Systematic Review Article

The Correlation Between the Surgical Margin and Survival in Patients with Colorectal Cancer Liver Metastasis: A Systematic Review and Meta-Analysis

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ABSTRACT

Surgery is by far the most effective treatment for patients with Colorectal Cancer Liver Metastases (CRLM). Furthermore, numerous studies have shown that surgical margins significantly impact patient survival and should be systematically evaluated. Given the modern era of chemotherapy, this review focuses on millimetre surgical margins and their impact on survival. A systematic search of 200 reports yielded 53 studies, and data on Overall Survival (OS) or Disease-Free Survival (DFS) stratified by surgical margin were collected. A Kruskal-Wallis test was conducted to compare the surgical margin subgroups: R1 (0 mm), <1 mm, 1-5 mm, 5-10 mm, and >10 mm. A meta-analysis was used to compare pairs R0 (>0mm)/R1(0mm) and >1 mm/<1 mm. All four meta-analyses reported a significant difference ($p<0.01$) between the pairs R0/R1 and >1 mm/<1 mm, with 95% CIs and PIs not intercepting the null line. The findings suggest a survival benefit of R0 resection with a minimum 1 mm margin. However, due to the current limitations of this review, we cannot draw a clinical conclusion regarding the optimal surgical margin to maximise survival in patients with CRLM.

Keywords: Margin; Colorectal Cancer Liver Metastases; Overall Survival; Disease-Free Survival; R0; R1

INTRODUCTION

Colorectal cancer makes up approximately 10% of all cancer cases and is the 2nd most common cancer in the world. It predominantly affects males and individuals aged 50 or older. (1) In Colorectal cancer, the liver is the primary location of metastasis, and over 25% of patients develop Colorectal Cancer Liver Metastases (CRLM) over the course of their illness. (2) As of this date, surgery is regarded as a potentially curative treatment for this disease. In fact, according to a meta-analysis conducted by Todeschini *et al*., "Liver resection (LR) is superior to Radiofrequency ablation (RFA) in terms of overall survival and disease-free survival for respectable CRLM". (3)

The reason the surgical margin is so crucial is that the surgeon must balance the benefits of improving survival in patients against the costs of reducing the future remnant liver. For example, Sakamoto *et al*. (2023) conducted a meta-analysis examining the impact of surgical margin on overall survival (OS) and disease-free survival (DFS). (4) They analysed factors that alter the "optimal surgical margin", including tumour number and size, response to chemotherapy, and distance from blood vessels. All these factors play a role in the margin that

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should be used, defeating the purpose of generalising a number. However, with the increasing number of clinical trials on surgical margins, it is imperative to systematically collate and analyse the data to determine a result.

This systematic review aims to identify the correlation between surgical margin and four survival metrics: 5-year OS, 5-year DFS, Median OS, and Median DFS. Firstly, the Kruskal-Wallis test, a non-parametric test, will be used to analyse significant differences between the surgical margins subgroups: R0, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. Subsequently, a meta-analysis will be conducted to compare pairs R0/R1 and >1 mm/<1 mm with respect to OS and DFS.

METHODS AND MATERIALS

Data Collection

On July 4, 2025, A systematic search was conducted in PubMed using the keywords ("R1" OR "margin") AND ("colorectal cancer liver metastasis" OR "CRLM"). A total of 200 abstracts were scanned and filtered down to 53 reports using PRISMA Guidelines (Figure 1). To be included, the reports had to contain data with the surgical margin as an independent variable and OS or DFS as the dependent variable. The reports also had to be a retrospective or prospective clinical trial, fully accessible, and written in English.

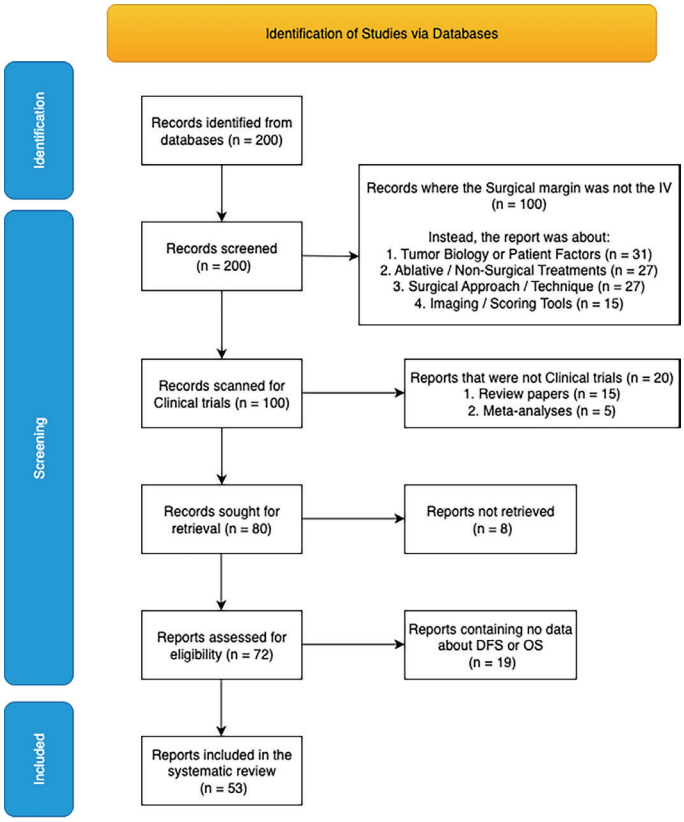

Figure 1. *The PRISMA diagram for systematic review.*

After filtration, data were collected from all reports for the four survival rates: 5-year OS, 5-year DFS, median OS, and median DFS, stratified by surgical margin. The surgical margins subgroups collected were R1 (0 mm), R0 (>0 mm), <1 mm, >1 mm, 1-5 mm, 5-10 mm, and >10 mm. The year of study and demographic features, such as the median age and the gender ratio, were also collected.

Data Analysis

Kruskal-Wallis test

Four Kruskal-Wallis tests were conducted in IBM SPSS Statistics for each dependent variable: 5-year OS, 5-year DFS, Median OS and Median DFS. All tests compared the surgical margins subgroups: R0, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. These specific ranges were chosen based on data availability and their mutual exclusivity. The number of studies, patient sizes, medians, and ranges of survival rates (DFS and OS) were summarised. This experimental data is presented in Table 2. Each Kruskal-Wallis test also produced a box-and-whiskers plot (Figure 2) stratified by surgical margin. The plot highlights the median, range, and 95% confidence intervals, excluding outliers. The median and range shown in the box-and-whisker plots differ from those in the tables because outliers were removed. Outliers were defined as points that were 1.5 times the Interquartile Range (IQR). Lastly, each test also produced a Pairwise Comparison table. The table stratified each possible pair (n = 10) amongst all samples and identified a p-value (Sig.) for each pair. The p-values were also adjusted using the Bonferroni correction (5), and significant p-values ($p<0.05$) were identified (Table 3).

