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Review Article

Prognostic Impact of Surgical Margin Width in Hepatectomy for Colorectal Liver Metastasis

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Abstract

As for resection for colorectal liver metastasis (CRLM), securing an adequate surgical margin is important for achieving a better prognosis. However, it is often difficult to achieve adequate margins for the resection of CRLM. So the current survival impact of sub-centi/millimeter surgical margins in hepatectomy for CRLM should be evaluated. In the current era of multidisciplinary treatment options, this review focused on the prognostic impact of a sub-centi/millimeter surgical margin width in hepatectomy for CRLM. We systematically reviewed retrospective studies that clearly described the surgical margin width for hepatectomy for CRLM. We selected studies conducted since 2000 that involved patients diagnosed as having CRLM. We focused on studies that investigated not only surgical margins, but also microscopic surgical curability such as R0 (microscopically complete resection) or R1 (microscopically incomplete resection), which clearly describe their definitions. Based on our literature review, 1, 2, or 5 mm was considered the minimum surgical margin width for hepatectomy for CRLM. Although a surgical margin width of 1 mm is acceptable for hepatectomy for CRLM, submillimeter margins, which are defined as R1 in many reports, are only acceptable for limited patients such as those who have undergone preoperative chemotherapy. Zero-mm margins are also acceptable in limited patients such as those who show a good response to preoperative chemotherapy. New chemotherapy agents have been reported to reduce the prognostic impact of a narrow surgical margin width. The incidence of margin recurrence, which is a major concern regarding R1 resection of CRLM, is about 20–30% according to the majority of earlier reports. As evaluations of the actual prognostic impact of the surgical margin remain difficult, further study is warranted.

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Introduction

The liver is the most frequent metastatic site in colorectal cancer.[1] Colorectal liver metastasis (CRLM) occurs in about 50% of patients with colorectal cancer.[1] Five-year overall survival rates among all patients with CRLM and those who undergo hepatectomy are 36.3% and 57.1%, respectively, according to nationwide reports in Japan.[2] As for resection for CRLM, securing a proper surgical margin is important for achieving a better prognosis.[3–6] For better survival outcomes in hepatectomy for CRLM, margins >10 mm have been recommended.[3–6] However, it is often difficult to achieve margins >10 mm in patients with multiple bilobar CRLM or whose tumor is adjacent to major vessels.[3] Recent advances in surgical procedures and perioperative chemotherapies have led to an increase in the number of patients indicated for potentially curative resection, even for multiple bilobar CRLM.[7,8] Regarding surgical procedures, two-stage hepatectomy including associating liver partition and portal vein ligation for staged hepatectomy, major vascular resection and reconstruction, combined local ablation therapy, and parenchymal-sparing hepatectomy (PSH) are reportedly useful options to treat multiple bilobar CRLM.[1,7–13] Furthermore, more precise evaluation of hepatic function reserve, portal vein embolization, and conversion chemotherapy, including molecular targeted agents, are considered useful perioperative management strategies for multiple bilobar CRLM. However, for these multidisciplinary treatments, the surgical margin for multiple bilobar CRLM is too narrow to preserve remnant liver volume. In addition, to preserve hepatic function reserve and enable re-hepatectomy for intrahepatic recurrences, PSH is reportedly a useful surgical option with comparable prognostic outcomes and fewer postoperative complications compared with major hepatectomy (MH).[10–13] However, unlike MH, PSH can reduce the surgical margin width to preserve liver parenchyma or major vessels. Therefore, reports of the usefulness of sub-centi/millimeter surgical margins have been increasing.[3] A sub-centi/millimeter surgical margin can provide a better prognosis than if the patient does not undergo resection, and is considered an acceptable treatment strategy, especially for patients undergo-

Keywords: Surgical margin; Colorectal liver metastasis; Chemotherapy.
Abbreviations: CEA, carcinoembryonic antigen; CRLM, colorectal liver metastasis; DFS, disease-free survival; MH, major hepatectomy; OS, overall survival; PSH, parenchymal-sparing hepatectomy; RFS, recurrence-free survival.
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ing perioperative chemotherapy for multiple CRLM.[3] In addition, R1 resection may be possible for patients who undergo hepatectomy after showing a good response to preoperative chemotherapy.[14] Therefore, the current survival impact of sub-centi/millimeter margin surgical margins in hepatectomy for CRLM should be evaluated. In the current era of multidisciplinary treatment options, this review focused on the prognostic impact of a sub-centi/millimeter surgical margin width in hepatectomy for CRLM.

Literature search

As it is difficult to determine the surgical margins for hepatectomy for tumor resection preoperatively, to our knowledge, no randomized controlled trials regarding the surgical margin width for CRLM have been conducted. So we systematically reviewed retrospective studies that clearly described the surgical margin width for hepatectomy for CRLM. We selected studies conducted since 2000 that involved patients diagnosed as having CRLM. We focused on studies that investigated not only surgical margins, but also microscopic surgical curability such as R0 (microscopically complete resected) or R1 (microscopically incomplete resected), which clearly describe their definitions. The definition of R0/1 was varied among studies, and surgical margin widths of <1 mm[14–29] and 0 mm[1,30–34] were both defined as R1. We conducted a meta-analysis using RevMan software (version 5.4.1; Cochrane Collaboration, Oxford, UK). Dichotomous outcomes were shown by risk difference and 95% confidence intervals. Heterogeneity among the included trials was evaluated by a forest plot. The I-squared and chi-squared statistics were used to evaluate statistical heterogeneity. When $I^2<50\%$ or $p>0.1$ in the chi-squared test, indicating significant heterogeneity, a fixed-effects model was adopted. Otherwise, a random-effects model was used.

