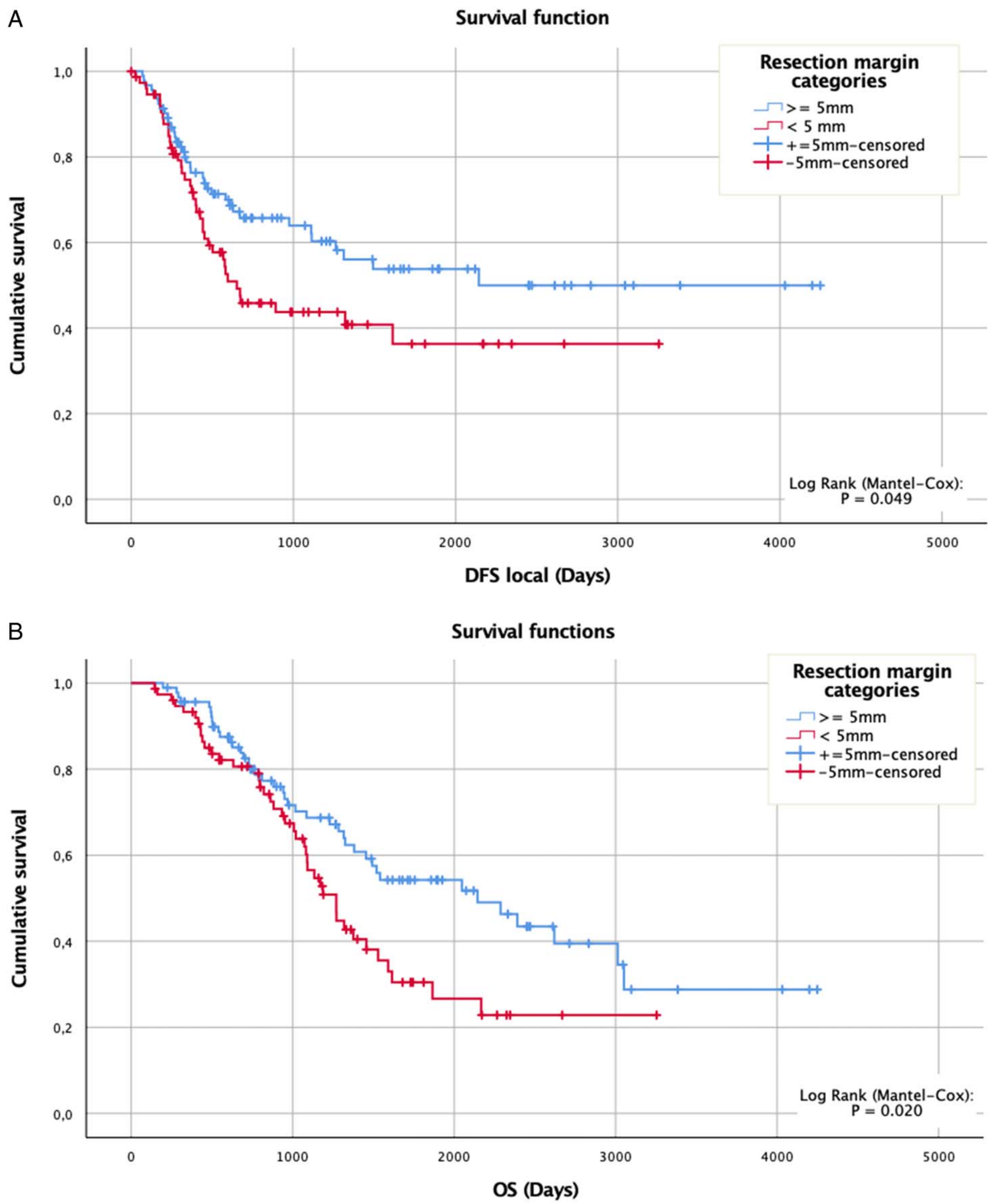

Figure 2. Survival curves for local DFS and OS according to resection margins. Kaplan–Meier curves show significantly better survival for cases having resection margins at least 5 mm both for (A) local DFS ($P = 0.049$) and (B) OS ($P = 0.020$). DFS, disease-free survival; OS, overall survival.

linked to the number of metastases and therefore disease burden, which could influence survival. Finally, including positive R1 resections in the less than 5 mm group may have negatively affected this group survival data and prevented us from correctly assessing the outcomes linked with 1–5 mm margins.