Meta-analysis

A total of four meta-analyses were conducted between two dependent variables for two pairs (R0/R1) and (>1mm/<1mm). These pairs were chosen based on data availability and mutual exclusivity. Before each meta-analysis, studies reporting 5-year OS or DFS for each pair were collected. The 5-year OS or DFS and the number of patients in each surgical margin subgroup were used to calculate the number of patients who survived for 5 years in each margin subgroup. This data

was entered into the binary meta-analysis, and a forest plot was created (Figures 3A, 4A, 5A, 6A). Information on the Risk Ratio (RR), lower and upper bounds, p-value, and weights for each study is provided in Tables 5, 6, 7, and 8 for each dependent variable. The studies in this meta-analysis represent a small sample of the larger population of patients with CRLM; therefore, they are subject to substantial sampling variation. Therefore, a random-effects model was used to provide a more realistic outcome. (6)

Heterogeneity and Publication bias

Heterogeneity is a critical consideration, especially in a surgical meta-analysis, as it reveals true differences across populations. In meta-analyses, I^2 is commonly used to understand heterogeneity, but according to Borenstein [2023], it measures heterogeneity as a percentage rather than its magnitude and is therefore not particularly relevant to clinical practice. (7) Consequently, this systematic review also produces a 95% Prediction Interval (PI), which is larger than the 95% CI and accounts for between-study heterogeneity. It allows us to predict the true effect size in a future comparable study and estimate the proportions of studies that will yield results below and above a clinically relevant threshold (RR=1). Using the mean and 95% CIs retrieved from SPSS, 95% PI was calculated using an online meta-analysis website. (8) This value was cross-checked against SPSS findings to ensure accuracy.

Publication bias is also a critical consideration in each of these meta-analyses, given the history of surgical margins. Dating back to when Halsted first introduced radicalism in surgery, surgeons are inherently biased towards achieving larger margins. In the modern era of chemotherapy and invasive treatment, a large margin may not be necessary and could even be potentially detrimental to the patient. Due to this inherent bias, researchers may not publish insignificant or opposing results, which we must test for in all the meta-analyses. Therefore, using the mean and 95% CIs retrieved from SPSS, an Egger's test was conducted using an online meta-analysis website. (8)

RESULTS

Demographics

Across all 53 studies, 26,658 patients were included. Of these, 36 were retrospective clinical trials, and 17 were prospective. The median age for all patients was 62.6 years; 13,788 were males, and 8,652 were females. Thirty-two studies defined the pair R1/R0 as 0 mm/>0 mm, and the other 21 studies defined it as <1 mm/>1 mm. Therefore, for the simplicity of this report, R1 and R0 have been defined as (0 mm) and (>0 mm), respectively. Both pairs have been analysed in different meta-analyses to make this report more comprehensive (Table 1).

Table 1. A table summarising the demographics of the entire test population. *The surgical margins were segregated into mutually exclusive subgroups. The pairs (R0/R1) and (>1 mm/<1 mm) were analysed by meta-analyses, and the subgroups (R1, >1 mm, 1-5 mm, 5-10 mm, >10 mm) were analysed using Kruskal-Wallis tests.*

Demographics	Category	Patient number (n = 26,658)
Gender	Males	13788
	Females	8652
Surgical Margin (mm)	R1 (0)	2753
	R0 (>0)	12359
	>1	2370
	<1	5841
	1-5	2002
	5-10	1528
	>10	1901

Kruskal-Wallis test comparing R1, <1 mm, 1-5 mm, 5-10 mm, and >10 mm

5-year Overall Survival

More studies contributed to both the R1 (n = 14) and <1 mm (n = 14) subgroups than to the other three subgroups (n = 7 each) (Table 2). Despite this, the number of patients was relatively homogeneous across all study subgroups, ranging from 1537 in the <1 mm subgroup to 984 in the 5-10 mm subgroup.

The box-and-whisker plot (Figure 2A) compares 5-year OS across the five surgical margin subgroups: R1, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. The statistical differences were summarised in Table 3. The pairs with (1-5 mm), (5-10 mm), and >10 mm have adjusted p-values of 1 (Table 3). In this review, we didn't observe statistical significance between subgroups, indicating that all subgroups with >1 mm have similar 5-year OS rates. In fact, the only significant pairs are (R1 vs 1-5 mm) (p = 0.008), (R1 vs 5-10 mm) (p = 0.003), and (R1 vs >10 mm) (p = 0.009) (Table 3).

Table 2. A statistical summary of the Kruskal-Wallis tests for each surgical margin, covering 5-year overall survival, 5-year disease-free survival, median overall survival, and median disease-free survival.

		R1	<1 mm	1- 5 mm	5-10 mm	>10 mm
5-year Overall Survival (%)	No. Studies	14	14	7	7	7
	Patients	1260	1537	1404	984	1214
	Min	0.00	0.00	20.40	40.70	37.00
	Median	26.30	38.20	55.50	53.00	53.00
	Max	49.30	58.30	70.00	65.00	70.70
5-year Disease-Free Survival (%)	No. Studies	10	12	4	4	6
	Patients	1161	959	716	342	1773
	Min	0.00	3.50	0.00	15.00	34.80
	Median	16.10	17.85	26.70	33.60	39.45
	Max	28.90	60.00	40.00	35.00	45.00
Median Overall Survival (Months)	No. Studies	16	9	3	3	3
	Patients	1624	987	154	80	84
	Min	16.80	18.00	25.80	36.20	36.20
	Median	34.00	37.00	57.80	60.00	60.00
	Max	58.40	72.10	60.00	75.60	120.00
Median Disease-Free Survival (Months)	No. Studies	11	9	3	3	4
	Patients	1057	937	154	80	84
	Min	1.60	6.00	10.30	10.00	15.70
	Median	10.20	12.00	15.10	12.50	24.00
	Max	19.00	30.00	16.00	31.50	31.50

Table 3. A summary of all the Kruskal-Wallis tests to assess the significant differences in the 5-year Overall Survival, 5-year Disease-Free Survival, Median Overall Survival, and Median Disease-Free Survival between the five subgroups of surgical margins: R1, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. *Each row tests the null hypothesis that the distributions of Samples 1 and 2 are identical. Asymptotic significances (2-sided tests) are displayed. All values have been adjusted for multiple tests using the Bonferroni correction, and the significant p-values (<0.05) are highlighted in bold.*

Sample 1 (mm) Sample 2 (mm)	5 year-OS		5 year-DFS		Median OS		Median DFS	
	Z-value	Adj. p-value	Z-value	Adj. p-value	Z-value	Adj. p-value	Z-value	Adj. p-value
R1 (<1)	1.766	0.774	0.802	1.000	0.815	1.000	0.727	1.000
R1 (>10)	3.319	**0.009**	1.181	1.000	1.168	1.000	0.836	1.000
R1 (1-5)	3.363	**0.008**	1.755	0.793	2.029	0.424	1.039	1.000
R1 (5-10)	3.595	**0.003**	3.681	**0.002**	2.078	0.377	2.596	0.094
(<1) (>10)	-1.827	0.677	0.614	1.000	0.639	1.000	0.379	1.000
(<1) (1-5)	1.870	0.614	1.195	1.000	1.467	1.000	0.581	1.000
(<1) (5-10)	2.099	0.358	-3.067	**0.022**	-1.514	1.000	-2.068	0.387
(1-5) (5-10)	0.038	1.000	-0.474	1.000	-0.660	1.000	-0.160	1.000
(1-5) (>10)	0.239	1.000	-1.826	0.678	-0.698	1.000	-1.243	1.000
(5 - 10) (>10)	-0.201	1.000	-1.307	1.000	-0.038	1.000	-1.072	1.000

