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Resection Margin and Survival in 2368 Patients Undergoing Hepatic Resection for Metastatic Colorectal Cancer: Surgical Technique or Biologic Surrogate?

Eran Sadot, MD¹, Bas Groot Koerkamp, MD, PhD¹, Julie N. Leal, MD¹, Jinru Shia, MD², Mithat Gonen, PhD³, Peter J. Allen, MD¹, Ronald P. DeMatteo, MD¹, T. Peter Kingham, MD¹, Nancy Kemeny, MD⁴, Leslie H. Blumgart, MD¹, William R. Jarnagin, MD¹, and Michael I. D'Angelica, MD¹

¹Department of Surgery, Memorial Sloan Kettering Cancer Center, New York

²Department of Pathology, Memorial Sloan Kettering Cancer Center, New York

³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York

⁴Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York

Abstract

OBJECTIVE—The impact of margin width on overall survival (OS) in the context of other prognostic factors after resection for colorectal liver metastases (CRLM) is unclear. We evaluated the relationship between resection margin and OS utilizing high-resolution histologic distance measurements.

METHODS—A single institution prospectively maintained database was queried for all patients who underwent an initial complete resection of CRLM between 1992–2012. R1 resection was defined as tumor cells at the resection margin (0 mm). R0 resection was further divided into 3 groups: 0.1–0.9 mm, 1–9 mm, 10mm.

RESULTS—A total of 4915 liver resections were performed at MSKCC between 1992 and 2012, from which 2368 patients were included in the current study. Half of the patients presented with synchronous disease, 43% had solitary metastasis, and the median tumor size was 3.4cm. With a median follow-up for survivors of 55 months, the median OS of the R1, 0.1–0.9 mm, 1–9 mm, and 10mm groups were 32, 40, 53, and 56 months, respectively ($p < 0.001$). Compared to R1 resection, all margin widths, including submillimeter margins correlated with prolonged OS ($p < 0.05$). The association between the margin width and OS remained significant when adjusted for all other clinicopathologic prognostic factors.

CONCLUSIONS—Resection margin width is independently associated with OS. Wide margins should be attempted whenever possible. However, resection should not be precluded if narrow margins are anticipated, as submillimeter margin clearance is associated with improved survival.

Corresponding author: Dr. Michael I. D'Angelica, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, U.S.A, dangelim@mskcc.org, Tel: +1-212-639-3226 Fax: +1-212-717-3218.

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The prolonged OS observed with submillimeter margins is likely a microscopic surrogate for the biologic behavior of a tumor rather than the result of surgical technique.

Introduction

The impact of surgical margin width on outcomes after hepatectomy for metastatic colorectal cancer is unclear and the prognostic meaning of these margins in the context of other clinical and pathologic factors has not been well studied. Conflicting results have been reported with respect to the optimal margin width¹⁻⁴ and a few studies have suggested a lack of any prognostic impact for positive margins.^{5,6} These discrepancies in previous studies can be attributed to a limited sample size,^{5,7} failure to adjust for modern chemotherapy regimens¹, different surgical transection techniques, and varying definitions of the resection margin clearance/involvement. Thus, physicians do not have conclusive data about margin width to utilize in developing therapeutic strategies for patients with resectable metastatic colorectal cancer to the liver.

The definition of microscopic margin involvement (R1 resection) in colorectal liver metastases (CRLM) has been a point of contention. This definition may be influenced by the tumor growth pattern as it has been demonstrated that growth pattern correlates with both R1 resection rate and survival⁸. Furthermore, it has been reported that 95% and 70% of microsatellite lesions, when present, are located within 1cm and 2mm from the tumor margin, respectively.^{9,10} Thus, a one-millimeter margin may be satisfactory for tumors with a well circumscribed growth pattern but insufficient for tumors that are more microscopically invasive, as it is more likely that tumor cells will be left behind. The relationship between the margin width and survival is further compounded by preoperative treatment with modern chemotherapy, as well as, improving surgical and ablative techniques. It is possible that as these therapies evolve, so too will the relationship between the resection margin width and outcome.