Subcentimeter surgical margins

We reviewed previous studies that evaluated subcentimeter surgical margins (Table 1).[11,15,18,21,22,25,31,32,35-39] The majority of earlier reports that evaluated the feasibility of subcentimeter surgical margins were published before 2014. Angelsen *et al*.[15] and Nuzzo *et al*.[31] reported that compared with >5 mm, a surgical margin of <5 mm increased the margin/local recurrence rate and reduced the time to recurrence. Kokudo *et al*.[35] investigated micrometastases classified into groups based on the distance from the tumor (<2 mm, 2–4 mm, 5–9 mm, and ≥10 mm), and found that 2 mm was the minimum acceptable surgical margin width because micrometastases were rare beyond 2 mm. Konopke *et al*.[36] reported that surgical margin widths of 0 mm or 1–2 mm were associated with poor recurrence-free survival (RFS) compared with those of 3–5 mm and 6–9 mm, but no significant difference in overall survival (OS) was seen. According to Pawlik *et al*.,[18] no significant differences in OS were found among 1–4, 5–9, and ≥10 mm, all of which had better prognosis than <1 mm. In addition, several reports suggested that 1 mm was the minimum acceptable surgical margin width to achieve better survival, and that other factors such as tumor biology or features had a stronger impact on survival.[21,22,37,38] Hamady *et al*.[38] reported no significant difference in recurrence rates between subcentimeter and ≥10-mm margins based on propensity-matched analyses. Several papers concluded that hepatectomy for CRLM with subcentimeter margins provided a survival benefit.[14,32,37,39,40] Based on our literature review (Table 1), 1, 2, or 5 mm was considered the minimum surgical margin width for hepatectomy for CRLM.

Submillimeter surgical margins

To evaluate the survival impact of submillimeter margins, we reviewed studies that assessed differences in survival at a surgical margin width cutoff point of 1 mm (Table 2).[11,14-20,23-29,32,34,37-39,41–43] In contrast to studies that evaluated subcentimeter margin widths, the majority of the studies evaluating the clinical impact of submillimeter margins were published after 2014, which may imply that subcentimeter margins have recently become an acceptable treatment option.[3]

The number of hepatic lesions was greater and the greatest tumor diameter was larger in the <1 mm than in the ≥1 mm group (Fig. 1A, B), and more aggressive disease was considered to have been included in the <1 mm group. Although the rate of preoperative chemotherapy varied, >70% of the patients in the studies published after 2016 underwent preoperative chemotherapy (Fig. 1C, D). Moreover, de Haas *et al*.[14] reported a significantly higher rate of preoperative chemotherapy in the 0 mm than in the ≥1 mm group.

Both 5-year OS and 5-year RFS were poor in the <1 mm group compared with the ≥1 mm group usually (Fig. 1E, F).[14–17,19–21,23–26,41–42,44] However, neither Bodingbauer *et al*.[25] nor Postriganova *et al*.[39] found any significant differences in OS or disease-free survival (DFS) between the <1 and ≥1 mm groups.[25,39] Furthermore, several reports concluded that even if a surgical margin width <1 mm had a worse prognosis in univariate analyses, it was not an independent prognosticator in multivariate analysis.[15,18,21,25,26] In other words, a narrow surgical margin could result from more aggressive disease, which might have led to worse survival.

As for subgroups with a surgical margin <1 mm, Vigano *et al*.[29] and Procopio *et al*.[41] reported that surgical margins of <1 mm adjacent to major vessels had a better prognosis than those not adjacent to major vessels (<1 mm at parenchyma) and was comparable with that of ≥1 mm surgical margins. Takamoto *et al*.[27] reported that ≤1 mm margins had worse OS than did those >1 mm, but narrow ≤1 mm margins (≤4 cm^2) showed better survival than did broad ≤ mm margins. In addition, Sasaki *et al*.[20] reported that except for the largest tumor, surgical margins <1 mm had a prognosis comparable to that of those with margins ≥1 mm and better than with <1 mm margins in the largest tumor. Other reports found no differences in long-term prognosis among ≥1 and <1 mm margin groups when patients were limited to those who had undergone preoperative chemotherapy with a good response or had *KRAS* wild-type tumors.[16,23,28–30] Based on our literature review, a surgical margin width of 1 mm is acceptable for hepatectomy for CRLM. However, submillimeter margins, which are defined as R1 in many reports, are acceptable only for a limited number of patients such as those who have undergone preoperative chemotherapy.

Zero-mm margins

Zero-mm margins (exposed tumor, involved margin) are associated with poor survival in many cases.[22,31,33,42,45,46] Memeo *et al*.[11] reported that R1 (0 mm) had poor OS compared with R0 (≥1 mm) even after propensity-matched analysis. In the most recent report, Ausania *et al*.[1] reported that 0 mm margins had significantly worse survival, compared with <1 mm margins. However, de Haas *et al*.[14] reported that 0 mm margin resection (R1) had comparable OS/DFS compared with R0 (≥1 mm). Ayez *et al*.[30] also reported that patients who underwent preoperative chemotherapy had comparable survival (OS and DFS) between R0 (>0 mm) and R1 (0 mm). In addition, 0 mm margins, which are defined as R1, in patients with highly advanced bilobar tumor or who had a good

Table 1. Studies evaluating subcentimeter surgical margins

Author	Year of publication	Period	Follow-up period, M	Margin	Summary	Minimum acceptable margin width
Kokudo *et al.*[35]	2002	1980–2000	Median 29.1	<2 mm (*n*=45)	Surgical margin width did not have a negative impact on survival. Cut-end recurrence was rare in margins <2 mm. Micrometastasis was rarely seen within <2 mm around the main tumor.	≥2 mm
				2–4 mm (*n*=36)		
				5–9 mm (*n*=53)		
				≥10 mm (*n*=49)		
Pawlik *et al.*[18]	2005	1990–2004	Median 29	<1 mm (*n*=45)	Positive surgical (<1 mm) margin had a negative impact on survival. However, surgical margin width, if negative, did not affect survival or recurrence.	≥1 mm
				1–4 mm (*n*=129)		
				5–9 mm (*n*=85)		
				≥10 mm (*n*=298)		
Bodingbauer *et al.*[25]	2007	2000–2003	Median 33	<1 mm (*n*=43)	Margin status did not correlate with either OS or DFS.	Positive margin (<1 mm) accepted
				1–9 mm (*n*=110)		
				>9 mm (*n*=23)		
Are *et al.*[32]	2007	1991–2003	Median 42	Involved (*n*=112)	Margin width of >10 mm is optimal, but subcentimeter resection was also associated with favorable outcomes.	>10 mm
				<1 mm (*n*=138)		
				1–5 mm (*n*=261)		
				5–10 mm (*n*=164)		
				>10 mm (*n*=344)		
Konopke *et al.*[36]	2008	10 years	Median 28	0 mm (*n*=29)	Surgical margins of 0 mm and 1–2 mm had a negative impact on RFS and hepatic-RFS, but not OS.	>2 mm
				1–2 mm (*n*=51)		
				3–5 mm (*n*=58)		
				6–9 mm (*n*=48)		
				≥10 (*n*=147)		
Nuzzo *et al.*[31]	2008	1992–2005	Mean 39	0 mm (*n*=9)	Surgical margin width was a strong prognostic factor and surgical margins ≤5 mm worsened surgical margin recurrence, OS, and DFS.	>5 mm

