



The impact of R1 resection for colorectal liver metastases on local recurrence and overall survival in the era of modern chemotherapy: An analysis of 1,428 resection areas



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ABSTRACT

Background: It is still unclear whether a positive surgical margin after resection of colorectal liver metastases remains a poor prognostic factor in the era of modern perioperative chemotherapy. The aim of this study was to evaluate whether preoperative chemotherapy has an impact on reducing local recurrence after R1 resection, and the impact of local recurrence on overall survival.

Methods: Between 2000 and 2014, a total of 421 patients underwent resection for colorectal liver metastases at our unit after preoperative chemotherapy. The overall number of analyzed resection areas was 1,428.

Results: The local recurrence rate was 12.8%, significantly higher after R1 resection than after R0 (24.5% vs 8.7%; $P < .001$). These results were also confirmed in patients with response to preoperative chemotherapy (23.1% after R1 vs 11.2% after R0; $P < .001$). At multivariate analysis, R1 resection was the only independent risk factor for local recurrence ($P < .001$). At the analysis of the 1,428 resection areas, local recurrence significantly decreased according to the increase of the surgical margin width (from 19.1% in 0 mm margin to 2.4% in ≥ 10 mm). At multivariable logistic regression analysis for overall survival, the presence of local recurrence showed a significant negative impact on 5-year overall survival ($P < .001$).

Conclusion: Surgical margin recurrence after modern preoperative chemotherapy for colorectal liver metastases was still significantly higher after R1 resection than it was after R0 resection. Local recurrence showed a negative prognostic impact on overall survival. R0 resection should be recommended whenever technically achievable, as well as in patients treated by modern preoperative chemotherapy.

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Introduction

Hepatic resection together with perioperative chemotherapy is currently the only treatment option that can offer a chance of long-term outcome in patients with colorectal liver metastases (CRLM), resulting in 5-year survival rates of 40%,^{1–3} and exceeding 50% in selected patients.^{4–6}

The surgical margin status has been considered to be one of the most powerful prognostic factors for overall survival (OS). His-

torically, the anticipated inability to achieve a 1-cm margin was considered to be a contraindication to liver resection for CRLM in many centers.^{7–9} A resection margin greater than 10 mm was initially defined as the ideal distance owing to the observation that, in the absence of preoperative chemotherapy, microsatellite lesions were located within 1 cm of the tumor border.¹⁰ Over the years, the definition of the recommended safe width of the surgical margin associated with improved survival has evolved, decreasing from 5 mm¹¹ to 2 mm,¹² and then to 1 mm.^{13,14} Recent advances in hepatobiliary surgical techniques, together with the use of more effective perioperative chemotherapy, have increased the indications for liver resection for CRLM,^{15,16} including patients with more advanced disease, those with multiple and bilobar CRLM,

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and those with CLRM close to the major vascular structures. For these reasons, the reported rates of liver resection with positive margins have progressively increased in surgical series,¹⁷ showing that potential cure can be achieved in approximately 4% to 18% of R1 selected patients treated by aggressive modern perioperative chemotherapy.^{18,19} The dogma that the anticipated inability to resect all disease with negative margins should be considered a contraindication to liver resection for CRLM has been challenged in the era of modern chemotherapy. Furthermore, some recent studies showed that R1 resection in patients treated with perioperative modern chemotherapy was associated with similar long-term survival to that after R0 resection.^{20,21} However, these results are controversial and not confirmed in other large series with perioperative chemotherapy in which the positive resection margin remained a strong poor prognostic factor of OS.^{22–24} The crucial issue related to the margin status is the surgical margin recurrence rate, which has rarely been reported in these studies. Whether modern preoperative chemotherapy has an impact on reducing local recurrence rate after R1 resection has not been documented, and the clinical impact of local recurrence on overall survival remains controversial.

The aim of our study was to evaluate the impact of surgical margin width on the risk of local recurrence in patients treated with modern preoperative chemotherapy and the influence of local recurrence on OS.

Methods

Inclusion criteria

This study included patients who underwent primary hepatectomy (first liver resection) for CRLM in our unit between January 2000 and December 2014. The inclusion criteria were as follows: administration of preoperative chemotherapy, a minimum follow-up ≥ 2 years, complete resection of all CRLM, and the absence of unresectable extrahepatic disease. The exclusion criteria were as follows: patients treated with concomitant radiofrequency ablation, and incomplete liver resection (R2 resections).

Preoperative assessment

All patients were evaluated in our center by a multidisciplinary team including surgeons, oncologists, and radiologists. In our policy there were no predefined criteria of unresectability with regard to number, size, and bilaterality of CRLM.²⁵ Lesions were defined as resectable when all disease could be removed with negative margins, leaving an adequate liver remnant.²⁶ Unresectability was defined as technical unresectability because of inadequate liver remnant or the inability to remove all CRLM either by a 1- or 2-stage procedure. An anticipated risk of R1 resection was not a contraindication to liver resection, although our preferred policy has always been to obtain a tumor-free margin of 1 cm or more whenever possible.

Preoperative chemotherapy

All patients included in this study underwent preoperative chemotherapy. Indications to preoperative chemotherapy were as follows: initially unresectable CRLM or marginally resectable CRLM (high risk of R1 resection owing to number, size, or ill location of CRLM; ≥ 3 synchronous CRLMs).