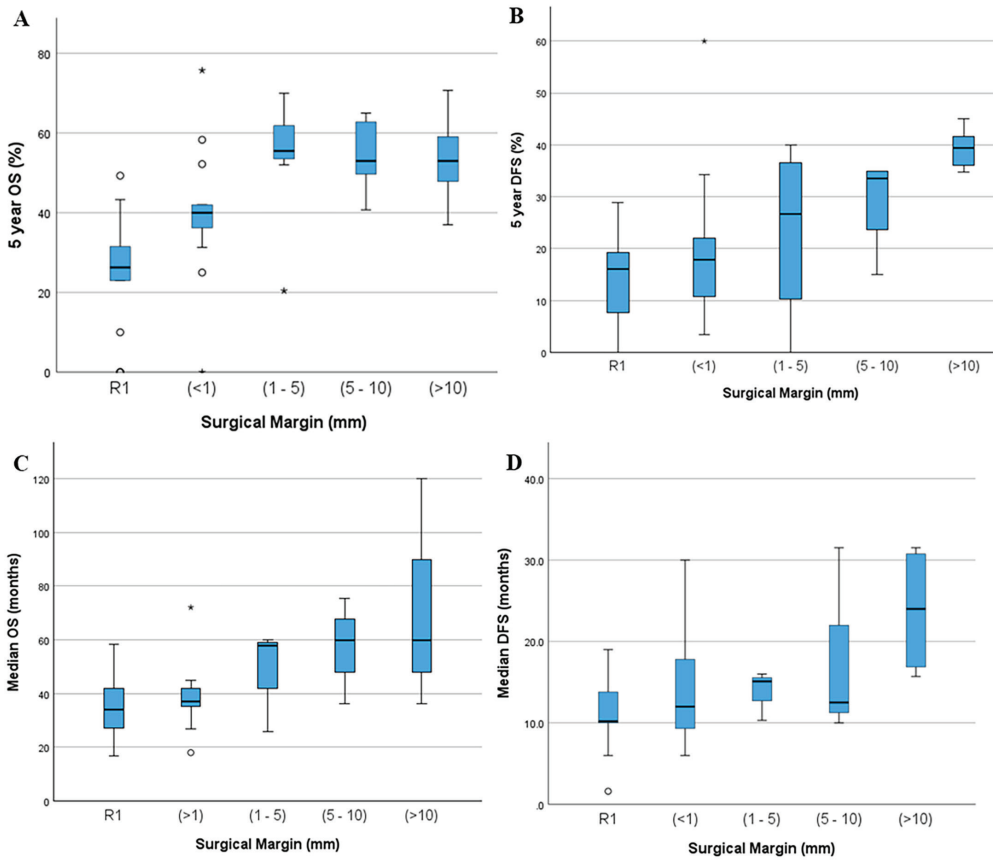

Figure 2. Surgical margin–stratified survival outcomes based on Kruskal–Wallis analyses. *Box-and-whisker plots show survival outcomes across five surgical margin subgroups (R1 [0 mm], <1 mm, 1–5 mm, 5–10 mm, and >10 mm). (A) 5-year overall survival (OS). (B) 5-year disease-free survival (DFS). (C) Median overall survival (OS). (D) Median disease-free survival (DFS). Boxes represent the interquartile range (IQR) with the median indicated by the central line; whiskers represent the range excluding outliers. Mild outliers (>1.5× IQR from the box) are denoted by open circles (○), and extreme outliers (>3× IQR) by asterisks (*). Pairwise statistical comparisons and Bonferroni-adjusted p-values are provided in Table 3.*

From this data, there is a disparity in survival between subgroups smaller than 1 mm (R1 and <1 mm) and those greater than 1 mm (1-5 mm, 5-10 mm, and >10 mm). To investigate this disparity, a binary meta-analysis is presented later in this report.

5-year Disease-Free Survival

For the 5-year DFS, the number of studies contributing to each subgroup was heterogeneous, ranging from 4 in the 1-5 mm and 5-10 mm subgroups to 12 in the < 1 mm subgroup (Table 2). Furthermore, the number of patients was heterogeneous across studies, ranging from 1773 in the subgroup >10 mm to 342 in the subgroup 5-10 mm.

The box-and-whisker plot (Figure 2B) compares 5-year DFS across the five surgical margin subgroups: R1, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. The statistical differences were analysed using the Kruskal-Wallis test, and the pairwise values are summarised in Table 3. Although the median 5-year DFS increases with increasing surgical margin, the subgroups 1-5 mm and 5-10 mm include data from only 4 studies (Table 2). Therefore, additional clinical research involving these subgroups is needed to improve the reliability of the analysis. The only significant pairs are (<1 mm, >10 mm) ($p = 0.022$) and (R1, >10 mm) ($p = 0.002$) (Table 3).

Median Overall Survival

For the Median OS, the number of studies was relatively heterogeneous. There was a maximum of 16 in the R0 subgroup and a minimum of 3 in the surgical margin subgroups: 1-5 mm, 5-10 mm, and >10 mm. Furthermore, the number of patients varied widely

across studies, ranging from 80 in the 5-10 mm subgroup to 1624 in the R1 subgroup. The box-and-whisker plot (Figure 2C) compares Median OS across the five surgical margin subgroups: R1, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. The statistical significance for each pairwise comparison on median OS is summarised in Table 3. There are no significant p-values ($p < 0.05$) as shown by the Pairwise comparisons of the Kruskal-Wallis test**.**

Table 2 suggests a positive correlation between surgical margin and median OS. There is a significant difference in median survival between the surgical margin subgroups: <1 mm (37.00 months) and 1-5 mm (57.80 months). (Table 2). However, the analysis did not detect any significance between pairs for Median OS (Table 3). This may be because three surgical margin subgroups (1-5 mm, 5-10 mm, and >10 mm) each include data from only three studies (Table 2).

Median Disease-Free Survival

For Median DFS, the number of studies varies, ranging from 3 in the 1-5 mm and 5-10 mm subgroups to 11 in the R1 subgroup (Table 2). Furthermore, the number of patients was highly heterogeneous across studies, ranging from 1057 in R1 to only 80 in subgroup 5-10 mm (Table 2).

The box-and-whisker plot (Figure 2D) compares median DFS across the five surgical margins: R1, <1 mm, 1-5 mm, 5-10 mm, and >10 mm. The statistical differences between the pairwise values are summarised in Table 3. There are no significant p-values ($p < 0.05$) as shown by the Pairwise comparisons of the Kruskal-Wallis test (Table 3). This analysis did not detect any significance between pairs for Median OS. However, this may be because two surgical margin subgroups (1-5 mm and 5-10 mm) contain data from only three studies.

Meta-Analysis between surgical margin pairs, R0/R1 and >1 mm/<1 mm

Comparing the Overall Survival between subgroups R0 and R1

As shown in Section 5-year Overall Survival, it is valuable to conduct a meta-analysis comparing R1 and R0 to obtain a more accurate p-value. 13 of 53 included studies stratified data by 5-year OS for R1 and R0. Although the number of studies was the same, the number of patients was heterogeneous: 4773 in R0 and 1260 in R1. There is a significant disparity between the median 5-year OS for R0 and R1 (26.80% vs 55.97%) (Table 4).