(continued)

Table 1. *(continued)*

Author	Year of publication	Period	Follow-up period, M	Margin	Summary	Minimum acceptable margin width
				≤2 mm (*n*=16)		
				3–5 mm (*n*=29)		
				6–9 mm (*n*=20)		
				≥10 mm (*n*=111)		
Vandeweyer *et al*.[37]	2009	1992–2007	Median 48.7	≤1 mm (*n*=67)	No significant differences in OS were found among subcentimeter margins other than those ≤1 mm. Beneficial effect of margins >1 mm could not be demonstrated.	>1 mm
				>1 <4 mm (*n*=44)		
				≥4 <10 mm (*n*=63)		
				≥10 mm (*n*=87)		
Muratore *et al*.[21]	2010	1999–2007	Median 56.5	<1 mm (*n*=175)	No significant differences in RFS among subcentimeter margins other than those <1 mm. Tumor biology, but not the width of the negative resection margin, affected RFS.	≥1 mm
				1–2 mm (*n*=42)		
				3–5 mm (*n*=81)		
				6–10 mm (*n*=52)		
Lordan *et al*.[22]	2010	1996–2006	NR	<1 mm (*n*=14)	No significant differences in OS among subcentimeter margins other than those <1 mm. Clear margin did not affect survival.	≥1 mm
				1–3 mm (*n*=48)		
				>3 mm, 5 mm < (*n*=17)		
				>5 mm, 10 mm < (*n*=55)		
				≥10 mm (*n*=104)		
Postriganova *et al*.[39]	2014	1998–2012	Median 31	0 mm (*n*=17)	Surgical margins <1 mm had comparable survival compared with those ≥10 mm.	0 mm
				0 mm <1 mm (*n*=16)		
				1 mm <3 mm (*n*=31)		
				3 mm <10 mm (*n*=55)		
				≥10 mm (*n*=36)		
Angelsen *et al*.[15]	2014	1998–2010	NR	<1 mm (*n*=48)	R1 resection was a poor prognostic factor. Resection margins <5 mm increased local recurrence and shortened RFS.	≥5 mm
				1–4 mm (*n*=77)		

(continued)

Table 1. *(continued)*

Author	Year of publication	Period	Follow-up period, M	Margin	Summary	Minimum acceptable margin width
				5–9 mm (n=46)		
				≥10 mm (n=71)		
Hamady *et al*.[38]	2014	1987–2010	Median 33	<1 mm (n=663)	No significant difference in DFS in the ≥1 mm groups. The <1 mm group showed worse DFS than did the others.	≥1 mm
				1–4.9 mm (n=852)		
				5–9.9 mm (n=439)		
				≥10 mm (n=761)		
Memeo *et al*.[11]	2017	2006–2013	NR	0 mm (patient number NR)	R1 had a negative impact on OS, even after propensity score matching.	≥1 mm
				1–5 mm (patient number NR)		
				>5 mm (patient number NR)		

DFS, disease-free survival; NR, not reported; OS, overall survival; RFS, recurrence-free survival.

Table 2. Studies evaluating submillimeter surgical margins

Author	Year of publication	Study period	Follow-up period	Surgical margin width	Patient number	Synchronous, %	Tumor number	Largest tumor size, mm	Pre-CTx, %	Post-CTx, %	5-yearOS, %	*p*-value	5-year DFS, %	*p*-value
Pawlik *et al*.[18]	2005	1990–2004	Median 29	<1 mm	45	42	≥2, 55%	Median, 35	NR	60	17.1	0.005	RR, 51	0.003
				≥1 mm	512						≥62.3		RR, 39.5	
Are *et al*.[32]	2007	1991–2003	Median 42	Involved	112	64.9	≥2, 49.7%	>50, 33.3%	33	NR	26	Ref	NR	NR
				<1 mm	138						29	0.59		
				≥1 mm	769						35–45	0.07–<0.01		
Bodingbauer *et al*.[25]	2007	2000–2003	Median 33	<1 mm	43	58	≥2, 70%	>50, 19%	55–59	90.1	MST 38.9	0.373	MST, 11.2	0.343
				≥1 mm	133	52–56.4	≥2, 53.4%	>50, 21.8%			Not reached		MST, 12.4–15.9	
Welsh *et al*.[24]	2008	1987–2005	Median 26.4	<1 mm	80	42.5	>3, 35%	≥50, 36.3%	46.2	NR	CSS, 17.8	<0.001	IHRFS, 26.6	0.001

(continued)