The response to chemotherapy (4 courses) was assessed every 2 months by the multidisciplinary team and was determined by using the Response Evaluation Criteria in Solid Tumors.²⁷ Complete response was defined as disappearance of all target lesions; partial

response was defined as an at least 30% decrease in total tumor size.

In cases of initially unresectable CRLM, liver resections were performed as soon as resectability was technically possible, without waiting for a complete response to chemotherapy. In cases of marginally resectable CRLM, liver resections were usually performed after 4 courses of chemotherapy.

Surgical procedure

Liver resections were defined according to the International Hepato-Pancreato-Biliary Association (IHPBA) terminology.²⁸ Resections of 3 or more segments were classified as major hepatectomies. The surgical technique used in our unit for liver resection has been described previously.²⁹ Parenchymal transection was performed by the Cavitron ultrasonic surgical aspirator (CUSA 200; Valleylab, Boulder, CO) and wet bipolar forceps. Hepatic pedicle clamping was not routinely started at the beginning of liver resection, but was used only in cases in which bleeding was hindering a clear view of the operative field.

Pathologic examination

The surgical resection margin was defined as the minimum width between the transection plane and the CRLM in the resected specimen fixed with formalin. R0 resection was defined by the absence of microscopic tumor invasion of the resection margin (tumor-free margin ≥ 1 mm). R1 resection was defined as a complete macroscopic resection with microscopic tumor invasion of the resection margin (surgical-free margin 0 mm). The resection margin width of all specimens was evaluated and for each specimen corresponded to a resection area in the liver remnant. When patients underwent resection on multiple liver sites, they were classified as R1 if at least 1 resection margin was 0 mm. Furthermore, the minimum surgical margin width was defined for each specimen, and its impact on local recurrence in the corresponding resection area was analyzed.

Ras mutations were assessed in DNA of the CRLM-resected specimens. Routine polymerase chain reaction–based primer extension assay was performed to look for mutations in *Kras* codons 12 and 13 in all patients.

Follow-up

The follow-up included a hepatic ultrasound 3 months after surgery and an abdominal and a chest computed tomography scan every 6 months. The pattern of metastatic recurrence was classified as extrahepatic or hepatic, and the site of hepatic recurrence was classified as “local” in cases of recurrence on the surgical margin or as “other intrahepatic site” in other cases.

Late results included 5-year OS and disease-free survival rates, recurrence rate, and site of recurrence.

Statistical analysis

The differences between subgroups were tested using the Pearson χ^2 test. Statistical significance was defined as $P < .05$. A multivariable logistic regression model was then built to estimate the odds of R1 resection and of local recurrence after the surgical procedure. Variables significant at the 0.2 level in the univariate analysis were used in model building. The final model included only variables significant at the 0.05 level at the multivariable analysis. The results of the logistic regression model are expressed as odds ratios with 95% confidence intervals.

The Kaplan-Meier method was used to analyze OS, which was defined as the time between the date of liver resection and the

date of death or the last follow-up. Differences between subgroups in OS were tested with the log-rank test, and the multivariate analysis used stepwise Cox regression. Statistical analysis was performed using SPSS software (version 19; SPSS Inc).

Results

Between January 2000 and December 2014, a total of 630 patients underwent curative liver resection for CRLM in our unit. A total of 2 patients (0.3%) died during the postoperative course and were excluded from the study. Another 207 patients did not fulfill the inclusion criteria: 185 patients (29.4%) did not undergo preoperative chemotherapy; 13 (2.1%) underwent R2 resection, and 9 (1.4%) were treated with concomitant radiofrequency ablation. The remaining 421 patients underwent preoperative chemotherapy, and they were the subjects of our study.

Preoperative chemotherapy

Oxaliplatin-based chemotherapy was administered to 198 patients (47.0%) and irinotecan-based chemotherapy was administered to 190 patients (45.1%). Both oxaliplatin and irinotecan were administered in the same regimen in 25 patients (6.0%). Eight patients (1.9%) underwent other chemotherapy regimens.

Associated targeting agents were administered in 248 patients (59.0%): bevacizumab in 140 (33.2%), cetuximab in 100 (23.7%), and both in 8 (1.9%).

There were 82 patients (19.5%) who underwent more than 12 cycles of chemotherapy, and more than 1 line of chemotherapy was administered in 49 patients (11.6%).

According to the RECIST criteria, complete/partial response was observed in 261 patients (62.0%), stabilization of the disease was observed in 92 (21.9%), and progression was observed in 68 (16.1%).

Clinical and operative risk factors for R1 resection

The rate of R1 resection was 26.1% (110 patients). R1 resection was significantly higher in patients with more than 3 metastases ($P < .001$), with bilobar disease ($P = .001$), in patients who underwent multiple resections (≥ 3 ; $P = .001$), and in those who required intraoperative blood transfusions ($P < .001$; Table 1). At the multivariable logistic regression analysis, more than 3 metastases and intraoperative blood transfusions were the only independent risk factors for R1 resection (Table 2).

Analysis of local recurrence

After a median follow-up period of 31.5 months (range 3–181 months), tumor recurrence was observed in 297 patients (70.5%): 115 patients (38.7%) developed only extrahepatic recurrence, 102 (34.4%) developed only hepatic recurrence, and 80 (26.9%) developed both extrahepatic and hepatic recurrence.