As shown in the forest plot (Figure 3A), the random-effects model estimates an RR of 1.48 ($p < 0.01$). SPSS found $\tau^2 = 0.0184$, and $I^2 = 67.5\%$, suggesting moderate heterogeneity amongst studies; the 95% PI ranged from 1.06 to 1.99. The funnel plot does not suggest publication bias (Figure 3B). The Egger's test does not support the presence of funnel plot asymmetry (intercept: 1.04, 95% CI:-1.14 - 3.22, t: 0.934, p-value: 0.37).

Table 4. Comparison of the 5-year Disease-free survival (DFS) and 5-year Overall Survival (OS) between surgical margin pairs (R1, R0) and (>1 mm, <1 mm).

		R1	R0	<1 mm	>1 mm
5-year Overall Survival (%)	No. of Studies	13	13	13	13
	No. of Patients	1260	4773	1935	4732
	Min(%)	0.00	33.80	0.00	38.00
	Median (%)	26.80	55.00	38.20	52.00
	Max (%)	49.30	68.00	58.30	75.70
5-year Disease-Free Survival (%)	No. of Studies	9	9	8	8
	No. of Patients	1063	5025	692	2729
	Min (%)	0.00	22.00	3.50	24.50
	Median (%)	17.05	35.50	17.85	32.35
	Max (%)	28.90	58.80	60.00	37.50

Comparing the Disease-Free Survival between subgroups R0 and R1

9 Studies out of 53 contained data stratified by 5-year DFS, with 5-year DFS reported for both R1 and R0. Although the number of studies was the same, the number of patients was heterogeneous: 5025 for R0 and 1063 for R1. There is a significant disparity in the median 5-year OS between the subgroups R0 and R1 (17.05% vs 35.50%) (Tables 4 and 6).

As shown in the forest plot (Figure 4A), the random-effects model estimates an RR of 1.28 ($p < 0.01$). SPSS found $\tau^2 = 0$, and $I^2 = 0\%$, suggesting negligible to no heterogeneity amongst studies; therefore, a 95% PI was not calculated. The funnel plot does not suggest publication bias (Figure 4B). The Egger's test does not support the presence of funnel plot asymmetry (intercept: 0.86, 95% CI:-0.28 - 2, t: 1.479, p-value: 0.183).

Comparing the Overall Survival between surgical margin subgroups >1 mm and <1 mm

13 of 53 studies included data stratified by 5-year OS for the surgical margin subgroups >1 mm and <1 mm. Although the number of studies was the same, the number of patients was heterogeneous: 4732 in the R0 subgroup and 1935 in the <1 mm subgroup. There is a significant disparity between the 5-year OS for R0 and R1, as reflected in both the mean (14.23%) and the median (18.20%) (Tables 4 and 7).

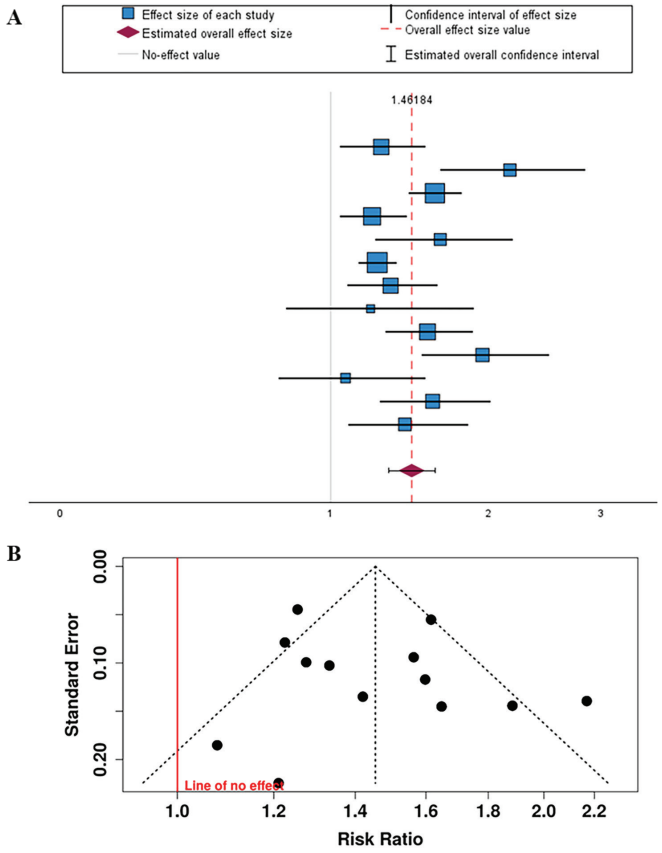

Figure 3. ***Meta-analysis of 5-year overall survival (OS) comparing surgical margin subgroups R1 versus R0.*** *(A) Forest plot showing risk ratios (RRs) and 95% confidence intervals (CIs) for individual studies and the pooled effect estimate using a random-effects model. The overall RR is indicated by the red dashed line, and the x-axis is plotted on a logarithmic scale. (B) Funnel plot assessing potential publication bias among studies evaluating OS between R1 and R0 subgroups. Each dot represents an individual study, with RR = 1.0 corresponding to the null line.*

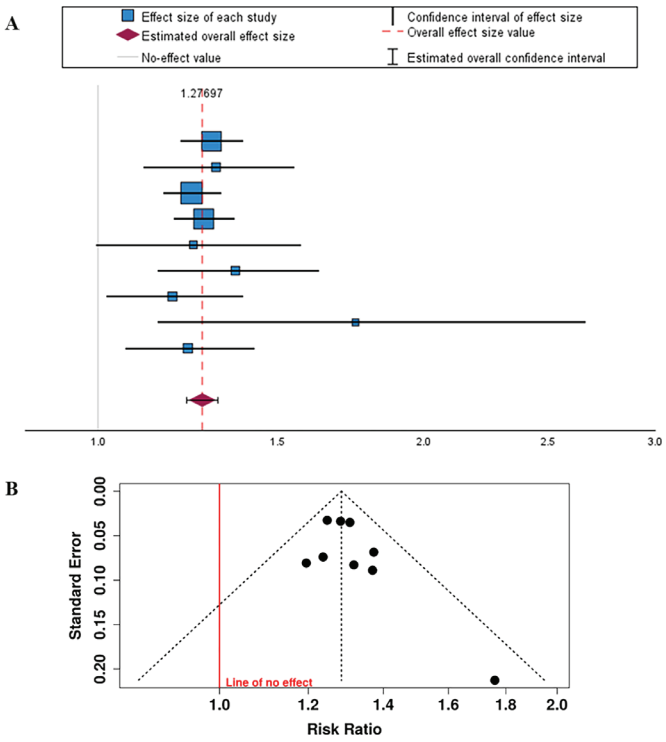

Figure 4. ***Meta-analysis of 5-year disease-free survival (DFS) comparing surgical margin subgroups R1 versus R0.*** *(A) Forest plot showing risk ratios (RRs) and 95% confidence intervals (CIs) for individual studies and the pooled effect estimate using a random-effects model. The overall RR is indicated by the red dashed line, and the x-axis is plotted on a logarithmic scale. (B) Funnel plot assessing potential publication bias among studies evaluating DFS between R1 and R0 subgroups. Each dot represents an individual study, with RR = 1.0 corresponding to the null line.*

As shown in the forest plot (Figure 5A), the random-effects model estimates an RR of 1.36 ($p < 0.01$). SPSS found $\tau^2 = 0.0056$, and $I^2 = 41.5\%$, suggesting moderate heterogeneity amongst studies; the 95% PI ranged from 1.14 to 1.64. The funnel plot does not suggest publication bias (Figure 5B). The Egger's test does not support the presence of funnel plot asymmetry (intercept: -1.17, 95% CI:-2.58 - 0.24, t: -1.62, p-value: 0.134).