Table 2. *(continued)*

Author	Year of publication	Study period	Follow-up period	Surgical margin width	Patient number	Synchronous, %	Tumor number	Largest tumor size, mm	Pre-CTx, %	Post-CTx, %	5-yea-rOS, %	*p*-value	5-year DFS, %	*p*-value
				≥1 mm	849	44.3	>3, 14.3%	≥50, 35.0%	33	88	39.7		60.2	
de Haas *et al.*[14]	2008	1990–2006	NR	0 mm	202	58	≥2, 68%	Mean, 56	81	88	57	0.27	29	0.12
				≥1 mm	234	46	≥2, 50%	Mean, 39	67	78	61		20	
Vandeweyer *et al.*[37]	2009	1992–2007	Median 56.4	≤1 mm	67	27	NR	NR	NR	NR	25	0.04	18.6	0.14
				>1 mm	194						42.7		23.6	
Andreou *et al.*[16]	2013	1997–2010	Median 32	<1 mm	52	65	≥2, 62%	≥30, 49%	100	69	26	0.017	NR	NR
				≥1 mm	326						55			
Angelsen *et al.*[15]	2014	1998–2010	NR	<1 mm	48	45.5	Median, 2	Median, 30	32.8	25.0	16.1	0.011	0	0.127
				≥1 mm	194					15.1	42.5		24.5	
Postriganova *et al.*[39]	2014	1998–2012	Median 31	<1 mm	33	54.5	≥2, 42%	Median, 29	NR	NR	54	0.988	36	0.978
				≥1 mm	122	59.8	≥2, 26.2%				45–53		37–49	
Hamady *et al.*[38]	2014	1993–2001	NR	<1 mm, R2	663	49.9	≥5, 14%	≥50, 36.5	49	NR	NR	NR	20	<0.001
				≥1 mm	2,052								33	
Pandanaboyana *et al.*[19]	2015	1993–2011	Median 31.4	<1 mm	390	61.3	NR	≥50, 40.3	40.0	NR	MST, 2.28Y	<0.001	MST, 1.04Y	<0.001
				≥1 mm	865	52.6		≥50, 32.6	42.1		MST, 2.7Y		MST, 1.52Y	
Truant *et al.*[26]	2015	2000–2010	Mean 43	<1 mm	59	67.8	Mean, 3.3	Mean, 47	72.9	52.5	39.1	0.01	15.2	0.021
				≥1 mm	214	53.8	Mean, 2.6	Mean, 35	62.1	59.3	54.2		31.1	
Vigano *et al.*[41]	2016	2004–2013	Median 33.2	<1 mm parenchyma	107	47.7	>3, 55.1%	>50, 24.3%	53.3	39.3	32.5	0.068	LR, 19.6	0.002
				<1 mm vascular	46	50.0	>3, 63.0%	>50, 19.6%	63.0	39.1	59.4		LR, 4.3	NS
				≥1 mm	95	48.4	>3, 30.5%	>50, 21.1%	46.3	45.3	54.3		LR, 5.3	Reference
Laurent *et al.*[23]	2016	1999–2010	Median 32	<1 mm	19	53	>3, 32%	Median, 50	86	55	44	0.047	8	0.082
				≥1 mm	172	67	>3, 20%	Median, 35			61		22	
Brudvik *et al.*[17]	2016	2005–2013	Mean 26	<1 mm	48	22.9	≥2, 54.2%	Mean, 35	85.4	NR	Hazard ratio, 2.423	0.001	NR	NR

(continued)

Table 2. *(continued)*

Author	Year of publication	Study period	Follow-up period	Surgical margin width	Patient number	Synchronous, %	Tumor number	Largest tumor size, mm	Pre-CTx, %	Post-CTx, %	5-yearOS, %	*p*-value	5-year DFS, %	*p*-value
				≥1 mm	585	30.1	≥2, 52.3%	Mean, 27	86.2		Reference			
Sadot *et al.*[42]	2016	1992–2012	NR	0 mm	245	52	>3, 43%	≥50, 39%	Perioperative, 93%		24	Reference	NR	NR
				0.1–0.9 mm	160						26	<0.05		
				≥1 mm	1,956	50	>3, 21%	≥50, 29%			46–48	<0.05		
Takamoto *et al.*[27]	2016	2007–2015	Median 30	≤1 mm	163	64	≥8, 37%	>50, 32%	49	NR	36.6	0.004	3.5	<0.001
				>1 mm	72						75.5		29.7	
Margonis *et al.*[34]	2016	2003–2015	Median 28.9	≤1 mm	105	57.1	Median, 2	Median, 25	79.0	69.2	42.4	0.001	NR	NR
				>1 mm	380						57.1			
Sasaki *et al.*[20]	2017	2000–2015	Median 30.3	Largest tumor <1 mm	45	NR	Median, 3	Median, 27	77.8	81.0	MST 36.5	0.002	NR	NR
				Non-largest tumor <1 mm	50		Median, 3	Median, 25	66.0	75.5	MST 53.3	0.66		
				≥1 mm	156		Median, 2	Median, 23	65.4	76.0	MST 66.6	Ref		
Hosokawa *et al.*[43]	2016	2000–2009	At least >60	0 mm	141	62.1	≥2, 75	55.9	93.2	NR	36	0.37	NR	NR
				≥1 mm	130	NR	NR	NR	NR		34			
Memeo *et al.*[11]	2017	2006–2013	NR	0 mm	NR	48.4	≥2, 75.1	≥50, 25.1	64.7	NR	58	0.0002	NR	NR
				≥1 mm	NR	39.3	≥2, 54.9	≥50, 16.7	70.9	NR	76–80			
Xu *et al.*[28]	2019	2006–2016	Median 30	<1 mm	67	NR	Median, 3	Median, 30	100	77.6	38.2	0.001	10.5	0.002
				≥1 mm	147		Median, 2	Median, 25		72.8	53.2		26.5	
Procopio *et al.*[29]	2020	2008–2016	Median 26	<1 mm Parenchyma	141	53%	>3, 62%	>50, 28%	74	50	30	0.002	15	<0.0001
				<1 mm Vascular	91		>3, 63%	>50, 18%	78	52	29	0.062	25	0.010
				≥1 mm	142		>3, 40%	>50, 15%	72	59	37	Reference	39	Reference

CSS, cancer-specific survival; CTx, chemotherapy; DFS, disease-free survival; IHRFS, intrahepatic recurrence-free survival; MST, median survival time; NR, not reported; NS, not significant; OS, overall survival; RFS, recurrence-free survival; RR, recurrence rate.