The local recurrence rate was 12.8% (54 patients). Only local recurrence was observed in 14 patients. In 40 patients, local recurrence was associated with recurrence in other sites: in 34 it was associated with “other intrahepatic site” recurrence, and in 6 it was associated with extrahepatic recurrence. The local recurrence rate was significantly higher after R1 resection than that after R0 resection: 24.5% vs 8.7%, respectively ($P < .001$; Table 3).

Of the 261 patients with a response to preoperative chemotherapy, 7 showed a complete response with 1 or more disappearing CRLM. In 4 patients, all the disappearing CRLM were found at laparotomy by palpation and by intraoperative ultrasound. In 3 patients, 7 CRLM were not found during surgery, and they were not resected. Early liver recurrence was observed in 1 of these 3 patients 6 months after resection.

Table 1

Characteristics of the 421 patients who underwent preoperative chemotherapy.

Variable	R0 (n=310)	R1 (n=111)	P value
Age (years)			
<70 (%)	238 (76.8)	80 (72.1)	.322
≥ 70 (%)	72 (23.2)	31 (27.9)	
Primary tumor			
<i>Location</i>			
Colon (%)	206 (66.4)	80 (72.1)	.276
Rectum (%)	104 (33.6)	31 (27.9)	
N stage			
N0 (%)	128 (41.3)	42 (37.8)	.524
N+ (%)	182 (58.7)	69 (62.2)	
Liver metastases			
<i>Timing of diagnosis</i>			
Synchronous (%)	226 (72.9)	71 (64.0)	.076
Metachronous (%)	84 (27.1)	40 (36.0)	
<i>Largest size (cm)</i>			
<5 cm (%)	243 (78.4)	81 (73.0)	.245
≥ 5 cm (%)	67 (21.6)	30 (27.0)	
<i>No. of metastases</i>			
≤ 3 metastases (%)	246 (79.4)	65 (58.6)	<.001
>3 metastases (%)	64 (20.6)	46 (41.4)	
<i>Distribution</i>			
Unilobar (%)	191 (61.6)	49 (44.1)	.001
Bilobar (%)	119 (38.4)	62 (55.9)	
Portal vein embolization / ligation	29 (9.3)	15 (13.5)	.219
<i>Initial resectability</i>			
Resectable (%)	251 (81.0)	90 (81.1)	.979
Unresectable (%)	59 (19.0)	21 (18.9)	
Preoperative chemotherapy			
Irinotecan (%)	138 (44.5)	52 (46.9)	.672
Oxaliplatin (%)	151 (48.7)	47 (42.3)	.736
Both (%)	15 (4.9)	10 (9.0)	.110
Other (%)	6 (1.9)	2 (1.8)	.929
Targeting agents			
Bevacizumab (%)	104 (33.5)	36 (32.4)	.830
Cetuximab (%)	68 (21.9)	32 (28.8)	.143
Both	5 (1.6)	3 (2.7)	.470
<i>No. of cycles</i>			
≤ 12 (%)	255 (82.3)	84 (75.7)	.132
>12 (%)	55 (17.7)	27 (24.3)	
<i>No. of lines</i>			
1 (%)	279 (90.0)	93 (83.8)	.079
>1 (%)	31 (10.0)	18 (16.2)	
Radiological clinical response			
Complete / partial (%)	195 (62.9)	66 (59.5)	.521
Stabilization (%)	67 (21.6)	25 (22.5)	.842
Progression (%)	48 (15.5)	20 (18.0)	.533
Operative features			
<i>Two-stage hepatectomy</i>			
Yes (%)	16 (5.2)	8 (7.2)	.425
No (%)	294 (94.8)	103 (92.8)	
<i>Major hepatectomy</i>			
Yes (%)	141 (45.5)	44 (39.6)	.287
No (%)	169 (54.5)	67 (60.4)	
Multiple resections (≥ 3)	98 (31.6)	54 (48.6)	.001
<i>Intraoperative blood transfusions</i>			
Yes (%)	15 (4.8)	17 (15.3)	<.001
No (%)	295 (95.2)	94 (84.7)	

Table 2

Risk factors for R1 resection: multivariable logistic regression analysis.

	P value	Multivariable analysis		
		OR	95% CI	P value
>3 metastases	<.001	2.061	1.213–3.500	.007
Blood transfusions	.001	3.566	1.673–7.597	.001
Bilobar	.001			
Multiple resections (≥ 3)	.002			

CI, confidence interval; OR, odds ratio.

Table 3
Local recurrence rate according to the radicality of liver resection.

	No.	Local recurrence (no. of patients)		P value
		R0	R1	
All patients	421	8.7% (27/311)	25.5% (27/110)	<.001
Complete/partial response to chemotherapy	261	11.2% (22/196)	23.1% (15/65)	<.001
Cetuximab administration	100	11.6% (8/69)	48.4% (15/31)	<.001
Bevacizumab administration	140	10.6% (11/104)	16.7% (6/36)	.335
Ras wild-type	193	10.1% (14/138)	29.1% (16/55)	.001
Ras mutation	92	11.8% (8/68)	20.8% (5/24)	.273

Table 4
Risk factors for local recurrence after liver resection: multivariable logistic regression analysis.

