# Impact of Surgical Margin Width on Recurrence and Overall Survival Following R0 Hepatic Resection of Colorectal Metastases

## *A Systematic Review and Meta-analysis*

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**Objective:** To examine the impact of surgical margin width on survival following R0 hepatic resection for colorectal metastases (CRLM).

**Summary of Background Data:** Although negative resection margin is considered of paramount importance for the prognosis of patients with colorectal liver metastases, optimal resection margin width remains controversial.

**Methods:** Eligible studies examining the association between margin status after R0 hepatic resection for CRLM and survival, including overall survival (OS) and disease-free survival (DFS) were sought using the Medline, Cochrane, and EMBASE databases. Random-effects models were used for the calculation of pooled relative risks (RRs) with their 95% confidence intervals (95% CIs).

**Results:** Thirty-four studies were deemed eligible for inclusion representing a cohort of 11,147 hepatic resections. Wider resection margin (>1 vs <1 cm) was significantly associated with improved OS at 3 years (pooled RR = 0.86, 95% CI: 0.79–0.95), 5 years (pooled RR = 0.91, 95% CI: 0.85–0.97), and 10 years (pooled RR = 0.94, 95% CI: 0.88–1.00). Similarly, DFS was positively associated with >1 cm resection margin at 3, 5, and 10 years. Interestingly, >1 mm (vs <1 mm) resection margin was significantly associated with improved OS at all-time points. Meta-regression analyses did not reveal any significant modifying role of the study features under investigation, such as the administration of neoadjuvant/adjuvant therapy.

**Conclusions:** Importantly, our findings suggest that while a >1 mm margin is associated with better prognosis than a submillimeter margin, achieving a margin >1 cm may result in even better oncologic outcomes and should be considered if possible.

**Keywords:** margin, meta-analysis, prognosis

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Among all factors affecting prognosis after curative intent resection of colorectal cancer liver metastases (CRLM), only the resection margin is under the surgeon's direct control and can, in turn, be modified to achieve optimal outcomes.[1] As such, its prognostic implications have been the focus of surgical research for the last 3 decades. In the late 80s, Cady et al[2] and Ekberg et al[3] suggested that surgeons should ideally strive for a 2-cm margin, if feasible; otherwise, they should settle for a resection margin width of at least 1 cm. Although these values were selected in a somewhat arbitrary fashion, they would serve to determine CRLM resectability for more than a decade, without being seriously challenged. However, more recently, there have been developments in oncologic care and surgical technique that have triggered a rapid expansion of operative indications.[4] In fact, it could be argued that current practice in hepatic surgery is no longer limited by what can be removed, but rather by what will remain after resection.[5] Although no longer considered a criterion of resectability, the ''1 cm margin rule'' has underwent a limited revival, as some studies suggest that it may be associated with superior prognosis compared with narrower margins.[6–9] Other studies, however, have demonstrated that no additional prognostic benefit is derived from extending the margin width beyond 1 mm, thus further fueling the ongoing controversy.[10,11]

Similarly, expert conferences have been equally controversial and reflect a pervasive uncertainty regarding the practical implications of margin width. For example, while an expert consensus conference cosponsored by the American Hepato-Pancreato-Biliary Association, the Society for Surgery of the Alimentary Tract and the Society of Surgical Oncology in 2006 suggested that a wide (>1 cm) resection margin should remain the goal, a similarly constituted expert consensus conference held in 2012 was unable to make a ''definitive recommendation'' on the same topic.[12,13] Finally, in 2015, the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group convened and published a brief but clear statement; ''safe resection margins are still a goal of therapy; a minimal surgical clearance margin of 1 mm has been suggested as sufficient.''[14] Nonetheless, the optimal surgical margin for CLRM remains unknown.