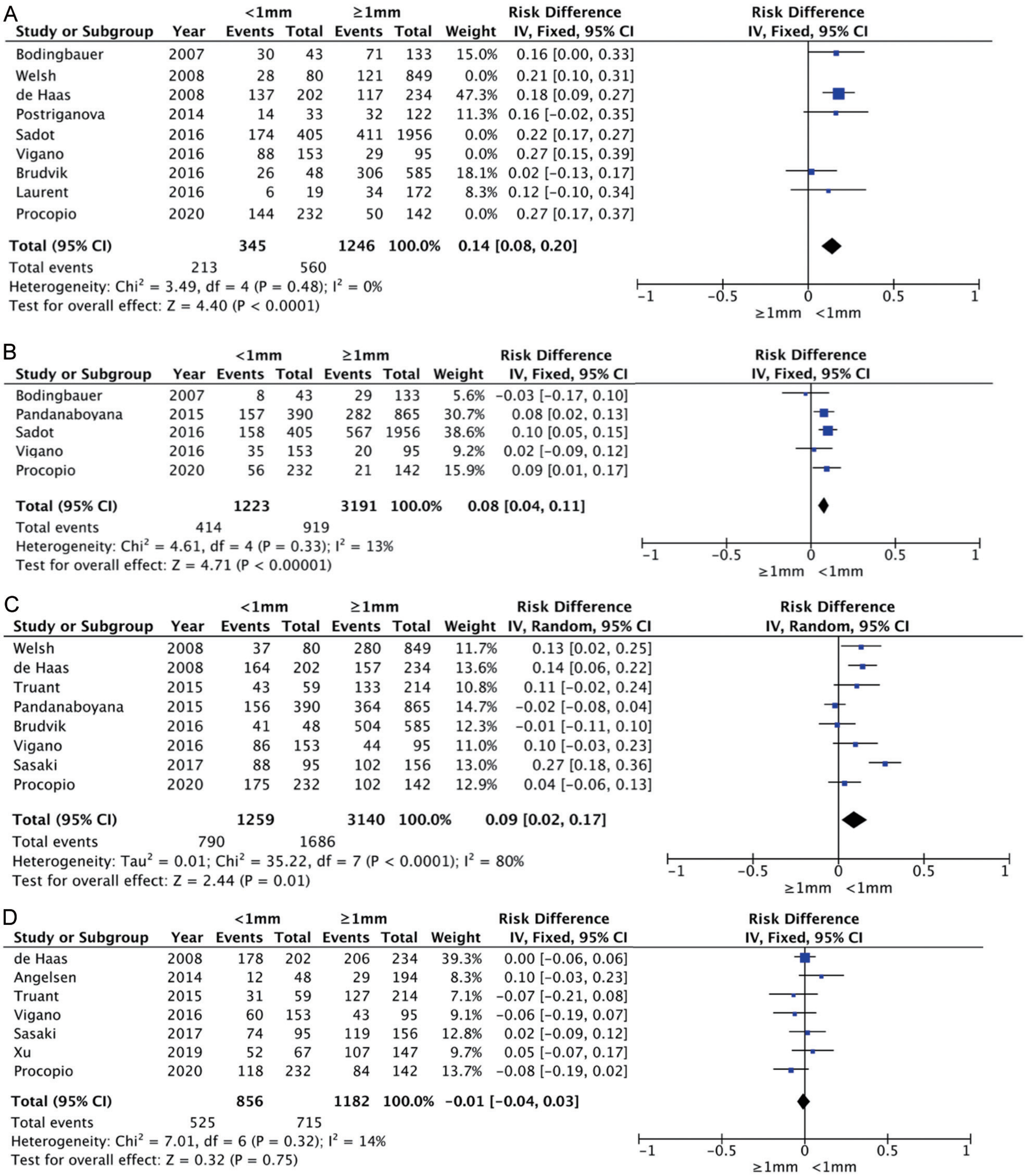

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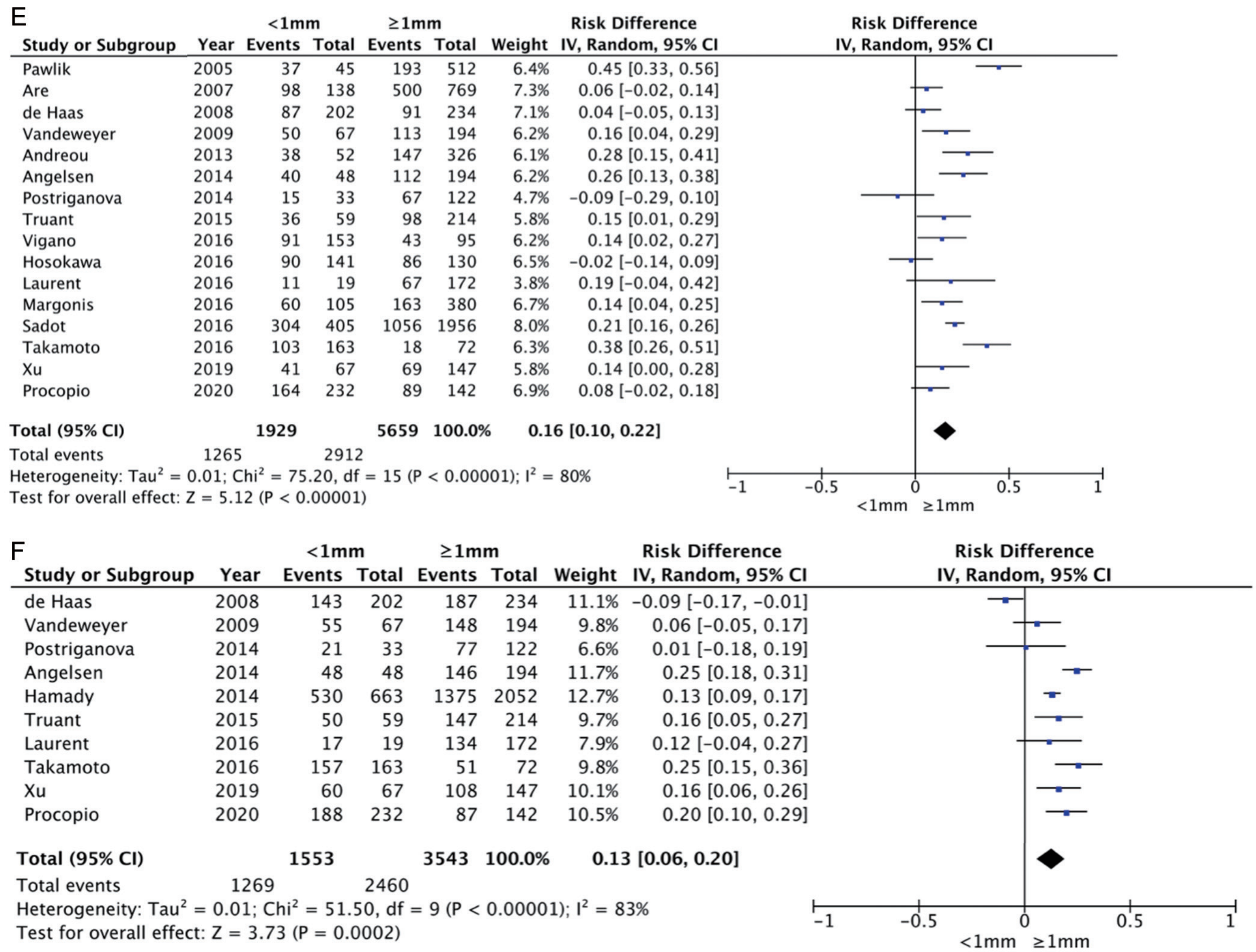
Fig. 1. Meta-analysis of studies evaluating the prognostic impact of a surgical margin width ≥1 mm in hepatectomy for colorectal liver metastasis. (A) Proportion of multiple tumors; (B) Proportion of tumors sized ≥50 mm; (C) Proportion of patients undergoing preoperative chemotherapy; (D) Proportion of patients undergoing postoperative chemotherapy; (E) 5-year overall survival; (F) 5-year recurrence-free survival.