Table 5. A table listing the RR, p-value, and weights for all studies included in the meta-analysis, showing the correlation between the subgroups R1/R0 and OS.

Authors	RR	Lower Range	Upper Range	P-value	Weight (%)
She *et al*. (9)	1.28	1.05	1.55	0.01	8.49
Oshi *et al*. (10)	2.17	1.65	2.85	0.00	6.50
Sakamoto *et al*. (11)	1.61	1.45	1.80	0.00	10.93
Mao *et al*. (12)	1.22	1.05	1.43	0.01	9.64
Lemke *et al*. (13)	1.65	1.24	2.19	0.00	6.25
Pandanaboyana *et al*. (14)	1.25	1.15	1.37	0.00	11.43
Margonis *et al*. (15)	1.33	1.09	1.63	0.01	8.30
Serrablo *et al*. (16)	1.22	0.78	1.88	0.38	3.67
Nuzzo *et al*. (17)	1.56	1.30	1.88	0.00	8.79
Chavez *et al*. (18)	1.95	1.42	2.50	0.00	7.08
Ardito *et al*. (19)	1.08	0.75	1.55	0.69	4.71
Lee *et al*. (20)	1.60	1.27	2.01	0.00	7.51
Brudvik *et al*. (21)	1.42	1.09	1.85	0.01	6.71
Overall	**1.46**	**1.32**	**1.62**	**0.00**	**100**

Table 6. A table that includes the RR, p-value, and weights of all studies included in the meta-analysis, showing the correlation between the surgical margin subgroups R1/R0 and DFS.

Authors	RR	Lower Range	Upper Range	P-value	Weight (%)
Perrin *et al*. (22)	1.30	1.22	1.40	0.00	24.71
Oshi *et al*. (10)	1.32	1.12	1.55	0.00	4.35
Sakamoto *et al*. (11)	1.25	1.17	1.33	0.00	28.18
Pandanaboyana *et al*. (14)	1.28	1.20	1.37	0.00	25.38
Serrablo *et al*. (16)	1.25	1.20	1.57	0.05	2.28
Nuzzo *et al*. (17)	1.37	1.15	1.63	0.00	3.98
Chavez *et al*. (18)	1.19	1.02	1.40	0.03	4.85
Ardito *et al*. (19)	1.76	1.16	2.67	0.01	0.68
Brudvik *et al*. (21)	1.24	1.07	1.43	0.00	5.59
Overall	**1.28**	**1.23**	**1.32**	**0.00**	**100**

Comparing the Disease-Free Survival between surgical margin subgroups >1 mm and <1 mm

8 of 53 studies included data stratified by 5-year DFS into surgical margin subgroups: >1 mm and <1 mm. Although the number of studies was the same, the number of patients was heterogeneous: 2729 in the R0 subgroup and 692 in the <1 mm subgroup. There is a significant disparity in 5-year DFS between the surgical margin subgroups (>1 mm and <1 mm), with the median difference being 14.50% (Tables 4 and 8).

As shown in the forest plot (Figure 6A), the random-effects model estimates an RR of 1.21 ($p < 0.01$). SPSS found $\tau^2 = 0$, and $I^2 = 0\%$, suggesting no measured heterogeneity amongst studies; therefore, a 95% PI was not calculated. The funnel plot does not suggest publication bias (Figure 6B). The Egger's test does not support the presence of funnel plot asymmetry (intercept: -0.15, 95% CI:-1.7 - 1.4, t: -0.191, p-value: 0.855).

Table 7. A table that includes the RR, p-value, and weights of all studies included in the meta-analysis, showing the correlation between the surgical margin subgroups 1mm/<1mm and OS.

Authors	RR	Lower Range	Upper Range	P-value	Weight (%)
Takamoto *et al*. (23)	1.29	1.02	1.62	0.03	6.54
Kim *et al*. (24)	1.72	1.12	2.65	0.01	2.46
Iwaki *et al*. (25)	1.22	0.77	1.93	0.40	2.20
Ai *et al*. (26)	1.06	0.83	1.36	0.64	5.99
Wang *et al*. (27)	1.53	1.35	1.73	0.00	12.50
Mils *et al*. (28)	1.40	1.28	1.53	0.00	15.58
Sasaki *et al*. (29)	1.41	1.21	1.64	0.00	10.72
Martínez-Cecilia *et al*. (30)	1.25	1.09	1.42	0.00	12.20
Xu *et al*. (31)	1.30	1.01	1.69	0.04	5.69
Tranchart *et al*. (32)	1.12	0.85	1.47	0.43	5.19
Montalti *et al*. (33)	1.10	0.57	2.11	0.78	1.15
Pourfaraji *et al*. (34)	1.60	1.43	1.79	0.00	13.51
Sasaki *et al*. (35)	1.34	1.05	1.70	0.02	6.28
Overall	**1.36**	**1.27**	**1.47**	**0.00**	**100**

Table 8. The individual studies included in the meta-analysis for the correlation between >1mm/<1mm and DFS

Authors	RR	Lower Range	Upper Range	P-value	Weight (%)
Takamoto *et al*. (23)	1.27	1.15	1.40	0.00	19.12
Kim *et al*. (24)	1.06	0.85	1.33	0.59	3.72
Ai *et al*. (26)	1.18	1.01	1.38	0.03	8.16
Wang *et al*. (27)	1.15	1.05	1.26	0.00	22.29
Martínez-Cecilia *et al*. (30)	1.21	1.12	1.32	0.00	26.57
Xu *et al*. (31)	1.22	1.07	1.38	0.00	11.84
Tranchart *et al*. (32)	1.21	1.01	1.47	0.04	5.33
Montalti *et al*. (33)	1.32	1.02	1.71	0.04	2.87
Overall	**1.21**	**1.15**	**1.26**	**0.00**	**100**

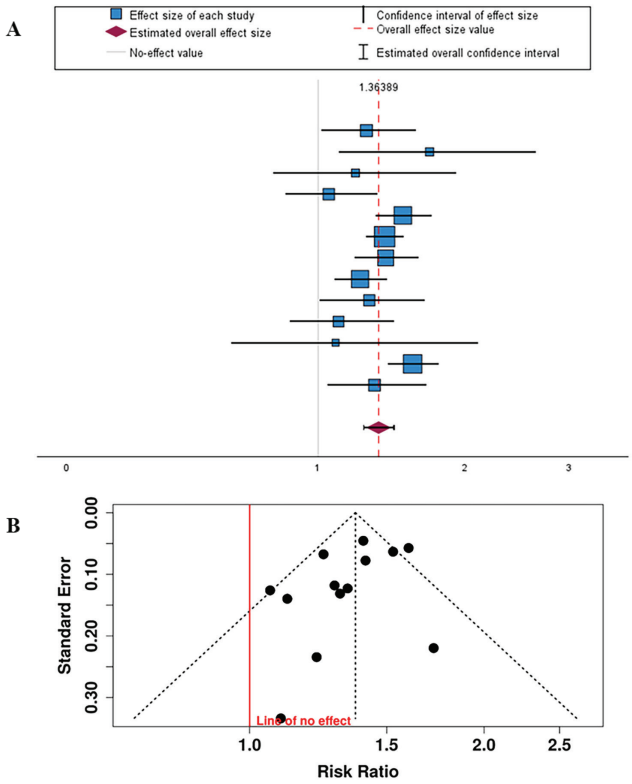

Figure 5. ***Meta-analysis of 5-year overall survival (OS) comparing surgical margin subgroups <1 mm versus >1 mm.*** *(A) Forest plot showing risk ratios (RRs) and 95% confidence intervals (CIs) for individual studies and the pooled effect estimate using a random-effects model. The overall RR is indicated by the red dashed line, and the x-axis is plotted on a logarithmic scale. (B) Funnel plot assessing potential publication bias among studies evaluating OS between <1 mm and >1 mm subgroups. Each dot represents an individual study, with RR = 1.0 corresponding to the null line.*