We hypothesized that the width of the resection margin is associated with survival in a continuous manner, as it is influenced by various therapeutic, clinical, and pathologic factors. Therefore, the current dichotomy with regard to microscopic margin involvement (R0/R1) may inadequately represent the prognostic importance of margin width. The aim of this study was to assess the continuous relationship between the resection margin width and survival utilizing high-resolution histologic distance measurements while adjusting for all established contemporary risk factors.

METHODS

Study design

A total of 4915 liver resections for all diagnoses were performed at Memorial Sloan Kettering Cancer Center (MSKCC) between 1992 and 2012. After review of operative details and diagnoses we included 2626 patients who had undergone liver resection of CRLM at MSKCC with the following exclusion criteria applied; 1) Repeat hepatectomy (n=203), 2) R2 resection (residual macroscopic disease, n=48), and 3) Other stage IV cancer (n=7). We included all other patients in order to study sub-groups in whom margin width

may not have prognostic importance. A waiver of Health Insurance Portability and Accountability Act authorization was obtained and patient demographics, clinicopathologic characteristics, and survival data were obtained from a prospectively maintained database. These data were supplemented with additional chart review where necessary. All liver resections were performed using a standard technique as reported previously. The liver was typically transected with the “Kelly clamp” crush technique¹¹. Some patients underwent a combination of resection and intraoperative ablation at the same setting. All pathological specimens were reviewed and confirmed by MSKCC pathologists.

Methods of measurement

Histopathologic assessment of liver tumors has been standardized at MSKCC since 1991 and includes the number of tumors, size of the largest tumor, and numerical report of the surgical margin width in tenths of millimeter. This high-resolution histologic distance measurement relies on standard microscopic margin width measurement (ie, the pathologist calculates the distance by taking into account the total magnification of the microscope and the length of the measured object within the microscope field), which is employed in various cancers.¹² The final margin width was judged as the distance of the lesion closest to the transected liver surface. In the case of multiple tumors, the closest margin was recorded as the final margin. A narrow margin group was defined as either margin clearance less than 1mm or involved margins. Definitions and measurements of other prognostic factors and clinical risk score calculation were previously reported.¹³ Measurement of the number of CRLM included resected viable tumors, resected non-viable tumors (ie, complete pathologic response to preoperative chemotherapy), and ablated tumors. Disease-free interval (DFI) was defined as the time interval from resection of the primary colorectal cancer to diagnosis of liver metastasis. Synchronous CRLM was considered as DFI of zero and any CRLM with DFI above zero was defined as metachronous disease. Serum CEA levels were recorded as the highest value within 3 months prior to resection. Modern systemic chemotherapy was defined as either oxaliplatin or irinotecan. Perioperative chemotherapy was defined as any chemotherapy administered within 3 months of surgery. Major resections were defined as those consisting of 3 or more liver segments.¹⁴ Two-stage hepatectomy,¹⁵ radiofrequency/microwave ablation,¹⁶ and hepatic artery pump infusion^{17,18} were performed as previously described. Concurrent extrahepatic disease (EHD) was defined as EHD known at the time of the hepatic resection and either resected at the same time or within 6 months of hepatectomy as previously reported.¹⁹

Data analysis

Descriptive and comparative statistics were performed using Stata version 13.1 software (StataCorp LP, College Station, TX). Continuous variables were compared using the Student *t* test or Mann-Whitney test, as appropriate by the type of distribution. Categorical variables were compared using χ^2 or the Fisher exact test depending on the number of observations. Overall survival (OS) distributions were estimated from the time of CRLM resection using the Kaplan-Meier method and patients alive at last follow-up were censored. Groups were compared using log-rank test and the multivariate analysis used stepwise Cox regression. All tests were 2-sided and statistical significance was defined at $P < 0.05$.

RESULTS

Demographics

A total of 4915 liver resections were performed at MSKCC between 1992 and 2012, from which 2368 patients were included in the current study. The median age was 61 years (IQR: 51–69) and 43% were female (Table 1). Half of the patients presented with synchronous disease, 43% had solitary metastasis, and the median tumor size was 3.4cm (IQR: 2.1–5.5).