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Study or Subgroup	Year	<1mm Events	<1mm Total	≥1mm Events	≥1mm Total	Weight	Risk Difference IV, Random, 95% CI
Pawlik	2005	37	45	193	512	6.4%	0.45 [0.33, 0.56]
Are	2007	98	138	500	769	7.3%	0.06 [−0.02, 0.14]
de Haas	2008	87	202	91	234	7.1%	0.04 [−0.05, 0.13]
Vandeweyer	2009	50	67	113	194	6.2%	0.16 [0.04, 0.29]
Andreou	2013	38	52	147	326	6.1%	0.28 [0.15, 0.41]
Angelsen	2014	40	48	112	194	6.2%	0.26 [0.13, 0.38]
Postriganova	2014	15	33	67	122	4.7%	−0.09 [−0.29, 0.10]
Truant	2015	36	59	98	214	5.8%	0.15 [0.01, 0.29]
Vigano	2016	91	153	43	95	6.2%	0.14 [0.02, 0.27]
Hosokawa	2016	90	141	86	130	6.5%	−0.02 [−0.14, 0.09]
Laurent	2016	11	19	67	172	3.8%	0.19 [−0.04, 0.42]
Margonis	2016	60	105	163	380	6.7%	0.14 [0.04, 0.25]
Sadot	2016	304	405	1056	1956	8.0%	0.21 [0.16, 0.26]
Takamoto	2016	103	163	18	72	6.3%	0.38 [0.26, 0.51]
Xu	2019	41	67	69	147	5.8%	0.14 [0.00, 0.28]
Procopio	2020	164	232	89	142	6.9%	0.08 [−0.02, 0.18]
Total (95% CI)			**1929**		**5659**	**100.0%**	**0.16 [0.10, 0.22]**
Total events		1265		2912			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 75.20$, df = 15 ($P < 0.00001$); $I^2 = 80\%$
Test for overall effect: Z = 5.12 ($P < 0.00001$)

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Study or Subgroup	Year	<1mm Events	<1mm Total	≥1mm Events	≥1mm Total	Weight	Risk Difference IV, Random, 95% CI
de Haas	2008	143	202	187	234	11.1%	−0.09 [−0.17, −0.01]
Vandeweyer	2009	55	67	148	194	9.8%	0.06 [−0.05, 0.17]
Postriganova	2014	21	33	77	122	6.6%	0.01 [−0.18, 0.19]
Angelsen	2014	48	48	146	194	11.7%	0.25 [0.18, 0.31]
Hamady	2014	530	663	1375	2052	12.7%	0.13 [0.09, 0.17]
Truant	2015	50	59	147	214	9.7%	0.16 [0.05, 0.27]
Laurent	2016	17	19	134	172	7.9%	0.12 [−0.04, 0.27]
Takamoto	2016	157	163	51	72	9.8%	0.25 [0.15, 0.36]
Xu	2019	60	67	108	147	10.1%	0.16 [0.06, 0.26]
Procopio	2020	188	232	87	142	10.5%	0.20 [0.10, 0.29]
Total (95% CI)			**1553**		**3543**	**100.0%**	**0.13 [0.06, 0.20]**
Total events		1269		2460			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 51.50$, df = 9 ($P < 0.00001$); $I^2 = 83\%$
Test for overall effect: Z = 3.73 ($P = 0.0002$)

Fig. 1. *(continued)*

response to chemotherapy had a better prognosis compared with R2.[34,43,47,48] Therefore, 0 mm margins are acceptable only in a limited number of patients such as those who had a good response to preoperative chemotherapy.

Margin (local, cut-end) recurrence

One major concern regarding R1 resection of CRLM is margin (local, cut-end) recurrence. However, even for patients with R1 resection, the incidence of margin recurrence is about 20–30% according to the majority of previous reports (Table 3).[1,15,18,21,26,29,31,35,39,41,46] Vigano *et al*.[41] found no significant difference in the incidence of margin recurrence between R0 and R1-vascular groups, but the R1-parenchyma group was associated with a significantly higher incidence of margin recurrence compared with the others. Furthermore, they found no differences in the isolated margin recurrence rate among the three groups, or in the margin recurrence rate when limited to patients with a good response to preoperative chemotherapy or with large/multiple CRLM.[41] Truant *et al*.[26] reported a similar margin recurrence rate between R0 and R1 among patients who underwent preoperative chemotherapy. Postriganova *et al*.[39] reported comparative OS among R1 and R0 after salvage re-hepatectomy in patients with liver recurrence, including margin recurrences. Salvage resection for margin recurrence was reportedly performed in 32.1–78.6% of the patients with margin recurrence,[1,15,26,35,41,46] and may improve OS.

