

# Factors affecting surgical margin recurrence after hepatectomy for colorectal liver metastases

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**Background:** Hepatic recurrence after resection of colorectal liver metastasis (CLM) occurs in 50% of patients during follow-up, with 2.8% to 13.9% presenting with surgical margin recurrence (SMR). The aim of this study is to analyze factors that related to SMR in patients with CLM undergoing hepatectomy.

**Methods:** Demographics, clinical and survival data of patients who underwent hepatectomy were identified from a prospectively maintained, institutional review board (IRB)-approved database between 2000 and 2012. Statistical analysis was performed using univariate Kaplan Meier and Cox proportional hazard model.

**Results:** There were 85 female and 121 male patients who underwent liver resection for CLM. An R0 resection was performed in 157 (76%) patients and R1 resection in 49. SMR was detected in 32 patients (15.5%) followed up for a median of 29 months (range, 3–121 months). A half of these patients had undergone R1 (n=16) and another half R0 resection (n=16). Tumor size, preoperative carcinoembryonic antigen (CEA) level and margin status were associated with SMR on univariate analysis. On multivariate analysis, a positive surgical margin was the only independent predictor of SMR. The receipt of adjuvant chemotherapy did not affect margin recurrence. SMR was an independent risk factor associated with worse disease-free (DFS) and overall survival (OS).

**Conclusions:** This study shows that SMR, which can be detected in up to 15.5% of patients after liver resection for CLM, adversely affects DFS and OS. The fact that a positive surgical margin was the only predictive factor for SMR in these patients underscores the importance of achieving negative margins during hepatectomy.

**Keywords:** Colorectal liver metastasis (CLM); surgical margin recurrence (SMR); liver resection

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## Introduction

In 2013, 142,000 new patients with colorectal cancer were diagnosed in the United States (1). Although, the incidence and mortality of colorectal cancer have been declining over the recent years, about 10–25% of these patients present with synchronous liver metastasis; while another 20–50% will develop metachronous liver metastases during the course of their disease (2–6). Liver resection is the only potentially curative treatment in these patients, resulting in

5-year survival rates of 32% to 58% (2,3,6–11). However, hepatic recurrence occurs in 50% of patients during follow-up, with 2.8% to 13.9% presenting with surgical margin recurrence (SMR) (6,11–15). SMR is not reported consistently in the hepatectomy literature. Furthermore, there are very few studies focusing on the incidence and predictors of SMR (12,14,15).

The aim of this study is to define the incidence and identify predictors of SMR after hepatectomy in patients with colorectal liver metastasis (CLM).

**Table 1** Demographic, clinical and perioperative data of study patients (n=206)

Parameter	N
Age	62.1±11.2
Gender (F/M)	85/121
ASA status	2.7±0.5
Primary tumor (colon/rectum)	129/77
Type of metastasis (synchronous/metachronous)	79/127
Liver involvement (unilobar/bilobar)	178/28
Number of liver metastases	1.7±1.1
Tumor size (cm)	3.8±2.3
Preoperative CEA level (ng/mL)	80.6±321.1
Type of resection (minor/major)	133/73
Estimated blood loss (mL)	604±709
Blood transfusion, n (%)	29 (14%)
Operative time (min)	261±103
Margin status (R0/R1)	157/49
Complications	60 (29%)
ICU stay	62 (30%)
Hospital stay (day)	6.5±4.0

Continuous data are presented as mean ± standard error of the mean. F, female; M, male; ASA, American Society of Anesthesiologist score; CEA, carcinoembryonic antigen; ICU, intensive care unit.

**Table 2** Oncological parameters in the study groups

Parameters	N (%)
Preoperative chemotherapy	166 (80.0)
Postoperative chemotherapy	120 (58.0)
Surgical margin recurrence	32 (15.5)
New liver recurrence	62 (30.0)
New extrahepatic disease	76 (36.8)

## Materials and methods

Patients who underwent liver resection for CLM between April 2000 and April 2012 were identified from a prospectively maintained, institutional review board (IRB)-approved database. The details of the surgical technique were described previously (16). An intraoperative ultrasound was performed in all procedures, whereas frozen section was not performed routinely to assess margins. An R0 resection was defined as no malignant cells seen at surgical margin on final pathology.

A major hepatic resection was defined as three or more liver lobe resection according to Brisbane International Hepato-Pancreato-Biliary Association (IHPBA) classification (17). The patients were followed up with abdominopelvic and chest CTs quarterly for the first 2 years and then biannually. The scans were reviewed by independent radiologists. An SMR was defined as a recurrence seen along the resection line on follow-up imaging. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were not obtained routinely in follow-up.