Nevertheless, this study shows a significant and positive mild correlation between larger margins and greater survival rates ($P < 0.01$). It therefore appears that a wider margin should always be attempted if possible. In fact, this study simply highlights the significantly better outcome associated with 5 mm and more margins; it does not suggest that the inability to achieve a 5-mm margin clearance should be considered a contraindication to surgery. Our data is hence not in contradiction with prior studies stating that a 1-mm margin is enough to obtain cure, especially if compared to no surgery, but our data add to the available literature that, when feasible, a larger margin should be obtained.

Positive outcomes associated with 5 mm margins appear clearer for low AJCC stages at diagnosis. Larger margins seem to have a

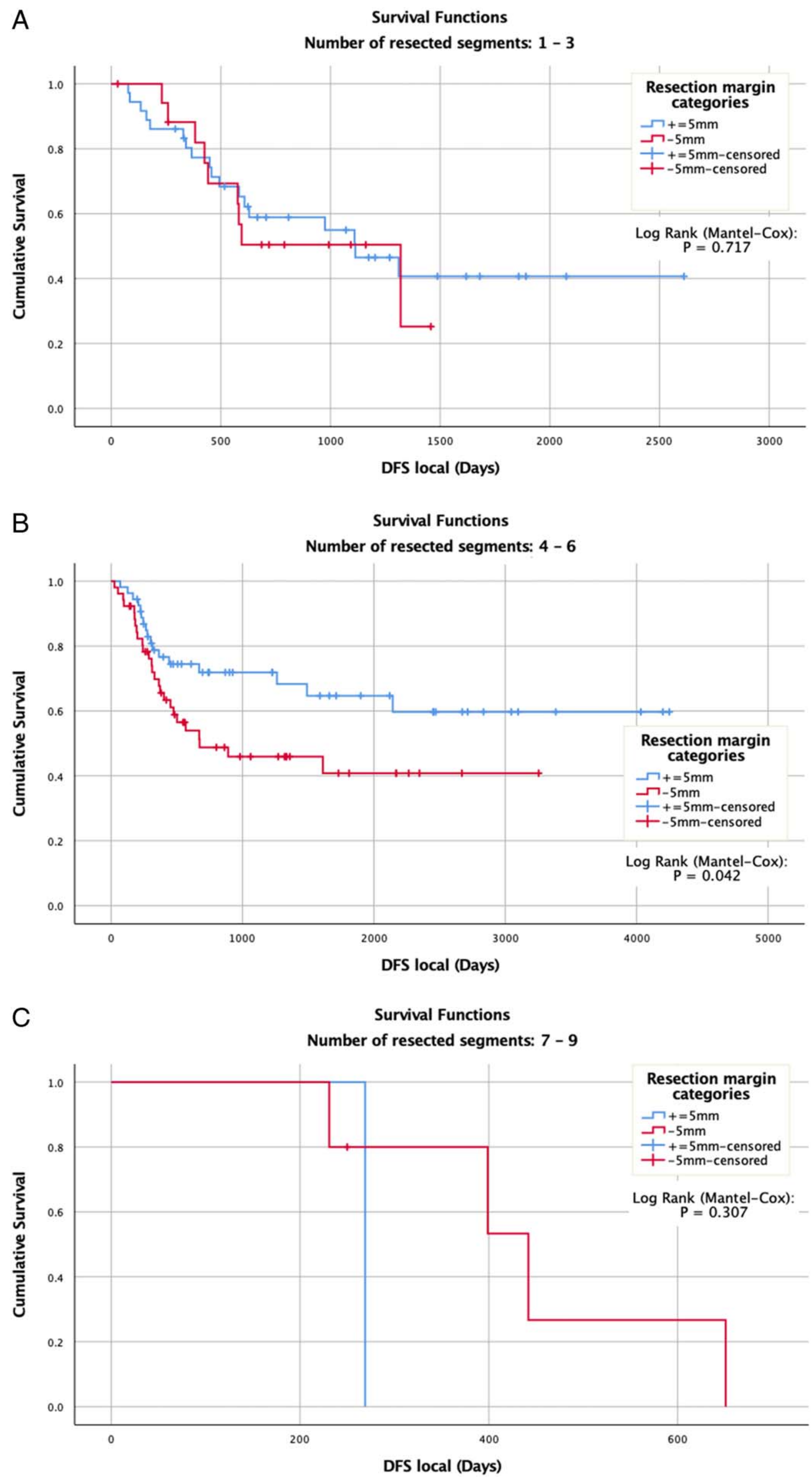

Figure 3. Survival curves for local DFS according to margins and number of resected liver segments. Kaplan–Meier DFS curves for margin groups for (A) 1–3 segments hepatectomy ($P = 0.717$), (B) 4–6 segments hepatectomy ($P = 0.042$) and (C) for 7–9 segments ($P = 0.307$). DFS, disease-free survival.

greater impact on the prognosis of patients with low AJCC stages at presentation. This study found greater survival rates in AJCC stage II cases with at least 5 mm margins, as opposed to smaller margins ($P = 0.009$ for DFS and $P = 0.02$ for OS). This difference was also found for stage III cases, to a lesser degree. This might be explained by a different tumour biology whereas upfront metastatic disease is usually considered more aggressive and more dependent on systemic treatment rather than local treatment alone. In a 2016 study assessing surgical margins' impact on prognosis, Sadot *et al.* acknowledged that surgical margins were an independent predictor of survival but observed that biological behaviour of the tumour was more likely to explain long-term outcomes in submillimetre margins[7,25,26]. Tumour biology has been proven to influence prognosis and must be considered a potential confounder. In fact, one recent report suggests that HER2-positive tumours grow more aggressively given the levels of HER2 overexpression seen in patients with advanced-stage cancers at diagnosis[25,26]. Additionally, some authors addressed the trend towards worse OS associated with HER2-positive disease compared to HER2-negative tumours[27,28]. HER2 can therefore be considered a negative predictive biomarker in metastatic CRC[29]. BRAF