Conditions for improved prognosis after R1 hepatectomy

To evaluate the survival impact of new chemotherapy agents such as oxaliplatin or irinotecan for patients with a narrow surgical margin, we evaluated papers published since 2000, mainly from Europe and the USA, where more than 80% of patients in the study cohort had undergone preoperative chemotherapy with new chemotherapy agents. Pandanaboyana *et al*.[19] reported that preoperative chemotherapy did not have a positive impact on OS in patients with R1 (<1 mm) compared with R0 (≥1 mm), but Ayez *et al*.[30] found no significant difference in OS or DFS between R1 (0 mm) and R0 (>0 mm) among patients had undergone preoperative chemotherapy. Andreau *et al*.[16] found no significant difference in OS between R1 (<1 mm) and R0 (≥1 mm) among patients with a good pathological response (0–49% residual possible tumor cells pathologically) to preoperative chemotherapy. In addition, de Haas *et al*.[14] conducted a study that included a

Table 3. Studies evaluating margin (local, cut-end) recurrence

Author	Year of publication	Study period	Follow-up period	Surgical margin width	Patient number	Pre-CTx, %	Response* to pre-CTx, %	Margin recurrence, %	*p*- value	5-year OS, %	*p*-value
Kokudo *et al.*[35]	2002	1980–2000	Median 29.1	<2 mm	45	NR	NR	20	NR	34.7	0.90
				≥2 mm	138			7.2		43.8–50.2	
Pawlik *et al.*[18]	2005	1990–2004	Median 29	<1 mm	45	NR	NR	11	NR	17.1	0.005
				≥1 mm	512			3.1		≥62.3	
Wakai *et al.*[46]	2008	1989–2004	Median 127	0 mm	10	0	-	30	0.015	MST, 18	<0.0001
				<10 mm	51			3.9		MST, 33	
				≥10 mm	29			0		MST, 89	
Nuzzo *et al.*[31]	2008	1992–2005	Mean 39	0 mm	9	NR	NR	71.4	NR	0	0.01
				>0 mm	174			4.0		39.1	
Angelsen *et al.*[15]	2014	1998–2010	NR	<1 mm	48	32.8	95.5	33.3	0.0001	16.1	0.011
				≥1 mm	194			12.4		42.5	
Muratore *et al.*[21]	2010	1999–2007	Median 56.5	<1 mm	55	45.5	NR	23.6	<0.001	NR	
				≤1 cm	175	36.2		6.9		44.5	0.9
				>1 cm	84	34.5		3.6		45.9	
Postriganova *et al.*[39]	2014	1998–2012	Median 31	<1 mm,	33	NR	NR	6.1	0.232	54	0.988
				≥1 mm	122			0.8		45–53	
Truant *et al.*[26]	2015	2000–2010	Mean 43	<1 mm	59	72.9	95.3	16.9 (31.3% of recurrences)	0.025	39.1	0.01
				≥1 mm	214	62.1	93.2	5.6 (13.4% of recurrences)		54.2	
Vigano *et al.*[41]	2016	2004–2013	Median 33.2	<1 mm parenchyma	107	53.3	68.4	19.6	0.002	32.5	0.068
				<1 mm vascular	46	63.0	72.4	4.3	NS	59.4	
				≥1 mm	95	46.3	93.2	5.3	Reference	54.3	
Procopio *et al.*[29]	2020	2008–2016	Median 26	<1 mm parenchyma	141	74	92	21.3	<0.001	30	0.002
				<1 mm vascular	91	78		7.7	NS	29	0.062
				≥1 mm	142	72		6.3	Reference	37	Reference
Ausania *et al.*[1]	2022	2009–2018	Median 46.3	R1 contact	53	60.4	90	30.2	0.036	MST, 46	0.038
				R1<1 mm	24	50	90	8.3		MST, 69	

*Including complete/partial/stable. CTx, chemotherapy; MST, median survival time; NR, not reported; NS, not significant; OS, overall survival.

high rate of good responders to preoperative chemotherapy (90.0% with response + stabilization and 73.6% of whom had undergone preoperative chemotherapy), and found no significant difference in OS or DFS between R1 (0 mm) and R0 (≥1 mm). Tanaka *et al*.[47] reported significantly poorer OS in an R1 (0 mm) group compared with an R0 (>0 mm) group among all patients, but no significant difference when limited to patients with unresectable/marginally resectable cases who underwent preoperative chemotherapy. Hosokawa *et al*.[43] found no significant difference in OS between R1 (0 mm) and R0 (≥1 mm), and the patients who responded to preoperative chemotherapy achieved cure in 18% of R1 resections. New chemotherapy agents have been reported to reduce the prognostic impact of micrometastases around the resected tumor, and may provide comparable 5-year OS between R1 (<1 mm) and R0 (≥1 mm) groups.[14,15,23]

R1-vascular, small-R1 (≤4 cm^2), and R1 in smaller lesions in multiple metastases might be considered acceptable for improved prognoses in patients undergoing R1 hepatectomy.[20,27,29,41] Margonis *et al*.[48] reported that intraoperative re-resection in patients with R1 did not show a survival benefit and that tumor factors showed a stronger survival impact. Margonis *et al*.[34] also showed that R0 resection (>1 mm) only provided a survival benefit in patients with *KRAS* wild-type, and R1 (≤1 mm) had no survival impact on patients with *KRAS* mutant type. In contrast, Xu *et al*.[28] reported that R1 (<1 mm) was not an independent predictor of OS in patients with *RAS* wild-type with a good response to chemotherapy. Therefore, genetic mutation status might affect survival after hepatectomy for CRLM, but to the best of our knowledge, this has yet to be confirmed.

Prognostic factors other than surgical margins

Among the reports that did not find the surgical margin to be a prognostic factor, high preoperative carcinoembryonic antigen (CEA) value, node-positive primary lesion, larger tumor size, and higher number of tumors were identified as independent prognosticators in multivariate analysis.[14,15,18,20,21,26,35,40] CEA values of 10, 50, or 200 ng/mL, a tumor size >50 mm, and more than two, four, or five tumors were reported cutoff values.[14,18,20,21,35,40] Tumor or biologic factors are often considered prognostic factors stronger than surgical margin width.

Discussion

Earlier reports on hepatectomy for CRLM, considered that tumor surgical margins ≥10 mm were sufficient or desirable,[3,44] and subcentimeter surgical margins were also acceptable in many studies (Tables 1 and 2). Therefore, if it was difficult to secure a surgical margin ≥10 mm, large of a margin of subcentimeter length should be secured. This review found that a surgical margin of 5, 2, or 1 mm may be appropriate as a reference value.[15,31,35,36] Recent studies have reported that even a surgical margin ≥1 mm provides a sufficient prognostic advantage and might be a minimally acceptable surgical margin (Table 2 and Fig. 1). A possible explanation of why acceptable minimal surgical margin widths have become smaller over time may be advances in chemotherapy.[14] However, the 1 mm margin has become acceptable even for patients who have not undergone chemotherapy.[25] Therefore, another explanation could be the substantial advances in surgical techniques.[14] Regarding surgical procedures, various subgroup analyses of surgical margin status have been reported. Takamoto *et al*.[27] reported that narrow R1 (≤4 cm^2) was associated with better survival than broad R1. Vigano *et al*.[41] reported that R1-vascular had better survival than did R1-parenchyma. Recently, Procopio *et al*.[29] also reported that R1-parenchyma showed a worse prognosis than both R1-vascular and R0, but no significant difference was seen between R1-vascular and R0. These studies stress the importance of a precise surgical procedure for dissection at a point close to the tumor because dissection between the tumor and adjacent major vessels requires more accurate techniques to prevent both tumor exposure and injury to vessels. However, evaluating real surgical margins is difficult because they are affected by procedures such as parenchymal ablation/suction, that are considered a major limitation of studies assessing surgical margins.[2]