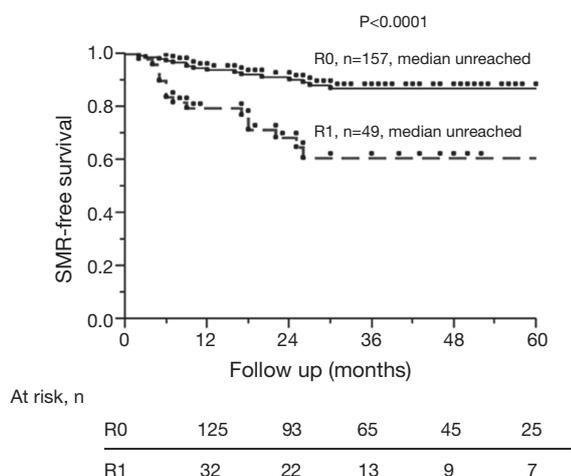
Demographic, clinical, and survival data were assessed with the univariate Kaplan–Meier analysis. Those parameters with a significance of  $P < 0.1$  on Kaplan–Meier univariate analyses were entered into a multivariate Cox proportional hazards model. Continuous data are presented as mean ± SEM. A  $P$  value of  $< 0.05$  was accepted for statistical significance.

## Results

There were a total of 206 patients with a mean age of 62.1±11.2. Eighty-five patients were female and 121 male. The average tumor size was 3.8 cm and number of tumors 1.7. Thirty-five percent (n=73) of the procedures were major and 65% (n=133) minor hepatectomies. An R0 resection was performed in 157 patients (76%) and R1 resection in 49 (24%). The patients were followed up for a median of 29 months (range, 3–121 months). An SMR was detected in 32 patients (15.5%), with an incidence of 32.6% (n=16) after an R1, and 10% (n=16) after an R0 resection ( $P < 0.0001$ ). Surgical margin width was  $< 5$  mm in 60 patients, 5–10 mm in 48,  $> 10$  mm in 43 and unknown in 6. In these subgroups, SMR was detected in 11%, 9%, 10%, and 0%, respectively. Demographic, clinical, intraoperative and oncological parameters are summarized in *Tables 1,2*.

On univariate analysis, factors affecting SMR were tumor size ( $P < 0.0001$ ), preoperative carcinoembryonic antigen (CEA) level ( $P < 0.0001$ ), and margin status ( $P < 0.0001$ ). On multivariate analysis, a positive surgical margin was the only independent predictor of SMR. A positive surgical margin was associated with a 3.6 fold-increased risk of SMR in follow-up ( $P = 0.0007$ , 95% CI: 1.7–7.4). There were 166 (80%) patients who received neoadjuvant chemotherapy. Surgical margin clearance was similar in patients who received and did not receive neoadjuvant chemotherapy (23% *vs.* 24%). The receipt of adjuvant chemotherapy did not affect SMR, either.

*Figure 1* shows the development of SMR for both the R0 and R1 resections in a Kaplan Meier format. After an R0



**Figure 1** Kaplan-Meier SMR-free survival in patients who underwent R0 and R1 resections. SMR, surgical margin recurrence.

and R1 resection, 5-year disease-free survival (DFS) was 19% and 11%, respectively ( $P=0.318$ ) and 5-year overall survival (OS) 54% and 51% ( $P=0.363$ ), respectively. SMR was an independent predictor of worsened DFS ( $P<0.0001$ ) and OS ( $P=0.009$ ) (Tables 3,4).

## Discussion

This study documents the incidence of SMR after liver resection in patients with CLM and analyzes the possible predictive factors. The incidence of R0 resection in our series (76%) is similar to that reported in the literature (4,11,13-15,18). This reflects our aggressive utilization of resection in the treatment of CLM. In this cohort of patients who had intense follow-up after hepatectomy with regular office visits and imaging studies, the incidence of SMR was 15.5%. A positive surgical margin was the only independent predictor of SMR. Furthermore, SMR was found to adversely affect both DFS and OS. The current study is one of the few reports in the literature critically analyzing SMR after hepatectomy and documenting an associated worse DFS and OS (11,12,19).

Hepatic resection is the only curative treatment for CLM, but recurrence develops in 50% of patients during follow-up, with up to 13.9% of recurrences occurring at the surgical margin (6,11-15). There is no consensus about the impact of positive surgical margin on SMR. Some authors have reported that an increased incidence of SMR after an R1 resection, whereas others have not shown a difference between R1 and R0 resection (12,14,15,18,20). Among

these studies, only one multicenter study, by Pawlik *et al.*, analyzed parameters that may affect SMR (12). In this report, a positive surgical margin was the only factor that affected SMR. The results of the current study are similar, with tumor size, CEA and margin status being associated with SMR in univariate analysis and margin status being the only independently predictor on multivariate analysis.

Although, the goal of a hepatic resection for CLM is to obtain negative margins, this is not possible in 7.6% to 27% of the patients (3,4,8,10,12,15,18). Larger tumor size, bilobar involvement, intraoperative blood transfusion, higher CEA levels and the presence of >3 tumors were reported to be risk factors for an R1 resection (11,18,21). In the current series, the incidence of a positive surgical margin was 24%. The effect of a positive surgical margin on survival is controversial. Some authors have reported worse DFS or OS with a positive surgical margin; whereas others have not (3,4,9,11-13,15,18,19,22). Recently Sadot *et al.* has reported a study of 2,368 patients who underwent liver resection for CLM from The Memorial Sloan Kettering Cancer Center. In this study it was shown that a larger surgical margin width was associated with better OS. Patients with surgical margin clearance of 1 mm or more had a better OS compared patients with submillimeter surgical margin. Patients with submillimeter surgical margin also had a better OS than patients with positive surgical margin (23). In the current study, the width of the negative surgical margin didn't affect DFS or OS but, SMR was found to negatively affect both DFS and OS. To the best of our knowledge, this association has not been analyzed or reported in the literature. Although some studies have suggested that R1 resections are still associated with long-term survival (6,13,15,18), our results show that every effort should be made for an R0 resection during liver resection.