mutations have also been associated with an unfavourable prognosis in the metastatic setting[28]. Because some mutations are so prevalent in advanced CRC stages, the biological aspect of the tumour might partly explain why upfront stage IV CRC is associated with worse survival[30,31]. On this subject, Chow and Chok have stated that synchronous disease (which by definition must include stage IV CRC) has been shown to have less favourable cancer biology[30–32]. This means that upfront stage IV CRC's impact on survival might be more adequately explained by tumour biology and not surgical technique. Tumour biology was not assessed for this section of the study but its link with surgical margins will be further researched.

The link between margins and outcome might not be as clear for patients with upfront stage IV AJCC CRC at diagnosis as there was no significant difference between margin groups in terms of OS and DFS ($P = 0.181$ and 0.584, respectively). This is in line with the idea that tumour biology is a more important factor for DFS than surgical margin alone at this stage. Few studies specify CRC stage at diagnosis or explore the link between cancer stage and hepatic margin clearance regarding patients' survival. Further research is needed to properly answer this question.

In a similar study, Nuzzo *et al.* (2008) obtained 10 mm margins for 72.7% of patients with metachronous metastases compared to only 27.3% of patients with synchronous metastases[19,24]. And so, another possible explanation for the difference in survival might be found in the lower likelihood of obtaining larger surgical margins in a synchronous setting. Altendorf-Hofmann *et al.* (2003) asserted that most authors have found superior results for metachronous lesions when comparing synchronous and metachronous metastases[2,22,23,32–37]. The author also noted that other older studies have seen similar outcomes for the two (synchronous and metachronous)[8,38–43] and so this correlation is somewhat controversial and may reflect a different treatment approach in patients with synchronous lesions. Larger margins might be more easily obtained in metachronous disease as these tumours tend to present with fewer and smaller lesions than in synchronous disease. This means that a 10-mm margin is more likely to be obtained for metachronous disease. Therefore, we could imagine that at equal tumour size, whether the liver metastasis is synchronous or metachronous has no influence on the surgical margins obtained.