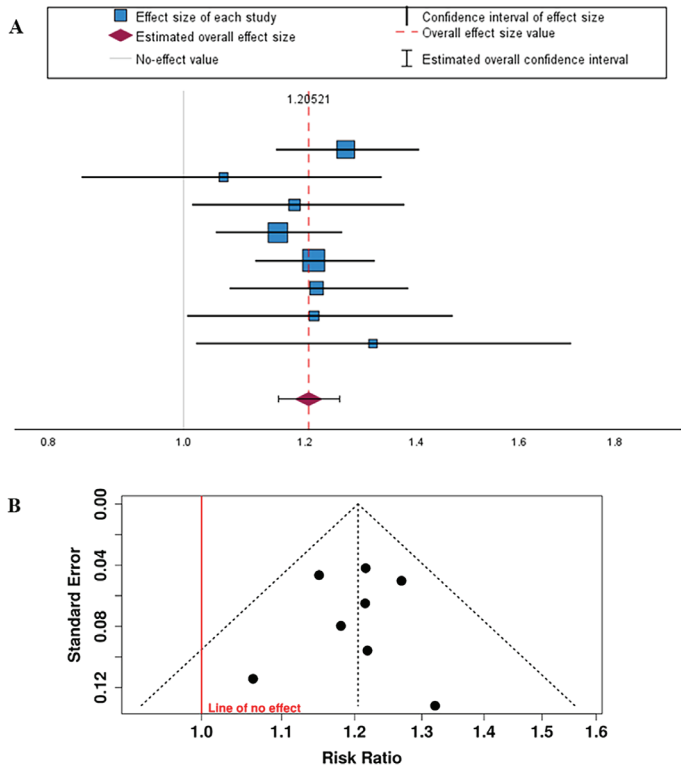

Figure 6. ***Meta-analysis of 5-year disease-free survival (DFS) comparing surgical margin subgroups <1 mm versus >1 mm.*** *(A) Forest plot showing risk ratios (RRs) and 95% confidence intervals (CIs) for individual studies and the pooled effect estimate using a random-effects model. The overall RR is indicated by the red dashed line, and the x-axis is plotted on a logarithmic scale. (B) Funnel plot assessing potential publication bias among studies evaluating DFS between <1 mm and >1 mm subgroups. Each dot represents an individual study, with RR = 1.0 corresponding to the null line.*

DISCUSSION

Interpretations of Sub-Group Analysis

To initially explore the relationship between surgical margin and OS and DFS, Kruskal-Wallis tests were used. The ranges used for our surgical margins were not all the same size, for instance, >1 and 1<x<5. Considering this, the data suggest that although increasing the surgical margin improves survival, there may be diminishing marginal gains in survival as the surgical margins increase. This is shown in the Kruskal-Wallis tests, which reveal no statistically significant differences across ranges above 1mm, suggesting a potential threshold at which a surgical margin increase is no longer beneficial. However, it is important to note that the Kruskal-Wallis test is nonparametric and has numerous limitations, including low statistical power, a high false-negative rate, and the inability to weight sample sizes.

Interpretations of the Meta-analyses

Meta-analysis is an appropriate statistical tool for analysing effects and providing a more weighted, confirmatory estimate of effect size. The Kruskal-Wallis tests identified significant pairs with <1 and R1; therefore, meta-analyses were conducted comparing R1/R0 and >1/<1 for each dependent variable (OS and

DFS). They suggested that positive margins (R1) were associated with poorer outcomes than negative margins (R0), and margins <1mm were associated with poorer outcomes than margins >1mm.

Furthermore, the effect size was greater for R1/R0 than for >1/<1, indicating the critical role of negative margins in improving survival. It also develops the exploratory idea from the Kruskal-Wallis test: diminishing marginal gains in survival as surgical margins increase.

Lastly, the effect size was greater in OS than in DFS, which is quite unusual, as DFS is thought to have a stronger relationship with the surgical margin. (36) A smaller margin would directly impact the incidence of microscopic residual traces of cancer in the liver, whereas the effect is not as direct for the OS. However, our findings align with existing meta-analyses such as those by Sakamoto *et al*. (4) and Margonis *et al*. (37).

Interpretations of Heterogeneity

A potential explanation for the result could be heterogeneity. As outlined in the methods section, it is a crucial factor to consider and may change how we view the effect size. Although all meta-analyses reached statistical significance, heterogeneity was greater for OS than for DFS. In fact, the meta-analyses for OS had what's classified as mild to high heterogeneity, whereas the meta-analyses for DFS had no measured heterogeneity. Therefore, the higher effect size for OS observed in the meta-analysis was inconsistent across studies, and further research is needed to determine whether the change in surgical margin has a greater effect on OS or DFS.

Despite this, the heterogeneity in the OS meta-analysis was not substantial enough to make the 95% PIs encompass both sides of the null; therefore, we can estimate that 0% of studies will favour R1 over R0, or favour <1mm over >1mm for both DFS and OS. According to Borenstein (2023), an effect size of 1.2-1.5 is considered moderate, with large effects for values of 1.5 or higher (8). Therefore, our results support the conclusion that margins >1mm will yield a moderately better survival; however, this systematic review and meta-analysis are strongly limited, as described in the next section.

Limitations

Confounding Variables

While most clinical studies included data on surgical margins, they also reported other significant confounding variables that affect OS and DFS. KRAS status may affect R1 and R0, but more clinical trials are needed to investigate this effect in a meta-analysis. One clinical study that examines both variables was conducted by Hatta *et al*. (38) and demonstrates that the resection margin has a greater effect on patients without KRAS mutations than on those with KRAS mutations.

All in all, the standard confounding variables were: Chemotherapy (9, 10, 15, 27, 32), KRAS mutation (11, 15, 25, 29, 31, 35, 38, 39, 40), tumour burden (10, 12, 41), type of resection (laparoscopic vs open) (30, 42), synchronous vs metachronous (32, 43), Pushing growth pattern (44, 45), BRAF mutation (46, 47), and intra-operative transfusion (28, 48)

Number of Studies

This systematic review was based on 53 clinical trials that provided survival data stratified by surgical margin. Studies varied in terms of patient size and the surgical margins analysed (Table 1). Furthermore, some studies were retrospective, sample sizes varied, and only a limited number provided patient counts stratified by both the confounding variable and the margin. For example, nearly all studies provided the number of males and females participating in the entire study, but only a limited number provided those demographics stratified by surgical margin. Therefore, although we were able to collect the total numbers of males and females across the entire meta-analysis, we were unable to remove their interference from the results.