Margin width characterization

Initially, the margin width was evaluated as a continuous variable (at tenths of millimeter intervals) to assess the interaction with OS. Figure 1 demonstrates a continuous interaction between the margin width and OS with an initial sharp increase in median OS in the narrow margin zone, until an inflection point around 3–4mm margin width, which is followed by a more gradual increase. Based on this plot, our previous experience,¹¹ and the historical importance of both 1-mm and 1-cm margins, the margin width was further analyzed in the following 4 categories: R1 resection (tumor cells involving the resection margin (0 mm)) and R0 resection was further subdivided into 3 groups (0.1–0.9 mm, 1–9 mm, 10 mm).

Margin width and Overall survival

The relationship between the described categories and OS is shown in Figure 2. With a median follow-up for survivors of 55 months, the median OS of the R1, 0.1–0.9 mm, 1–9 mm, and 10 mm groups were 32, 40, 53, and 56 months, respectively. Predictors of OS are described in Table 2, which demonstrates that margin width, including submillimeter margins (ie, 0.1–0.9 mm clearance), correlated with improved OS compared to R1 resection ($p < 0.05$). The association between the margin width and OS remained statistically significant in a multivariable model accounting for all chemotherapy and clinicopathologic prognostic factors. While margin clearance of 1mm or more was associated with improved OS compared to submillimeter margin clearance (HR=0.7; 95%CI: 0.6–0.8; $p < 0.001$), no difference in OS was observed between the 10 mm and 1–9 mm groups ($p = 0.2$; Fig. 2). Additionally, margin width (< 1 mm vs. ≥ 1 mm) remained significantly associated with OS in all clinico-pathologic subgroups including analyses of the following factors: disease-free interval, nodal status of the primary tumor, number of CRLM, CRLM size, clinical risk score, extrahepatic disease, use of intraoperative ablation, hepatic artery infusion pump chemotherapy use, or modern chemotherapy use (data not shown).

Narrow margin width (<1-mm margin width)

A logistic regression was utilized and demonstrates that ablation status, number (more than 3), size (more than 5 cm) of CRLM, and CEA >200 $\mu\text{g/L}$ were independent predictors of a narrow margin (width <1 mm) (Table 1). Since narrow margins may be predictable at pre-operative planning, we studied whether any factor was predictive of an R1 margin or outcome in these patients. Table 3 details the independent predictors of OS in the narrow margin group ($n=405$). Within this group of patients, a submillimeter margin clearance was independently associated with OS ($p = 0.02$) compared to an R1 resection while accounting for all other clinical and pathologic factors. No clinicopathological characteristics were

identified as predictors of a submillimeter margin clearance among the patients with a narrow margin (Table 4). Moreover, Figure 2 demonstrates that within the narrow margin group and the R1 group, 19 (5%) patients and 9 (4%) patients were identified as actual 10-year survivors, respectively.

DISCUSSION

At present, the impact of resection margin width on overall survival has not been definitively established. Recent series have yielded conflicting results^{1,2,5,6} and have been limited by inadequate sample size and/or failure to control for modern chemotherapy regimens. The current study attempted to overcome these limitations. We analyzed a large cohort (2368 patients) from a single institution, which allowed for adequate statistical power while adjusting for all recognized contemporary prognostic factors. We demonstrated an associated prolonged survival with margin clearance down to submillimeter width that was independent of all potentially confounding factors. These findings have important clinical implications for staging and treatment stratification.

A previous study by our group analyzed the correlation between the margin width and OS in patients who had been treated at MSKCC during the earlier decade of the present study (between 1991 and 2003).¹¹ That study reported a continuous relationship between the margin width and OS, including a prolonged OS with submillimeter width. However, in a multivariable model, statistical significance was not reached until a margin width of > 1 cm. The current study expands on previous reports, as it was adequately powered to detect a significantly prolonged OS down to submillimeter margin clearance. Importantly, this finding held up while accounting for all contemporary established clinical, therapeutic, and pathological risk factors. In other words, the prognostic importance of margin width was relevant for all sub-groups of patients.