Favourable outcome is also somewhat affected by the scale of hepatic resection. In fact, discrete and moderate hepatectomies seem to be associated with delayed local recurrence and improved DFS. Discrete and moderate hepatectomies also show better outcomes when 5 mm margins are achieved. Discrete hepatectomy was defined by the partial resection of 1–3 liver segments using Couinaud classification of hepatic segments, moderate and extended hepatectomy included, respectively, 4–6 and more than 6 liver segments. Literature has proven that smaller hepatectomies (1–3 segments) show a better median survival than hepatectomies of four segments and more[44,45]. In a 1995 study, Rougier *et al.* (1995) showed that the number of resected segments is a prognostic factor for patient survival. In their study, the median survival of patients who underwent resection of 1–3 segments was 10.3 months compared to only 5.9 months for resection of four segments and more ($P = 0.01$)[44,46]. On this subject, our study supports these findings: the association of larger margins with increased DFS does not appear to be as pertinent for extended resections. Additionally, Hamady *et al.*[13] showed that, when compared to major surgery (three or more segments), a significantly higher proportion of patients who underwent minor surgery (1–2 segments) are still disease-free 5 years after the operation. Our study shows significantly better survival for moderate hepatectomies (4–6 segments) ($P = 0.042$).

Again, these findings may be related to tumour biology. Some authors have put forward that tumour biology might have a stronger influence on the patient's survival than surgical margins, in fact, some say that the impact of surgical margins can be explained by the tumour biology involved. In a 2016 study involving 485 patients with known KRAS mutational status, Margonis *et al.* (2016) demonstrated that surgical resection margin had a variable impact on survival after resection of CRLMs depending on KRAS status[45,47]. This conclusion can partly explain why major hepatectomies are not as much affected by surgical margins as smaller hepatectomies. Cases who underwent extended liver resections probably involved more aggressive tumour biology, modifying patients' survival.

Unfortunately, most patients have advanced cancer when they receive a CRC diagnosis, as 56.5% of patients presented with upfront stage IV CRC. However, we evaluated the entire population of patients respecting our institution's criteria. Therefore, this is not proof of bias towards the selection of sicker patients but simply the reality of a lot of patients' diagnosis. The effect of the AJCC stage at diagnosis thus requires further research as our sample size of AJCC stages lower than IV is small and so harder to draw conclusions on.

Conclusions

In conclusion, this study provides evidence that the achievement of a wider margin of resection is associated with better DFS and OS in liver surgery for colorectal liver metastases. Our study showed a difference in DFS and OS with a 5-mm margin, supporting prior publications that the historical 1 cm margin rule may be unnecessary. A 5-mm margin seems sufficient and should be aimed for to provide liver tissue salvage. More research is necessary to establish whether patients in need of extended liver resection or with upfront metastatic disease have different benefits from wider margins than other patient populations. Also, research considering tumour biology and microenvironment as well as its impact on clean margin requirement is needed for better surgical planning and patient selection in the future.

HIGHLIGHTS

Liver metastasectomy margins

- '1 cm rule' not often achievable in surgical patients.
- 5 mm a safe cut-off inflection point.

- 5-mm margins good overall survival (OS) and disease-free survival (DFS) outcomes

Ethical approval

Ethical approval for this study was provided by the Ethical Committee of Sherbrooke University Hospital Center (CHUS), Sherbrooke, Canada, on 25 November 2016, number 2017-1611.

Consent

Written informed consent was obtained from patients for publication of this retrospective cohort study and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.M., S.F., and Y.C.: have contributed to study designing and data collection, data analysis and writing. S.C.-O.: has contributed to data analysis and writing.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Clinicaltrials.gov.
2. Unique identifying number or registration ID: NCT05 164419.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/ct2/results?cond=&term=NCT05164419&cntry=&state=&city=&dist=

Guarantor

Dr Collin, Department of Surgery, Université de Sherbrooke, and Centre Intégré Universitaire de Santé et de Services Sociaux de l'Estrie – Centre Hospitalier Universitaire de Sherbrooke (CIUSSSE – CHUS), is the Guarantor for this work.

Data availability statement

The data collected for this study are available by contacting me, Dr Collin, as the author of the manuscript at: Department of Surgery – University of Sherbrooke. Yves.Collin@usherbrooke.ca. Tel: +1 819 821 8000, Ext 73013.

Provenance and peer review

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