The primary aim of this systematic review and pooled analysis was to compare the impact of a <1 versus a >1 cm margin width on overall survival (OS) and disease-free survival (DFS), among patients who underwent an R0 resection for CRLM. Importantly, 2 separate subanalyses were conducted according to the 2 most commonly employed definitions of R0, namely margin width >1 mm or margin width >0 mm. To characterize the impact of the R1 margin subgroup on overall prognosis, an additional pooled analysis of OS and DFS following the achievement of a <1 versus a

>1 mm resection margin width was performed. Of note, unpublished data from Johns Hopkins University (JHU) were added in the analysis.

## METHODS

### Search Strategy and Eligibility of Studies

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] All potentially eligible publications were retrieved from the Medline, Cochrane, and EMBASE databases using the search algorithm [(colorectal OR rectal OR colon) AND (liver OR hepatic) AND resection AND (metastasis OR metastases) AND (margin OR margins)]. The final search date was July 01, 2016, and no restrictions were imposed with respect to publication language. Furthermore, the reference lists of all eligible studies and pertinent meta-analyses were systematically searched for additional relevant articles in a ''snowball'' procedure.

Studies were deemed eligible according to the PICO approach:

P: Patients diagnosed with colorectal liver metastases and eligible for surgical resection.
I: R0 hepatic resection for CRLM with available data on margin width.
C: Comparison of patient subgroups with different margin width, namely submillimeter, more than a millimeter, subcentimeter, and more than a centimeter.
O: OS and DFS at 1, 3, 5, and 10 years.

Studies reporting the long-term outcomes of margin subcategories only in the form of Kaplan-Meier curves were excluded. In the case of overlapping study populations, only the largest study was included. Article screening and study selection were performed by 2 reviewers (INS and IGT) independently; in case of discrepancies, the final decision was reached by team consensus.

### Data Extraction and Effect Estimates

The extraction of data comprised the first author's name, study year, journal, study period, study region, number of patients, number of patients with available margin data, patient age (range, mean), percentage of males, definition of margin status and the means through which it was ascertained, patient inclusion and exclusion criteria, follow-up period and determination of outcome (recurrence, death), definition of the start point for the calculation of survival, percentage of synchronous diagnosis of colorectal cancer and hepatic metastases (% of patients), previous administration of neo-adjuvant/adjuvant chemotherapy (% of patients), Dukes staging, location of the primary tumor (colon, rectum), nodal status, number of patients with bilobar liver metastases, presence of extrahepatic disease at hepatectomy, number and size of liver metastases, abnormal preoperative carcinoembryonic antigen (CEA) levels, margin subcategories (<1 vs >1 cm and/or <1 mm vs >1 mm), and data on long-term outcomes (numbers of alive/dead and recurrence-free/patients with recurrence at 1, 3, 5, and 10 years). All data were independently extracted by 2 reviewers (INS and IGT). All instances of disagreement were resolved through team consensus.

### Statistical Analysis

Statistical analyses included pooling of studies, as well as a meta-regression analysis. In view of the retrospective nature of all eligible studies, relative risks (RRs) for death/recurrence with their respective 95% confidence intervals (95% CIs) were calculated from the extracted data, thus allowing the comparison of long-term outcomes among patients with different margin widths (>1 vs <1 cm, as well as >1 vs <1 mm). RR values lower than 1 denoted a decreased risk of death (or recurrence) in the groups with surgical margins >1 cm (vs <1 cm) and >1 mm (vs <1 mm), respectively. In cases where the eligible studies included multiple subcentimeter margin subgroups, all were assigned to a unified ''<1 cm'' category for the purposes of our analysis. In case of zero cells, an appropriate continuity correction (addition of 0.5) was implemented.[16]

Random-effects (DerSimonian-Laird) models were used to calculate pooled effect estimates, as appropriate. Between-study heterogeneity was assessed through Cochran $Q$ statistic and by estimating $I^2$.[17] Separate analyses were performed by time point (1-, 3-, 5-, and 10-year OS and DFS) and surgical margin width (<1 vs >1 cm and <1 vs >1 mm). Predetermined subgroup analyses were also performed according to the definition of R0/R1 resection of hepatic metastases that was employed by eligible studies [R1 resection was defined as the presence of tumor cells either at the transection line (0 mm) or <1 mm from the transection line or <0.5 mm from the transection line]. Furthermore, a number of post hoc sensitivity analyses were performed: a subgroup analysis of studies published from 2001 onwards, a subgroup analysis of studies that performed re-review of the pathology specimens and a subgroup analysis that only included published data (excluding the data from our center).