The improved outcome observed with submillimeter margin clearance is likely a microscopic surrogate for the biologic behavior of a tumor rather than the results of surgical technique. It is unlikely that CRLM patients survive longer because a submillimeter margin clearance was technically achieved. Rather a submillimeter clearance is more likely obtained when patients have a favorable underlying tumor biology. These data suggest that the same surgical technique and gross surgical clearance may yield different histologic margins. This observation is reinforced by a subgroup analysis of the narrow margin group (< 1 mm), which represents patients who can be predicted pre-operatively to have a close margin. Within the narrow margin group, a submillimeter margin clearance was independently associated with prolonged OS while adjusting for all other clinical and pathologic factors. Moreover, no clinicopathological characteristics were identified as predictors of a submillimeter margin clearance among this group.

There are several biological phenomena that can be considered as potential confounders. Defining the resection margin status/width by histopathology harbors inherent limitations, as standard tissue section (5 µm thick) represent approximately 1:1000 of the area that is macroscopically suspicious of margin involvement.^{12,20} Therefore, the resection margin may well be involved by cancer cells in the tissue levels above or below the sections that

were submitted for microscopic examination, particularly in tumors with an invasive growth pattern. Brunner et al²¹ revealed that a compact growth pattern (confined by a capsule) was associated with both higher R0 rate and improved survival. A similar observation was noted by Nielsen et al⁸ who identified an infiltrative growth pattern as an independent predictor of poor survival, whereas favorable prognosis was correlated with a desmoplastic growth pattern, in which a fibrous rim separates the metastasis from the liver parenchyma. It is noteworthy that both studies^{8,21} reported that the compact growth pattern (confined by a capsule) was associated with an increased lymphocytic infiltrate at the *tumor margin*, which is a recognized favorable prognostic factor in colorectal cancer.^{22–25} Thus, a confounding effect can be attributed to the capsule subtype of tumor growth pattern, which was proposed as a mechanical and chemical barrier to local invasion by tumor cells.²⁶ Yet, it is notable that adjustment for contemporary prognostic factors was limited in these studies.^{8,21} Furthermore, the tumor growth pattern was not routinely evaluated at our institution and therefore was not analyzed in the present study.

Historically, a predicted inability to attain a clear resection margin was considered a contraindication to liver resection for CRLM. However, various cut-off distances have been proposed to determine the optimal margin width. Prior studies, including our own, often concluded that a 1cm margin clearance was an optimal cut-off and was associated with improved survival.^{2,11} This cut-off was supported by the observation that, in the absence of preoperative chemotherapy, 95% of microsatellite lesions, when present, were located within 1cm of the tumor border⁹. When modern systemic therapy regimens developed, a 1-mm margin was proposed as the standard of care.¹ It was speculated that more effective systemic therapy could “sterilize” malignant cells left behind near a close margin.⁵ However, Ng et al²⁷ recently studied the relationship between preoperative chemotherapy and the surgical margin. They observed that tumor involution consisted of randomly distributed cell death and a significantly higher proportion of irregular tumor borders after chemotherapy. This was associated with discrete nests of viable cells outside of the main tumor mass. These findings led the authors to suggest that a 1cm margin should be pursued, as this would more likely result in a negative margin.

The present study was designed to account for all the established contemporary prognostic factors and demonstrated an independent association between prolonged OS and either 1-cm, 1-mm, or submillimeter margin clearance. Among patients with a narrow margin (< 1 mm) we were unable to predict which patient would ultimately harbor a positive margin. Therefore, liver resection should not be precluded from any patient who is expected to undergo a resection with narrow margin. This is further reinforced by the actual 10-year survivors’ rates in the narrow margin group (5%) and the R1 group (4%), which are equivalent to cure rates²⁸. Additionally, the finding that improved survival was associated with margin clearance of more than 1 mm compared to submillimeter clearance advocates that surgical technique plays an important role.