Publication Bias

All the Egger's tests across the meta-analyses found p-values larger than 0.05. Consequently, they do not support funnel plot asymmetry, and the funnel plot does not suggest publication bias. However, Egger's test is known to be inaccurate with small sample sizes (n<10), resulting in a high false-positive rate and leading to misidentification of bias. Therefore, although Egger's test suggests no publication bias, we cannot be certain of its accuracy given the limited number of studies. (49)

Margin definitions

For simplicity, we had operationalised R1 as 0mm and R0 as >0mm, as it is the general definition in pathology for almost all cancers. However, some clinical studies define R1/R0 as <1mm/>1mm, especially in the literature about CRLM. Due to this variation, the definition may have been ambiguous in some cases, potentially leading to increased heterogeneity.

Future scope and recommendations

To deliver a more accurate analysis, we should control for all the confounding variables mentioned previously. We can do this by limiting the search to propensity-matched studies or randomised controlled trials, if sufficient studies are available, thereby reducing the number of confounding variables. We should then conduct a meta-regression, which would require more studies that stratify patients by both the confounding variable and the margin.

CONCLUSION

This systematic review suggests that surgical margin status is associated with survival outcomes in patients with CRLM. Meta-analyses and Kruskal–Wallis tests indicate a potential survival advantage for patients achieving an R0 resection with a minimum margin of 1 mm. The presence of 95% prediction intervals across all meta-analyses suggests that, with high confidence, individual studies tend to favor larger resection margins.

However, the evidentiary strength of these findings is limited by substantial heterogeneity, residual confounding, variability in margin definitions, potential publication bias, and the relatively small number of eligible studies. Consequently, these results should be interpreted as observational rather than as definitive clinical guidance regarding the optimal surgical margin width for maximizing survival in CRLM.

Future research should aim to better control for confounding variables by prioritizing propensity-matched studies or randomized controlled trials, where available. As additional stratified data become available, meta-regression analyses incorporating both margin width and key confounders will be essential to refine effect estimates and improve causal inference. Such efforts will help clarify whether a true margin-dependent survival benefit exists and guide evidence-based surgical decision-making.

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CONFLICT OF INTEREST

The author declares that there is no conflicts of interest related to this work.

REFERENCES

1. World Health Organisation (2023). Colorectal Cancer. (online) World Health Organisation. Available from: https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer (accessed on 2025-3-25)
2. Martin J, *et al*. Colorectal liver metastases: Current management and future perspectives. *World J Clin Oncol*. 2020; 11 (10): 761-808. https://doi.org/10.5306/wjco.v11.i10.761
3. Todeschini L, *et al*. ablation versus surgical resection in colorectal liver metastasis: insight from an umbrella review. *Front Oncol*. 2025; 4 (15): 1494996. https://doi.org/10.3389/fonc.2025.1494996
4. Sakamoto K, *et al*. Prognostic impact of surgical margin width in hepatectomy for colorectal liver metastasis. *J Clin Transl Hepatol*. 2023; 11 (3): 705-717
5. Lydersen S. Adjustment of p-values for multiple hypotheses: why, when and how. *Annals of the Rheumatic Diseases.* 2024; 83 (10): 1254-1255. https://doi.org/10.1136/ard-2024-225537
6. Dettori JR, *et al*. Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. *Global Spine Journal*. 2022; 12 (7): 1624-1626. https://doi.org/10.1177/21925682221110527
7. Borenstein M. How to understand and report heterogeneity in a meta-analysis: The difference between I2 and prediction intervals. *Integrative Medicine Research.* 2023; 12 (4). https://doi.org/10.1016/j.imr.2023.101014
8. Fekete JT, *et al*. MetaAnalysisOnline.com: an Online Tool for the Rapid Meta-Analysis of Clinical and Epidemiological Studies. *J Med Internet Res*. 2025; 6 (27): e64016. https://doi.org/10.2196/64016
9. She WH, *et al*. Relevance of chemotherapy and margin status in colorectal liver metastasis. *Langenbeck's Arch Surg.* 2021; 406 (8): 2725-2737. https://doi.org/10.1007/s00423-021-02205-w
10. Oshi M, *et al*. Higher tumour burden neutralises negative margin status in hepatectomy for colorectal cancer liver metastasis. *Ann Surg Oncol*. 2019; 26 (2): 593-603. https://doi.org/10.1245/s10434-018-6830-x
11. Sakamoto K, *et al*. Comprehensive data of 4502 patients newly diagnosed with colorectal liver metastasis between 2015 and 2017, and prognostic data of 2427 patients newly diagnosed between 2013 and 2014: third report of a nationwide survey in Japan. *J*