	Univariate analysis	Multivariable analysis		
	P value	OR	95% CI	P value
R1 resection	<.001	2.984	1.629–5.468	<.001
>3 metastases	.024			
Bilobar	.005			

CI, confidence interval; OR, odds ratio.

Of the 102 patients with liver-only recurrence, 13 underwent resection (12.7%). The possibility of resection was significantly higher in patients with liver recurrence in other sites than in patients with local recurrence (20.4%, 11/54 vs 4.2%, 2/48, respectively; $P = .01$).

Among the 54 patients with local recurrence, 3 (5.5%) underwent resection (2 with liver-only recurrence and 1 with concomitant extrahepatic resectable recurrence). The other 51 patients did not undergo resection because of concomitant multiple unresectable CRLM in 33 cases (64.7%), unresectable extrahepatic disease in 5 cases (9.8%), and unresectable local recurrence in 13 cases (25.5%).

Local recurrence and preoperative chemotherapy

The local recurrence rate after R1 resection was significantly higher than that after R0 resection in patients with complete or partial response to preoperative chemotherapy (23.1% vs 11.2%, respectively; $P < .001$) and after cetuximab administration (48.4% vs 11.6%, respectively; $P < .001$; Table 3).

Local recurrence and Ras mutational status

Ras mutational status was available for 285 patients. Ras mutation was documented in 92 patients (32.3%). The rate of R1 resection was not significantly different between Ras wild-type and Ras-mutated patients (55/193, 28.5% vs. 24/92, 26.1%, respectively; $P = .670$). In Ras wild-type patients, the local recurrence rate after R1 resection was significantly higher than it was after R0 resection (29.1% vs 10.1%, respectively; $P = .001$; Table 3).

Independent risk factors for local recurrence

At the multivariable logistic regression analysis, R1 resection was the only independent risk factor for local recurrence (Table 4).

Analysis of liver resection areas

Among the 421 patients, 1,428 resection areas were analyzed. A 0-mm resection margin width was documented in 178 areas (12.5%); a 1- to 4-mm width was documented in 339 areas (23.7%);

Table 5
Local recurrence according to the surgical margin width: Analysis of 1,428 liver resection areas.

Surgical margin	Local recurrence (No. of recurrences)	p
0 mm (178)	19.1% (34)	<0.001
1 - 4 mm (339)	6.8% (23)	
5 - 9 mm (325)	5.5% (18)	0.01
≥ 10 mm (586)	2.4% (14)	

a 5- to 9-mm width was documented in 325 areas (22.8%); and a 10 mm or greater width was documented in 586 areas (41.0%). During the follow-up period, 89 local recurrences (6.2%) were documented in the 1,428 liver resection areas analyzed. These 89 local recurrences occurred in 54 patients. The local recurrence rate significantly decreased according to the increasing of surgical margin width (Table 5).

Outcome

The 5-year OS for the total group of patients was 50.4%. On multivariable analysis, lymph node metastases of the primary tumor, size of metastasis 5 cm or greater, unresectable disease at diagnosis, stability or progression of the disease during chemotherapy, R1 resection, and intraoperative blood transfusions were independent predictors of poor OS (Table 6). R1 resection was associated with a significantly lower 5-year OS than R0 resection (33.7% vs 54.9%, respectively; $P = 0.002$; Fig. 1, A). R1 resection also was a poor prognostic factor for OS in the subgroup of patients who showed a response to preoperative chemotherapy (261 patients; Fig. 1, B).

At the multivariable analysis, the impact of all local recurrences on OS, together with the impact of other types of recurrence, were analyzed (Table 7). The risk of death in patients with recurrent disease in other sites of the liver or in extrahepatic sites increased significantly if local recurrence also occurred. Indeed, the risk of death in patients with liver recurrence in other intrahepatic sites significantly increased in cases of local recurrence [hazard ratio (HR) increased from 6.722–8.713; $P < .001$]. Furthermore, the risk of death in patients with extrahepatic recurrence together with liver recurrence in other intrahepatic sites significantly increased when local recurrence occurred (HR increased from 10.168–18.297;

Table 6
Univariate and multivariable analysis of OS in 421 patients.