As an observational retrospective study, this analysis has inherent selection limitations and the generalizability of these results may be restricted to specialized high-volume centers. Despite adjustment in a multivariable model, any study that spans a long period is exposed to temporal bias; however, an additional exclusive feature of our study is the consistent

Kelly clamp liver transection technique that was utilized. It is noteworthy that other well-known transection techniques may create a margin of different character than the Kelly clamp technique and the margin, as determined by the pathologist, may have different clinical relevance. In addition, poor response to preoperative chemotherapy as a reflection of an aggressive tumor phenotype, was suggested⁷ to correlate with poor survival and R1 resection rate. However, the present study did not include response data in the analysis, as preoperative chemotherapy was not routinely administered at our institution and a substantial portion of the patients were evaluated by preoperative MRI while criteria for morphologic response are currently CT-based. On the contrary, the present study is the most comprehensive and adequately powered single-institution analysis of the relationship between the resection margin width and survival. A prospective randomized trial assessing margin width would be very challenging, thus, it is our premise that the current analysis represents an optimal study design in order to establish appropriate benchmarks.

In conclusion, the resection margin width is an independent predictor of OS. In order to ensure a clear margin, wide margins should be attempted in all cases when this is safe and feasible. The improved outcome observed with a submillimeter margin width is likely a microscopic surrogate for the biologic behavior of a tumor. Thus, liver resection should not be precluded from any patient who is expected to undergo a resection with narrow margin, as cure can be achieved and an unpredictable submillimeter margin clearance is associated with improved survival. These findings emphasize the prognostic importance of a negative margin and have important clinical implications for staging, treatment, operative planning, and future study of the tumor margin microenvironment.

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Figure 1. Interaction between the resection margin width and overall survival

A smoothed-fit curve of the median overall survival for each patient depending on the resection margin width as a continuous variable. A continuous interaction between the margin width and OS is demonstrated with an initial sharp increase in median OS in the narrow margin zone, until an inflection point around 3–4-mm margin width, which is followed by a more gradual increase. This descriptive graph does not adjust for any confounder nor does it account for censoring over the follow-up time. Thus, no comparative analysis was performed.

Figure 2. Overall survival curves stratified according to four categories of resection margin width. X, P = NS; *, P < 0.05.

Table 1

Clinicopathologic characteristics of all patients (n=2368) stratified by margin width.

Characteristics	All patients (n=2368)	Margin Imm ⁺ (n=1956)	Margin <Imm ⁺ (n=405)	Univariate analysis (p-value)	Multivariate analysis (OR; 95%CI; p-value)
Age, years	61 (51–69)	61 (51–70)	60 (51–68)	0.07	NS
Operation period				1	NA
<2004	1177 (50%)	973 (50%)	201 (50%)		
2004	1191 (50%)	983 (50%)	204 (50%)		
Gender				0.3	NA
Female	1018 (43%)	849 (43%)	165 (41%)		
Male	1350 (57%)	1107 (57%)	240 (59%)		
Resection type				0.001	NS
Major resection only	1031 (49%)	852 (49%)	179 (49%)		
Major resection & Wedge	184 (9%)	134 (8%)	50 (14%)		
Minor resection only	509 (24%)	439 (26%)	69 (19%)		
Either wedge only or wedge & minor resection	362 (18%)	294 (17%)	64 (18%)		
Ablation				<0.001	1.6; 1.1–2.4; 0.01
No	2134 (90%)	1796 (92%)	332 (82%)		
Yes	234 (10%)	160 (8%)	73 (18%)		
Nodal status of primary				0.7	NA
Negative	907 (39%)	744 (38%)	157 (39%)		
Positive	1440 (61%)	1196 (62%)	243 (61%)		
Presentation sequence				0.5	NA
Metachronous	1187 (50%)	986 (50%)	197 (48%)		
Synchronous	1181 (50%)	970 (50%)	208 (52%)		
Disease-free interval (DFI)				0.2	NA
<12 months	1504 (64%)	1230 (63%)	269 (67%)		
12 months	864 (36%)	726 (37%)	136 (33%)		