Meta-regression analysis was performed in order to assess the potential impact of various study variables on the association between death/recurrence and surgical margin status. Meta-regression analysis was confined to 5-year OS and DFS analysis in order to maximize the number of eligible study arms, as appropriate.[17] It should be noted that the meta-regression analysis assessed the impact of systemic therapy (in the neo-adjuvant or adjuvant setting) on the prognostic implications of surgical margin by treating it as a binary variable (therapy was either administered or not). Importantly, the nature and effectiveness of the systemic therapy in question (regimen employed, type of biologic agent used, cycles administered, response etc.) could not be taken into consideration, due to the lack of sufficient data. Statistical analysis and meta-regression analysis were performed using STATA/SE version 13 (Stata Corp, College Station, TX).

### Risk of Bias

Regarding the risk of bias, the quality of the included studies was evaluated using the Newcastle-Ottawa Quality scale.[18] A follow-up duration of at least 5 years was considered adequate, while the maximum loss to follow-up rate deemed methodologically acceptable was 20%. Two reviewers (INS and IGT) working independently rated the studies and, in case of disagreement, the final decision was reached by team consensus.

Regarding publication bias, the 5-year OS and DFS analysis (ie, the analysis with the largest number of eligible studies) was employed to maximize the power of underlying tests, as appropriate.[17] Egger statistical test was implemented to assess the presence of publication bias; for the interpretation of Egger test, statistical significance was defined as $P$ <0.1.[19]

## RESULTS

### Description of Eligible Studies

The flow chart describing the process through which eligible studies were selected is presented in Fig. 1. After removing the duplicate results from the different databases, a total of 623 abstracts were identified and screened; 501 were excluded as irrelevant, 4 studies were excluded (Supplemental Table 1, http://links.lww.com/SLA/B333) due to overlap with 3 eligible studies,[20–22] 70 studies