The effect of chemotherapy on the development of SMR after an R0 or R1 resection is controversial. In one study, the receipt of adjuvant chemotherapy did not affect the SMR rate after an R0 or R1 resection (20). Eveno *et al.* has reported on 86 patients who underwent hepatectomy for CLM. An R0 resection was achieved in 73% and R1 resection 27%. Although the 5-year OS and DFS were not different between the two groups, intrahepatic recurrences and SMR were more frequent in the R1 group (52% *vs.* 27%, respectively) (15). In the present study, neo-adjuvant or adjuvant chemotherapy did not affect the incidence of SMR.

The limitations of the current study are the retrospective nature of data collection and the fact that multiple surgeons were involved in the procedures. Nevertheless, it critically

**Table 3** Univariate Kaplan-Meier and multivariate cox proportional hazard model for disease-free survival (DFS)

Variable	No. of patients	Median survival (months)	Univariate, P value	Multivariate	
				HR (95% CI)	P value
Age			0.793	–	–
≤65	120	15			
>65	86	20			
Gender			0.836	–	–
Female	85	18			
Male	121	17			
ASA status			0.010		
I-II	56	24			
III-IV	150	15		1.5 (1.0–2.3)	0.044
Primary tumor			0.08		
Colon	129	16		1.1 (0.6–1.1)	0.479
Rectum	77	21			
Metastases type			0.031		
Synchronous	79	14		1.5 (1.0–2.1)	0.019
Metachronous	127	20			
No. of metastases			0.027		
≤3	187	18			
>3	19	12		1.8 (0.9–3.1)	0.071
Tumor size			0.837	–	–
<3	82	15			
3–5	78	21			
>5	46	19			
Tumor location			0.476	–	–
Unilobar	178	18			
Bilobar	28	14			
Margin status			0.318	–	–
R0	157	19			
R1	49	14			
CEA (ng/mL)			0.067		
≤10	98	21			
>10	108	15		1.4 (1.0–2.0)	0.038
Resection type			0.146	–	–
Major	73	15			
Minor	133	21			
Preop chemotherapy			0.141	–	–
Yes	166	16			
No	40	34			
Postop chemotherapy			0.997	–	–
Yes	120	16			
No	86	18			
Surgical margin recurrence			<0.0001		
Yes	32	6.5		3.0 (1.9–4.5)	<0.0001
No	174	22			
Blood transfusion			0.227	–	–
Yes	29	15			
No	177	18			

Parameters showing a statistical significance  $P < 0.10$  on univariate analysis were entered into the multivariate model. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologist score; CEA, carcinoembryogenic antigen.

**Table 4** Univariate Kaplan-Meier and multivariate cox proportional hazard model of overall survival (OS)

Variable	No. of patients	Median survival (months)	Univariate, P value	Multivariate	
				HR (95% CI)	P value
Age			0.446	–	–
≤65	120	43			
>65	86	38			
Gender			0.263	–	–
Female	85	63			
Male	121	67			
ASA status			0.142	–	–
I-II	56	64			
III-IV	150	50			
Primary tumor			0.919	–	–
Colon	129	60			
Rectum	77	62			
Metastases type			0.397	–	–
Synchronous	79	60			
Metachronous	127	63			
No. of metastases			0.890	–	–
≤3	187	63			
>3	19	–			
Tumor size			0.417	–	–
<3	82	68			
3–5	78	64			
>5	46	45			
Tumor location			0.386	–	–
Unilobar	178	63			
Bilobar	28	–			
Margin status			0.363	–	–
R0	157	63			
R1	49	67			
CEA (ng/mL)			0.0002		
≤10	98	87			
>10	108	43		2.2 (1.4–3.5)	0.0003
Resection type			0.866	–	–
Major	73	60			
Minor	133	67			
Preop chemotherapy			0.352	–	–
Yes	166	60			
No	40	67			
Postop chemotherapy			0.941	–	–
Yes	120	63			
No	86	56			
Surgical margin recurrence			0.003		
Yes	32	38		2.0 (1.1–3.3)	0.010
No	174	64			
Blood transfusion			0.101	–	–
Yes	29	37			
No	177	63			

Parameters showing a statistical significance  $P < 0.10$  on univariate analysis were entered into the multivariate model. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologist score; CEA, carcinoembryogenic antigen.

analyzes an important issue in liver resection for CLM, SMR, for which there are scant data in the literature.

## Conclusions

An R1 resection is a risk factor for SMR, which adversely affects DFS and OS. Therefore, every effort should be made to achieve a negative margin during liver resection for CLM.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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