Variable	No. (%)	5-year OS (%)	Univariate analysis P value	Multivariable analysis	
				HR (95% CI)	P value
Age (years)					
<70	318 (75.5)	51.4	.738		
≥70	103 (24.5)	46.5			
Primary tumor					
<i>Location</i>					
Colon	286 (67.9)	48.1	.848		
Rectum	135 (32.1)	55.0			
<i>N stage</i>					
N0	170 (40.4)	58.4	.051	1.364 (1.001–1.858)	.049
N1	251 (59.6)	44.8			
Liver metastases					
<i>Timing of diagnosis</i>					
Synchronous	297 (70.5)	51.8	.409		
Metachronous	124 (29.5)	47.1			
<i>Largest size (cm)</i>					
<5	324 (77.0)	55.7	<.001	1.468 (1.042–2.069)	.028
≥5	97 (23.0)	33.1			
<i>No. of metastases</i>					
≤3	311 (73.9)	53.7	.093		
>3	110 (26.1)	40.8			
<i>Distribution</i>					
Unilobar	240 (57.0)	53.3	.295		
Bilobar	181 (43.0)	46.0			
<i>PVE/ligation</i>					
Yes	44 (10.5)	22.7	.012		
No	377 (89.5)	53.4			
<i>Initial resectability</i>					
Resectable	341 (81.0)	53.5	.011	1.783 (1.256–2.531)	.001
Unresectable	80 (19.0)	38.3			
Preoperative chemotherapy					
Irinotecan	190 (49.0)	52.6	.187		
Oxaliplatin	198 (51.0)	47.0			
Targeting agents					
<i>Cetuximab</i>					
Yes	100 (23.8)	51.6	.596		
No	321 (76.2)	49.8			
<i>Bevacizumab</i>					
Yes	140 (33.3)	56.3	.277		
No	281 (66.7)	47.5			
No. of cycles					
≤12	339 (80.5)	52.3	.057		
>12	82 (19.5)	41.1			
No. of lines					
1	372 (88.4)	53.4	.006		
>1	49 (11.6)	27.7			
Radiological clinical response					
Complete/partial	261 (62.0)	59.6	<.001	1.923 (1.401–2.641)	<.001
Stabilization/progression	160 (38.0)	35.0			
Operative features					
<i>Two-stage hepatectomy</i>					
Yes	24 (5.7)	21.4	.016		
No	397 (94.3)	52.2			
<i>Major hepatectomy</i>					
Yes	158 (37.5)	44.2	.054		
No	263 (62.5)	54.4			
<i>Multiple resections (≥3)</i>					
Yes	152 (36.1)	44.2	.054		
No	269 (63.9)	54.4			
<i>Radicality of resection</i>					
R0	311 (73.9)	54.9	.002	1.505 (1.081–2.094)	.015
R1	110 (26.1)	33.7			
<i>Blood transfusions</i>					
Yes	32 (7.6)	23.3	<.001	2.001 (1.244–3.220)	.004
No	389 (92.4)	52.6			

CI, confidence interval; PVE = portal vein embolization.

$P < .001$). Figure 2 shows the final model of HRs related to the type of recurrence. In this model, the HRs were assessed by direct standardization to adjust for the age of patients, the size of the CRLM, initial resectability, response to preoperative chemother-

apy, and number of lines of preoperative chemotherapy. In the curve, when local recurrence happened, the risk of death significantly increased independently from concomitant recurrences of other types (Fig. 2).

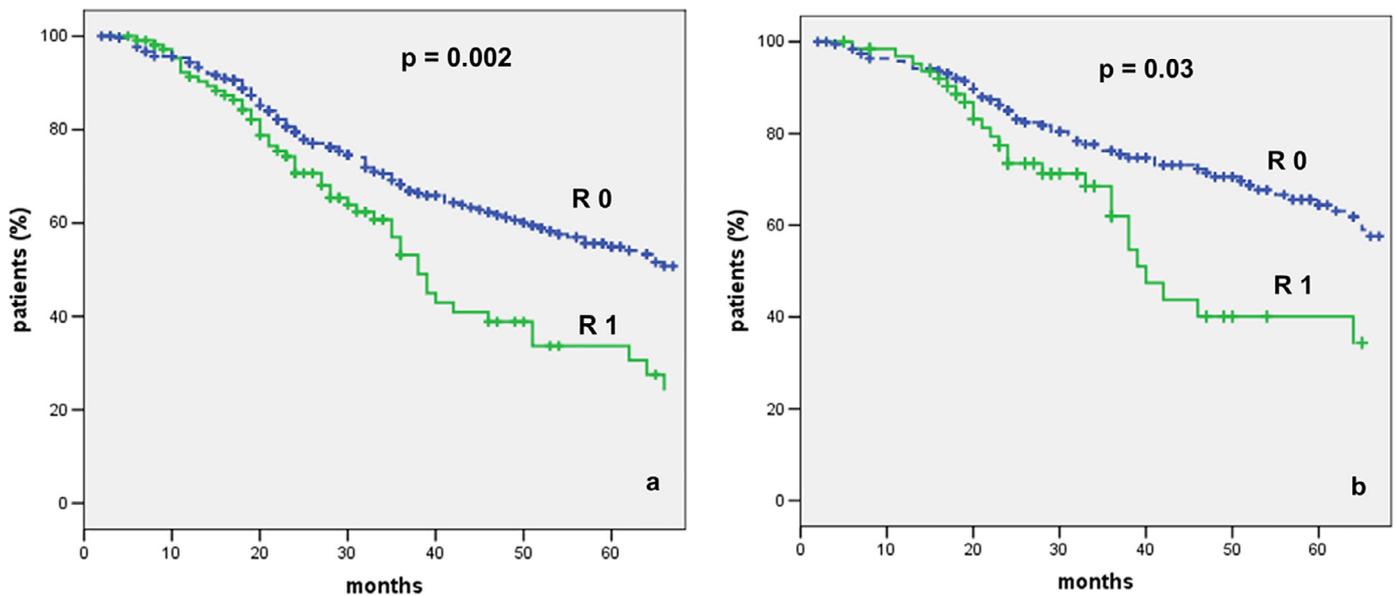


Fig. 1. The 5-year overall survival after R1 resection was significantly lower than it was after R0 resection (33.7% vs 54.9%, respectively; $P=0.002$; A); in the subgroup of patients who showed a response to preoperative chemotherapy, R1 resection was still associated with a significantly lower 5-year OS than was R0 resection (40.1% vs 64.4%, respectively; $P=0.03$; B).