Characteristics	All patients (n=2368)	Margin 1mm [†] (n=1956)	Margin <1mm [†] (n=405)	Univariate analysis (p-value)	Multivariate analysis (OR; 95%CI; p-value)
Solitary tumor					
Yes	1010 (43%)	901 (46%)	105 (26%)	<0.001	NA
No	1358 (57%)	1055 (54%)	300 (74%)		
CRLM number >3					
No	1780 (75%)	1541 (79%)	232 (57%)	<0.001	2.8; 2.1–3.7; <0.001
Yes	588 (25%)	415 (21%)	173 (43%)		
Size					
<5 cm	1654 (70%)	1398 (71%)	249 (61%)	<0.001	1.7; 1.3–2.3; <0.001
5 cm	714 (30%)	558 (29%)	156 (39%)		
CEA					
<200 µg/L	1950 (92%)	1631 (93%)	312 (87%)	<0.001	1.5; 1.1–2.2; 0.047
200 µg/L	178 (8%)	130 (7%)	48 (13%)		
Clinical risk score (CRS)					
<3	1124 (53%)	964 (55%)	160 (45%)	0.001	NA
3	987 (47%)	789 (45%)	198 (55%)		
Extrahepatic disease (EHD)					
No	2173 (92%)	1797 (92%)	370 (91%)	0.7	NA
Yes	195 (8%)	159 (8%)	35 (9%)		

Continuous variables are expressed as median (IQR); categorical variables are expressed as n (%). NA – not analyzed. NS – not significant; CEA - carcinoembryonic antigen.

[†] Seven patients had their margin status recorded only as positive/negative. Thus, they were excluded from these columns.

Table 2

Predictors of overall survival analysis in all patients (n=2368).

Characteristics	N (%)	Overall survival		Univariate		Multivariate	
		5Ys, %	Median, months	HR (95% CI)	P	HR (95% CI)	P
Age, years	2368 (100%)	43	50.6	1.01 (1.01–1.02)	<0.001	1.01 (1.004–1.015)	<0.001
Gender							
Female	1018 (43%)	42	50				NA
Male	1350 (57%)	44	52	0.96 (0.87–1.07)	0.5	NA	
Solitary tumor							
Yes	1010 (43%)	49	59	0.8 (0.7–0.9)	0.001	0.8 (0.7–0.9)	<0.001
No	1358 (57%)	39	45				
Size							
<5 cm	1654 (70%)	47	56	1.6 (1.4–1.7)	<0.001	1.4 (1.2–1.6)	<0.001
5 cm	714 (30%)	33	38				
CEA							
<200 µg/L	1950 (92%)	45	53	1.7 (1.4–2)	<0.001	1.3 (1.1–1.6)	0.009
200 µg/L	178 (8%)	27	35				
Nodal status of primary							
Negative	907 (39%)	51	63	1.4 (1.3–1.6)	<0.001	1.6 (1.4–1.7)	<0.001
Positive	1440 (61%)	38	45				
Disease-free interval (DFI)							
<12 months	1504 (64%)	42	50	0.99 (0.9–1.1)	0.9	NA	NA
>12 months	864 (36%)	45	52				
Presentation sequence							
Metachronous	1187 (50%)	44	50	0.98 (0.9–1.1)	0.8	NA	NA
Synchronous	1181 (50%)	42	50				

Characteristics	N (%)	Overall survival			Univariate		Multivariate	
		SYS, %	Median, months		HR (95% CI)	P	HR (95% CI)	P
Clinical risk score (CRS)								
<3	1129 (53%)	51	62		1.5 (1.3–1.6)	<0.001	NA	NA
3	987 (47%)	36	42					
Margin status¹								
0mm	245 (10%)	24	32		Ref	<0.001	Ref	<0.001
0.1mm–0.9mm	160 (7%)	26	40		0.7 (0.6–0.9)	0.04	0.7 (0.6–0.9)	0.03
1mm–9mm	1191 (50%)	46	53		0.5 (0.4–0.6)	<0.001	0.6 (0.5–0.7)	<0.001
10mm	765 (33%)	48	56		0.5 (0.4–0.6)	<0.001	0.5 (0.4–0.6)	<0.001
Perioperative chemotherapy								
No	172 (7%)	36	41		0.8 (0.6–0.9)	0.01	NA	NA
Yes	2193 (93%)	43	51					
Perioperative modern chemotherapy								
No	879 (38%)	38	45		0.75 (0.7–0.8)	<0.001	NS	NS
Yes	1442 (62%)	46	54					
Operation period								
<2004	1177 (50%)	39	44		0.7 (0.6–0.8)	<0.001	0.8 (0.7–0.9)	<0.001
2004	1191 (50%)	47	56					
Extrahepatic disease (EHD)								
No	2173 (92%)	45	52		1.7 (1.4–2.0)	<0.001	1.6 (1.3–1.9)	<0.001
Yes	195 (8%)	25	33					
HAIP								
No	1534 (65%)	37	44		0.65 (0.6–0.7)	<0.001	0.7 (0.6–0.8)	<0.001
Yes	834 (35%)	53	67					
Ablation								
No	2134 (90%)	43	51		1.02 (0.8–1.2)	0.9	NA	NA
Yes	234 (10%)	38	45					