In contrast to a 1 mm surgical margin width, a 0 mm margin had worse survival in many studies.[1,11,22,31,33,42,45,46] It is possible, however, that preoperative chemotherapy with a good response may counteract the observed negative impact of a 0 mm margin width. The margin recurrence also rate was not high (20–30%), even in patients with R1 resection (Table 3). Furthermore, even if margin recurrence has occurred, recent improvements in surgical procedures may provide a higher rate of salvage hepatectomy for margin recurrence and improve patient prognoses.[1,15,26,35,41,46] Because several previous reports that did not find a narrow surgical margin to be an independent predictor of survival found that aggressive tumor status was an independent predictor,[14,15,18,21,25,26] a narrow surgical margin might result from a more aggressive disease status. Indicators of aggressive status such as large tumor size, multiple tumors, bilobar distribution, or *RAS* mutant status are reportedly independent predictors of R1 resection.[14,17,24,31,32,36] In the case of multiple bilobar CRLM, the surgical margin must be narrow to preserve a sufficient remnant liver.[27,49] Continued advances in chemotherapy, including molecular targeted agents and genomic evaluation, may help solve the problem regarding surgical margin widths, but surgical procedures to achieve an adequate surgical margin width still are an important part of achieving a good long-term prognosis.[3] In contrast to the impact of preoperative chemotherapy for the prognosis of patients with a narrow surgical margin width, evidence supporting post-hepatectomy chemotherapy is weak. Although several studies have reported that the absence of post-hepatectomy chemotherapy was a poor prognostic factor,[20,21,26,28,41] to our knowledge, no reports have compared the prognosis of patients with a narrow surgical margin with or without post-hepatectomy chemotherapy.

A minimum surgical margin width (≥1 mm) might not be necessary and sufficient for all patients with CRLM. The appropriate surgical margin may differ for individual patients with CRLM. For example, a margin of >10 mm is recommended for patients such those with a solitary, small CRLM at the surface of the liver and distant from the major vessels. In contrast, a 1 mm surgical margin may be suitable for preserving the remnant liver in patients with multiple bilobar CRLM who undergo preoperative chemotherapy. Similarly, a narrow surgical margin width may be suitable for solitary lesions adjacent to major vessels. In Figure 2, we provide a flowchart of the treatment strategy for CRLM considering surgical margin width and various other factors. A prospective study that randomizes tumor resection with a narrow or wide margin for solitary, small, and superficial lesions distant from major vessels is needed to investigate the actual survival impact of narrow margins. However, as hepatectomy with a narrow margin requires a highly technically and precise parenchymal transection procedure, such a study should be undertaken by expert hepatic surgeons. In conclusion, evaluations of the actual prognostic impact of the surgical margin remain difficult and further study is needed.

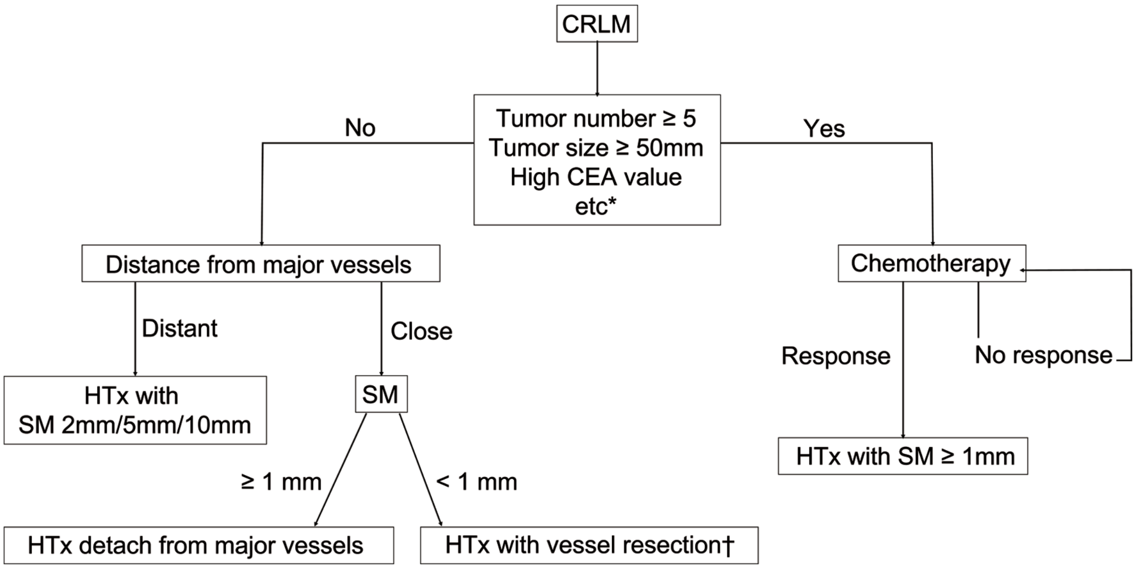

Fig. 2. Flowchart of the treatment strategy for colorectal liver metastasis considering surgical the margin width and other factors. *Extrahepatic lesion-positive or node-positive primary. †Detach from major vessels (SM 0 mm) and consider salvage HTx if local recurrence occurs. CEA, carcinoembryonic antigen; CLRM, colorectal liver metastasis; HTx, hepatectomy; SM, surgical margin width.

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Conflict of interest

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Author contributions

Study concept and design (KS, TB), acquisition of data (KS), analysis and interpretation of data (KS, TB), drafting of the manuscript (KS), critical revision of the manuscript for important intellectual content (TB, KO, KT, MH, NF, YT), administrative, technical, or material support (KS, TB), and study supervision (TB). All authors have made a significant contribution to this study and have approved the final manuscript.

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