Table 7
Impact of type of recurrence on OS.

Variable				HR	Std. err.	z	95% CI	P value
Type of recurrence								
Extrahepatic	Other intrahepatic sites	Local						
		R1 resection						
0	1	0	0	6.722	2.857	4.48	2.922–15.466	<.001
0	1	1	0	8.713	5.082	3.71	2.777–27.333	<.001
1	1	0	0	10.168	4.152	5.68	4.566–22.641	<.001
1	1	1	0	18.297	14.771	3.60	3.760–89.036	<.001
1	1	1	1	25.336	17.547	4.67	6.519–98.461	<.001

CI, confidence interval.

Discussion

This is the first large series showing that the risk of local recurrence after liver resection for CRLM was significantly higher after R1 resection than after R0 resection in patients treated with modern preoperative chemotherapy. From the analysis of 421 patients resected after chemotherapy, the overall local recurrence rate was 12.8%; but, it was significantly higher after R1 resection than after R0 resection (24.5% vs 8.7%; $P < .001$).

Among all prognostic factors after liver resection for CRLM, the width of the surgical margin is one that may be influenced by the conduct and expertise of the surgeon.³⁰ A resection margin greater than 1 cm was initially defined as the ideal safe width, based on the observation of micrometastases within 1 cm around the tumor border in patients without preoperative chemotherapy.¹⁰ During the last few decades, the safe surgical margin associated with better outcome has progressively moved from a width of 10 mm to a width of 1 mm.^{9–14} The Expert Group on OncoSurgery Management of Liver Metastases (EGOSLIM) stated that “a minimal surgical clearance margin of 1 mm has been suggested as sufficient.”³¹ Recently, 2 large series confirmed this statement, showing that a wider margin was not associated with improved OS.^{18,32} Memeo et al³³ analyzed the impact of margin status of 1,784 hepatectomies on OS: after obtaining comparable oncological data between R0 and R1 resection groups, R1 resection still represented a poor prognostic factor.³³

However, during the last years, the rate of R1 resections for CRLM has independently increased owing to the extension of the

criteria for resection, including patients with more advanced disease (multiple, bilobar, and large metastases), close to major vascular structures.^{15–17} In our study, the overall rate of R1 resections was 26.1%, but it was significantly higher in patients with multiple and bilobar disease, in patients who underwent multiple resections, and those who required intraoperative blood transfusions, an event which may be considered as an indicator of complex hepatectomies. Our policy has always been to obtain a tumor-free margin of 1 cm or greater whenever possible. However, an anticipated risk of R1 resection was not a contraindication to liver resection. R1 resection may become a necessity to obtain resectability in patients who would otherwise be unresectable, and should not be considered a technical error.²⁰

The current critical issue about R1 resection is the revisiting, by some recent studies, of its prognostic impact in patients resected in the modern era after aggressive and effective chemotherapy.^{20,21,34} These studies showed that the OS in such patients was similar after either R0 or R1 resection.^{20,21,34} They highlighted the impact of modern preoperative chemotherapy in improving OS whatever the surgical margin status. The theoretical explanation could be that modern chemotherapy may “sterilize” the tumor margins by destroying micrometastases in the periphery.³⁵ In this way, the adverse prognostic effect of R1 resection could be minimized.

On the other hand, other large series showed that a positive resection margin still remained a strong poor prognostic factor of OS, also in the era of modern chemotherapy.^{22–24} In a recent meta-analysis, Margonis demonstrated that R0 resection with surgical