Characteristics	N (%)	Overall survival		Univariate		Multivariate	
		5YS, %	Median, months	HR (95% CI)	P	HR (95% CI)	P
Two-stage resection							
No	2316 (98%)	43	51	1.02 (0.7–1.5)	0.9	NA	NA
Yes	52 (2%)	43	49				

NA – not analyzed; NS – not significant; HAIP – hepatic artery infusion pump; CEA - carcinoembryonic antigen.

Seven patients had the margin recorded only as positive/negative. Thus, they were excluded from these variables.

Table 3

Overall survival analysis in patients with narrow margin (width <1mm, n=405):

Characteristics	N (%)	Overall survival			Univariate			Multivariate		
		5YS%	Median, months		HR (95% CI)	P		HR (95% CI)	P	
Age, years	405 (100)	25%	34		0.99 (0.98–1.006)	0.4		NA	NA	
Gender										
Female	165 (41)	26%	32		1.1 (0.9–1.4)	0.5		NA	NA	
Male	240 (59)	23%	37							
Solitary tumor										
Yes	105 (26)	33%	42		0.8 (0.6–1.1)	0.2		NA	NA	
No	300 (74)	21%	32							
CRLM number >3										
No	232 (57)	32%	42		1.5 (1.2–1.9)	0.001		1.7 (1.3–2.3)	<0.001	
Yes	173 (43)	15%	28							
Size										
<5 cm	249 (61)	28%	41		1.5 (1.2–1.8)	0.002		1.1 (0.8–1.5)	0.4	
5 cm	156 (39)	19%	26							
CEA										
<200 µg/L	312 (87)	25%	36		1.04 (0.7–1.5)	0.8		NA	NA	
200 µg/L	48 (13)	20%	38							
Nodal status of primary										
Negative	157 (39)	34%	49		1.7 (1.3–2.2)	<0.001		1.5 (1.1–2.1)	0.004	
Positive	243 (61)	19%	28							
Disease-free interval (DFI)										
<12 months	269 (67)	25%	33		1.1 (0.9–1.5)	0.3		NA	NA	
>12 months	136 (33)	26%	41							

Characteristics	N (%)	Overall survival		Univariate		Multivariate	
		5YS%	Median, months	HR (95% CI)	P	HR (95% CI)	P
Presentation sequence							
Metachronous	197 (48)	28%	38	1.2 (0.9–1.5)	0.15	NA	NA
Synchronous	208 (52)	20%	32				
Clinical risk score (CRS)							
<3	160 (45)	31%	49	1.6 (1.2–2.1)	<0.001	NS	NS
3	198 (55)	19%	28				
Perioperative chemotherapy							
No	28 (7)	23%	34	1.05 (0.6–1.7)	0.9	NA	NA
Yes	377 (93)	25%	34				
Perioperative modern chemotherapy							
No	149 (38)	29%	36	1.04 (0.8–1.3)	0.7	NA	NA
Yes	251 (62)	21%	33				
Operation period							
<2004	201 (50)	20%	28	0.7 (0.5–0.8)	0.001	0.6 (0.4–0.8)	<0.001
2004	204 (50)	30%	44				
Extrahepatic disease (EHD)							
No	370 (91)	26%	37	1.7 (1.2–2.4)	0.002	1.9 (1.3–2.9)	0.001
Yes	35 (9)	8%	22				
HAIP							
No	249 (62)	22%	31	0.7 (0.5–0.9)	0.008	0.7 (0.6–0.9)	0.03
Yes	156 (38)	29%	43				
Ablation							
No	332 (82%)	26%	34	1.05 (0.8–1.6)	0.8	NA	NA
Yes	73 (18%)	17%	36				
Margin status							
				0.7 (0.6–0.9)	0.04	0.7 (0.6–0.9)	0.02