Hepatobiliary Pancreat Sci. 2023; 30 (5): 570-590. https://doi.org/10.1002/jhbp.1252
12. Mao R, *et al*. Interaction of margin status and tumour burden determines survival after resection of colorectal liver metastases: a retrospective cohort study. *Int J Surg*. 2018; 53: 371-777. https://doi.org/10.1016/j.ijsu.2017.12.001
13. Lemke J, *et al*. Survival and prognostic factors of colorectal liver metastases after surgical and nonsurgical treatment. *Clin Colorectal Cancer*. 2016; 15 (4): e183-192. https://doi.org/10.1016/j.clcc.2016.04.007
14. Pandanaboyana S, *et al*. Impact of margin status and neoadjuvant chemotherapy on survival and recurrence after liver resection for colorectal liver metastasis. *Ann Surg Oncol*. 2015; 22 (1): 173-179. https://doi.org/10.1245/s10434-014-3953-6
15. Margonis GA, *et al*. Tumor biology rather than surgical technique dictates prognosis in colorectal cancer liver metastases. *J Gastrointest Surg*. 2016; 20 (11): 1821-1829. https://doi.org/10.1007/s11605-016-3198-8
16. Serrablo A, *et al*. Impact of novel histopathological factors on the outcomes of liver surgery for colorectal cancer metastases. *Eur J Surg Oncol*. 2016; 42 (9): 1268-1277. https://doi.org/10.1016/j.ejso.2016.02.013
17. Nuzzo G, *et al*. Influence of surgical margin on recurrence pattern after liver resection for colorectal metastases: a single-center experience. *Surgery*. 2008; 143 (3): 384-393. https://doi.org/10.1016/j.surg.2007.09.038
18. Chavez MI, *et al*. Two-stage hepatectomy for bilateral colorectal liver metastases: a multi-institutional analysis. *Ann Surg Oncol*. 2021; 28 (3): 1457-1465. https://doi.org/10.1245/s10434-020-09459-6
19. Ardito F, *et al*. Giuliante F. Right and extended-right hepatectomies for unilobar colorectal metastases: impact of portal vein embolisation on long-term outcome and liver recurrence.
20. Lee KS, *et al*. Microscopic resection margins adversely influence survival after surgery for colorectal liver metastases: an open ambidirectional cohort study. *Int J Surg*. 2020; 83: 8-14. https://doi.org/10.1016/j.ijsu.2020.09.007
21. Brudvik KW, *et al*. Aggressive treatment of patients with metastatic colorectal cancer increases survival: a Scandinavian single-center experience. *HPB Surg*. 2013; 2013: 727095. https://doi.org/10.1155/2013/727095
22. Perrin T, *et al*. The Association Between Surgical Margin Status, Recurrence Patterns, and Oncologic Outcomes in Patients with Colorectal Liver Metastases. *Annals of Surgery*. 2025. https://doi.org/10.1097/SLA.0000000000006659
23. 23. Takamoto T., *et al*., Two-dimensional assessment of submillimeter cancer-free margin area in colo-rectal liver metastases. *Medicine (Baltimore)*. 2016; 95 (27): e4080. https://doi.org/10.1097/MD.0000000000004080
24. Kim NR, *et al*. Prognostic impact of R1 resection margin in synchronous and simultaneous colorectal liver metastasis resection: a retrospective cohort study. *World J Surg Oncol*. 2023; 21 (1): 169. https://doi.org/10.1186/s12957-023-03042-5
25. Iwaki K, *et al*. The impact of KRAS status on required surgical margin width for colorectal liver metastasis resection. *J Clin Med*. 2023; 12 (6): 2313. https://doi.org/10.3390/jcm12062313
26. Ai XN, *et al*. Analysis of survival factors after hepatic resection for colorectal cancer liver metastases: does the R1 margin matter? *Front Surg*. 2022; 9: 1020240. https://doi.org/10.3389/fsurg.2022.1020240
27. Wang HW, *et al*. Prognostic impact of resection margin status varies by GAME score for colorectal liver metastases. *J Surg Oncol*. 2021; 124 (4): 619-626. https://doi.org/10.1002/jso.26557
28. Mils K, *et al*. Improvement of postoperative and long-term outcomes over 3 decades: 1736 hepatectomies for colorectal liver metastasis. *Cir Esp*. 2024; 102 (5): 243-251. https://doi.org/10.1016/j.ciresp.2023.11.012
29. Sasaki K, *et al*. Prognostic impact of margin status after bevacizumab in colorectal liver metastasis resection. *Br J Surg*. 2017; 104 (7): 926-935. https://doi.org/10.1002/bjs.10510
30. Martínez-Cecilia D, *et al*. Impact of resection margins in laparoscopic vs open liver resection: a propensity-score analysis. *Surg Endosc*. 2021; 35 (2): 809-818. https://doi.org/10.1007/s00464-020-07452-4
31. Xu D, *et al*. Sub-millimeter surgical margin is acceptable in patients with good tumor biology after liver resection for colorectal liver metastases. Eur *J Surg Oncol*. 2019; 45 (9): 1551-1558. https://doi.org/10.1016/j.ejso.2019.03.010
32. Tranchart H, *et al*. Prognostic impact of positive surgical margins in the era of modern chemotherapy. *World J Surg*. 2013; 37 (11): 2647-2654. https://doi.org/10.1007/s00268-013-2186-3
33. Montalti R, *et al*. Impact of surgical margins on survival in parenchymal-sparing laparoscopic liver resections for colorectal metastases. *Surg Endosc*. 2015; 29 (9): 2736-2747. https://doi.org/10.1007/s00464-014-3999-3
34. Pourfaraji SM, *et al*. Long-term survival after hepatic resection for colorectal liver metastases: a single-center study in Iran. *BMC Surg*. 2024; 24 (1): 131. https://doi.org/10.1186/s12893-024-02420-4
35. Sasaki K, *et al*. Prognostic impact of determining resection margin status for multiple colorectal

metastases based on the largest lesion. *Ann Surg Oncol.* 2017; 24 (9): 2438-2446. https://doi.org/10.1245/s10434-017-5904-5

36. Konstantinou A, *et al*. A positive resection margin does not determine long-term survival following colorectal liver metastasis resection. *Annals of Hepato-Biliary-Pancreatic Surgery*. 2025; 29 (3): 252-268. https://doi.org/10.14701/ahbps.24-233
37. Margonis GA, *et al*. Impact of Surgical Margin Width on Recurrence and Overall Survival Following R0 Hepatic Resection of Colorectal Metastases: A Systematic Review and Meta-analysis. *Annals of Surgery.* 2018; 267 (6): 1047-1055. https://doi.org/10.1097/SLA.0000000000002552
38. Hatta AAZ, *et al*. Effects of resection margin and KRAS status on outcomes after resection of colorectal liver metastases. *HPB.* 2021; 23 (1): 90-98. https://doi.org/10.1016/j.hpb.2020.04.016
39. Ausania F, *et al*. Impact of microscopic incomplete resection on margin recurrence: R1-contact vs R1 < 1 mm. *J Hepatobiliary Pancreat Sci.* 2022; 29 (4): 449-459. https://doi.org/10.1002/jhbp.1107
40. Sakai N, *et al*. Differential effects of KRAS status by timing of colorectal liver metastases. *BMC Cancer*. 2021; 21 (1): 412. https://doi.org/10.1186/s12885-021-08144-5
41. Gomez D, *et al*. Morris-Stiff G, Wyatt J, Toogood GJ, Lodge JP, Prasad KR. Surgical technique and systemic inflammation influence long-term disease-free survival after hepatic resection. *J Surg Oncol*. 2008; 98 (5): 371-376. https://doi.org/10.1002/jso.21103
42. Tabchouri N, *et al*. Recurrence patterns after laparoscopic resection of colorectal liver metastases. *Surg Endosc*. 2018; 32 (12): 4788-4797. https://doi.org/10.1007/s00464-018-6229-6
43. Pagani M, *et al*. Hepatic resection for colorectal liver metastases: outcomes and prognostic factors-single-center experience. *J Clin Med*. 2023; 12 (6): 2170. https://doi.org/10.3390/jcm12062170
44. Jayme VR, *et al*. Infiltrative tumor borders in colorectal liver metastasis: should we enlarge margin size? *Ann Surg Oncol.* 2021; 28 (12): 7636-7646. https://doi.org/10.1245/s10434-021-09916-w
45. Falcão D, *et al*. Histopathologic patterns as prognostic markers after hepatectomy for colorectal liver metastases: pushing growth as an independent risk factor. *Eur J Surg Oncol.* 2018; 44 (8): 1212-1219. https://doi.org/10.1016/j.ejso.2018.03.023
46. Buisman FE, *et al*. Predicting 10-year survival after resection of colorectal liver metastases: an international biomarker-based study. *Eur J Cancer*. 2022; 168: 25-33. https://doi.org/10.1016/j.ejca.2022.01.012
47. Kobayashi S, *et al*. Survival outcomes of resected BRAF V600E mutant colorectal liver metastases: multicenter retrospective cohort. *Ann Surg Oncol*. 2020; 27 (9): 3307-3315. https://doi.org/10.1245/s10434-020-08817-8
48. Gomez D, *et al*. Interaction of tumour biology and tumour burden in hepatic resection outcomes for colorectal metastases. *HPB*. 2010; 12 (2): 84-93. https://doi.org/10.1111/j.1477-2574.2009.00127.x
49. Shi L, *et al*. A Bayesian approach to assessing small-study effects in meta-analysis of a binary outcome with controlled false positive rate. *Research synthesis methods.* 2020; 11 (4): 535-552. https://doi.org/10.1002/jrsm.1415