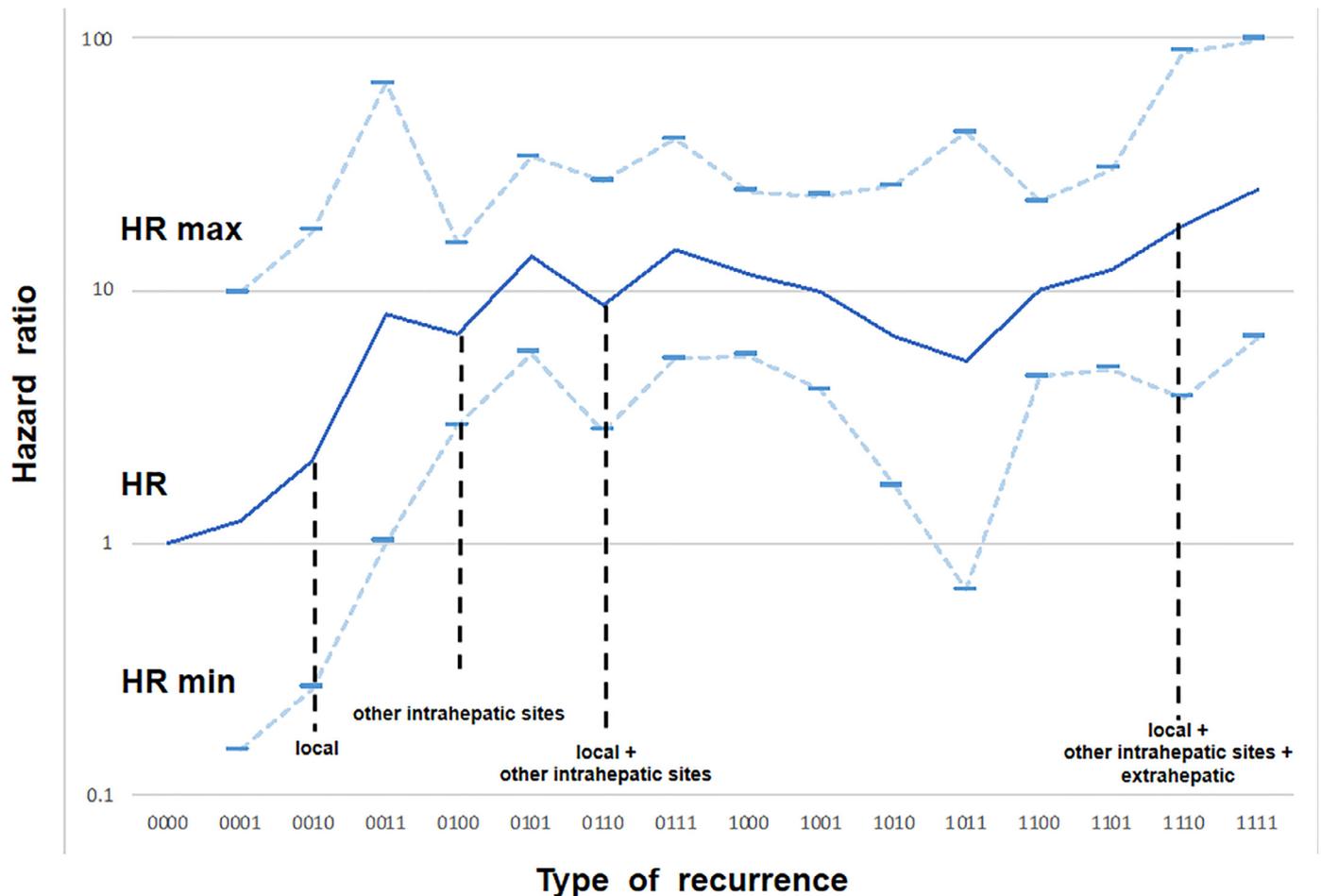


Fig. 2. The impact of type of recurrence on overall survival; final model of adjusted hazard ratio assessed by direct standardization to adjust for age of patients, size of colorectal liver metastases, initial resectability, response to preoperative chemotherapy, and number of lines of preoperative chemotherapy; type of recurrence (x axis): the sequence of numbers indicate extrahepatic recurrence-liver recurrence in other intrahepatic sites-local recurrence-R1 resection, respectively. 0 means absence of; 1 means presence of.

margin width of greater than 1 cm was associated with improved OS compared with R0 resection with surgical margin of less than 1 cm.³⁶ Interestingly, the administration of chemotherapy in this study did not seem to affect the relationship between margin status and OS.³⁶

For these reasons, it is still unclear whether a positive surgical margin remains a poor prognostic factor in the era of modern perioperative chemotherapy. The primary endpoint of most of the previous studies was the OS according to the margin status. In our study, R1 resection was associated with a significantly lower OS than after R0 resection (33.7% vs 54.9%, respectively; $P = .002$). These results were confirmed at the multivariable analysis. Interestingly, R1 resection remained a poor prognostic factor for OS also in the subgroup of patients who showed a response to preoperative chemotherapy.

However, additional research on the margin status in the contemporary era is needed.³⁶ A valid measure of the impact of the surgical margin width could be the analysis of local recurrence. Most recent studies focusing on surgical margin and preoperative modern chemotherapy generally reported the rate of intrahepatic recurrences, including recurrences in other intrahepatic sites that are not directly correlated with margin status.^{23,24} In our study, we focused on the local recurrence rate, defined as recurrence on the surgical margin, after liver resection in patients treated in the modern era (between 2000 and 2014) by effective preop-

erative chemotherapy. Indeed, all patients received oxaliplatin- or irinotecan-based chemotherapy before surgery, and associated targeting agents were administered in approximately 60% of patients. The overall local recurrence rate was 12.8%, and it reached 24.5% after R1 resection; therefore, it should not be considered to be a rare or insignificant issue. All the liver resection areas of the 421 resected patients were prospectively evaluated, and of the 1,428 areas, 89 showed local recurrence (6.2%). Interestingly, the rate of local recurrence significantly decreased according to the increasing of the surgical margin width, decreasing from 19.1% in 0-mm margins (R1 resection), to 2.4% in the greater than 1 cm margins, although all these patients were treated by effective preoperative chemotherapy. In patients with complete or partial response to chemotherapy, the rate of local recurrence was still significantly higher in R1 patients than in R0 patients (23.1% vs 11.2%, respectively; $P < .001$). In addition, in patients treated with cetuximab, the risk of local recurrence was significantly higher after R1 resection than it was after R0 resection. For these reasons, from a clinical point of view, the hypothesis that modern chemotherapy may destroy micrometastases in the periphery and reduce the risk of local recurrence was not confirmed by our results. Only the associated administration of bevacizumab showed a potential protective effect on the risk of local recurrence after R1 resection, whose difference with the risk after R0 resection did not reach significance. These data about the weaker association of local recurrence and

margin status in bevacizumab-treated patients may explain the results published by Sasaki.³⁷ Indeed, he showed that the tendency for better 5-year OS in R0 versus R1 resection did not reach significance in bevacizumab-treated patients (46.8% after R0 resection vs 33.0% after R1 resection; $P = .081$).