Characteristics	N (%)	Overall survival		Univariate		Multivariate	
		5YS%	Median, months	HR (95% CI)	P	HR (95% CI)	P
0mm	245 (61)	24%	32				
0.1mm–0.9mm	160 (39)	26%	40				

Continuous variables are expressed as median (IQR); categorical variables are expressed as n (valid percent). NA – not analyzed. HAIP – hepatic artery infusion pump; CEA - carcinoembryonic antigen.

Table 4

Characteristics of the R1 and the submillimeter (0.1–0.9mm) margin groups.

Variable	All patients with narrow margin (width <1mm, n=405)	R1 group (n=245)	Submillimeter (0.1–0.9mm) group (n=160)	Univariate analysis (<i>p</i> -value)
Age, years	60 (51–68)	60 (51–67)	61 (51–70)	0.4
Operation period				0.3
<2004	201 (50%)	116 (48%)	85 (53%)	
2004	204 (50%)	129 (52%)	75 (47%)	
Gender				0.9
Female	165 (41%)	100 (41%)	65 (41%)	
Male	240 (59%)	145 (59%)	95 (59%)	
Resection type				0.5
Major resection only	179 (49%)	104 (48%)	75 (52%)	
Major resection & Wedge	50 (14%)	32 (15%)	18 (12%)	
Minor resection only	69 (19%)	39 (17%)	30 (21%)	
Either wedge only or wedge & minor resection	64 (18%)	43 (20%)	21 (15%)	
Ablation				0.5
No	332 (82%)	198 (81%)	134 (84%)	
Yes	73 (18%)	47 (19%)	26 (16%)	
Nodal status of primary				0.2
Negative	157 (39%)	101 (42%)	56 (35%)	
Positive	243 (61%)	141 (58%)	102 (65%)	
Presentation sequence				0.15
Metachronous	197 (49%)	112 (46%)	85 (53%)	
Synchronous	208 (51%)	133 (54%)	75 (47%)	
Disease-free interval (DFI)				0.4
<12 months	269 (66%)	168 (69%)	101 (63%)	
12 months	136 (34%)	77 (31%)	59 (37%)	
Solitary tumor				0.5
Yes	105 (26%)	60 (25%)	45 (28%)	
No	300 (74%)	185 (75%)	115 (72%)	
CRLM number >3				0.2
No	232 (57%)	134 (55%)	98 (61%)	
Yes	173 (43%)	111 (45%)	62 (40%)	
Size				0.6

Variable	All patients with narrow margin (width <1mm, n=405)	R1 group (n=245)	Submillimeter (0.1–0.9mm) group (n=160)	Univariate analysis (<i>p</i> -value)
<5 cm	249 (61%)	153 (62%)	96 (60%)	
5 cm	156 (39%)	92 (38%)	64 (40%)	
CEA				0.2
<200 µg/L	312 (87%)	183 (85%)	129 (90%)	
200 µg/L	48 (13%)	33 (15%)	15 (10%)	
Clinical risk score (CRS)				0.7
<3	160 (45%)	94 (44%)	66 (46%)	
3	198 (55%)	120 (56%)	78 (54%)	
Extrahepatic disease (EHD)				0.3
No	370 (91%)	226 (91%)	142 (89%)	
Yes	35 (9%)	21 (9%)	18 (11%)	

Continuous variables are expressed as median (IQR); categorical variables are expressed as n (valid percent). NA – not analyzed. HAIP – hepatic artery infusion pump; CEA - carcinoembryonic antigen. P-values relates to the comparison between the R1 and submillimeter groups.