In a recent interesting article by Viganò,³⁸ a new proposal of R1 classification was described: the distinction between the standard “parenchymal” R1 resection (tumor exposure along the parenchymal transection line) and R1 “vascular” resection (CRLM detached from major intrahepatic vessels and exposed exclusively along the vessel). In this article, the authors showed that R1 “vascular” resection had oncological results similar to those of R0 resection.³⁸ In our study, it was not possible to exactly distinguish R1 parenchymal from R1 vascular resections in all the 1,428 liver resection areas. However, it should be noted that a “pure” R1 vascular resection with the exposure of the CRLM only in the area of detachment from the vessel is not frequent in the clinical practice. Indeed, in the series reported by Viganò,³⁸ the rate of R1 vascular resections was 10.6%, whereas R1 parenchymal resections represented the majority of cases (37.6%). For these reasons, we believe that these oncological results may need a prospective validation with larger series.

Brudvik et al showed that *Ras* mutations were associated with a higher rate of positive margins after resection of CRLM, suggesting a correlation between worse tumor biology and R1 resection.³⁹ At multivariate analysis, both *Ras* mutation and a positive margin independently predicted worse survival.³⁹ However, as they reported, their study did not provide data on margin recurrence. In our study, we evaluated the rate of local recurrence in a subgroup of 285 patients in whom *Ras* status was available. In *Ras* wild-type patients, local recurrence after R1 resection was significantly higher than it was after R0 resection. However, in *Ras*-mutated patients, the local recurrence rate was similar in both groups. This finding suggested that *Ras* wild-type CRLM clearly benefited from negative surgical margins, whereas in *Ras*-mutated patients, an R0 resection was not associated with an additional oncological benefit for local tumor recurrence.

These data may be interpreted as a pathological explanation of similar results published by Margonis et al.⁴⁰ In their article, they tried to determine the impact of surgical margin status on OS stratified by *Ras* mutational status, and they showed that an R0 margin provided a survival benefit only in *Ras* wild-type patients.⁴⁰

Several methods of liver transection are commonly practiced that may be related to different widths of surgical margins. In this series, the results are homogeneous because all patients were treated by the same technique with the use of the Cavatron ultrasonic surgical aspirator. However, it should be highlighted that in the literature, several articles reported the results of the radiofrequency-assisted precoagulation technique in liver resections.^{41,42} By this technique, the thermoablative energy by radiofrequency or microwave is used along the transection plane before starting liver resection. In this way, a zone of coagulative necrosis occurs, which may reduce the risk of bleeding during parenchymal transection and may help to “sterilize” the tumor margins.^{41,42} This technique may represent a possible oncologic benefit, owing to the additional safe margin obtained with the radiofrequency effect, especially in cases of preoperative planned R1 resection by necessity.

Finally, we tried to demonstrate whether local recurrence could show any impact on OS. In our multivariable analysis, we analyzed the impact of all local recurrences on OS, together with the impact of other types of recurrence. It was clear that the risk of death in patients with recurrent disease in other sites of the liver or in extrahepatic sites significantly worsens if local recurrence has also occurred. Indeed, we observed that the risk of death in patients with liver recurrence in other intrahepatic sites significantly in-

creased in cases of local recurrence (HR increased from 6.722 to 8.713; $P < .001$). Furthermore, the risk of death in patients with extrahepatic recurrence together with liver recurrence in other intrahepatic sites significantly increased with local recurrence (HR increased from 10.168–18.297; $P < .001$). Finally, in cases of liver recurrence, the possibility of resection was significantly higher in patients with liver recurrence in other sites than in patients with local recurrence. Only approximately 5% of patients with local recurrence underwent resection, and the cause of unresectability was liver-only local recurrence in approximately 25% of patients, which is not an insignificant proportion.

In other words, according to our results, the occurrence of local recurrence was associated with a negative impact on OS, independently from concomitant recurrences of other types.

It should be highlighted that in the era of modern chemotherapy, surgery remains the best treatment option for long-term outcome, and several studies still confirmed a better survival in patients who undergo resection of CRLM than in those who do not.⁴³ The impact of resection on OS is also evident in patients with complete response to preoperative chemotherapy.⁴³ Moreover, the significantly lower 5-year OS after R1 resection compared with after R0 resection, as shown in several studies like in our study, still represents the best long-term result in such patients, not achievable by chemotherapy alone.⁴³

Conclusion

Our study showed that local recurrence in patients treated by modern preoperative chemotherapy for CRLM was still significantly higher after R1 resection than it was after R0 resection. Local recurrence showed a negative prognostic impact on OS. R0 resection should be recommended, whenever technically achievable, in patients also treated by preoperative chemotherapy in the modern era. However, a 5-year OS similar to that observed in our study after R1 resection cannot be reached by other types of treatments. Therefore, the preoperative awareness of a likely need to perform an R1 resection “by necessity” should not be considered to be a contraindication to surgery.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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