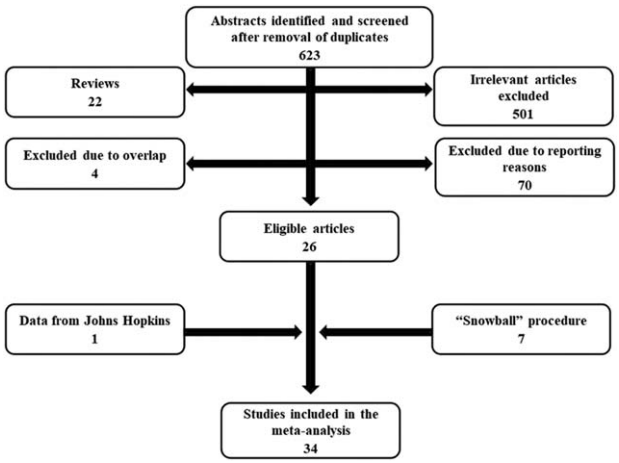


**FIGURE 1.** Study selection process.

were excluded due to issues with data reporting (Supplemental Table 2, http://links.lww.com/SLA/B333), and 22 studies were reviews (Supplemental Table 3, http://links.lww.com/SLA/B333).[20–26] The studies by Yamamoto et al,[27] Gayowski et al,[28] and Are et al[6] overlapped with the studies by Minagawa et al,[29] Iwatsuki et al,[30] and Sadot et al,[31] respectively; however data regarding 1-year survival from Yamamoto et al[27] and Gayowski et al[28] as well as data regarding 3-year survival from Are et al[6] were included, because they were not provided by their overlapping counterparts.[6,27–31] Furthermore, we elected not to exclude Tsai et al[32] despite the inclusion of 1 patient with involved margins in the study cohort, so as not to lose data from the remaining 154 patients with negative margins. The snowball procedure yielded 7 additional, eligible studies.[22,30–35] Furthermore, unpublished data from the Department of Surgery, Johns Hopkins University, regarding 467 patients who underwent R0 hepatic resection for CRLM were also included (Pawlik et al, 2016). In all, 34 studies were included in the present meta-analysis.[2,6,9–11,20–22,27–51] All studies were written in English. Overall, the total number of hepatic resections with data on surgical margins was 11,147. For the purpose of calculating outcomes, the time of hepatectomy was defined as time-point zero. Two alternative definitions were used by the included studies with respect to R0/R1 resection margins; R1 resection was defined as either the presence of tumor cells <1 mm from the transection line or the presence of tumor cells on the transection line (0 mm).[9–11,20–22,27,28,31,35–40,43–45,47–50] Separate data were collected regarding both definitions, when available (including JHU unpublished data).[6,10,22,50] The characteristics of the included studies are presented in Table 1 and Supplemental Tables 4 and 7, http://links.lww.com/SLA/B333.

## Comparison of the >1 cm versus <1 cm Margin Width Groups

Figure 2 is a ''bubble plot'' showing the percentage of >1 cm resection margins for each study per publication year. In case of overlapping study populations, only the most recent report was included. The size of the circles (or bubbles) on the graph represents the number of participants who underwent CRLM resection in each study. The prevalence of >1 cm resection margin widths in the studies reporting on liver resection performed for CRLM ranged from 18.1% to 90.3%. The results of the meta-analysis and the subgroup analyses are presented in Fig. 3 and Supplemental Figures 1-5, http://links.lww.com/SLA/B333.

In cases where data were available on both alternative definitions of microscopically positive margins, 2 separate survival analyses (>1 vs <1 cm margin width) were conducted. For these cases, the analysis in which R1 is defined as the presence of tumor cells on the transection line (0 mm) is presented in Fig. 3, whereas the analysis in which R1 is defined as the presence of tumor cells <1 mm from the transection line is presented in Supplemental Figure 1, http://links.lww.com/SLA/B333. The reported outcomes refer to 5-year OS.

A comprehensive analysis that examined 5-year OS (Table 2) pointed to a statistically significant association of a >1 cm margin width with improved survival (pooled RR = 0.91, 95% CI: 0.85–0.97) (Fig. 3). This protective association regarding 5-year OS was present in both the subset of studies that defined R1 as the presence of tumor cells <1 mm from the transection line (pooled RR = 0.91, 95% CI: 0.82–1.01) and in those defining R1 as tumor infiltration of the transection line (pooled RR = 0.90, 95% CI: 0.83–0.98).

Similarly, a wider (>1 cm) margin width was associated with improved 3- and 10-year OS (pooled RR = 0.86, 95% CI: 0.79–0.95, and pooled RR = 0.94, 95% CI: 0.88–1.00, respectively, but not with improved 1-year OS (pooled RR = 0.87, 95% CI: 0.60–1.27). The results of the previously described analyses that employed alternative definitions of R1 closely followed the main analysis for all time points.

Accordingly, DFS was positively associated with >1 cm resection margins at the 3-year (pooled RR = 0.93, 95% CI: 0.86–1.00), 5-year (pooled RR = 0.88, 95% CI: 0.81–0.96, Supplemental Figures 2 and 3, http://links.lww.com/SLA/B333), and 10-year time points (pooled RR = 0.95, 95% CI: 0.91–0.99).

## Nested Analysis in the 5 Studies Providing Both Definitions

A total of 5 studies (including the unpublished JHH data) had all relevant data needed to express R1 using both definitions commonly employed in the literature. Supplemental Figure 4, http://links.lww.com/SLA/B333 presents the >1 cm vs. 1–10 mm comparison and Supplemental Figure 5, http://links.lww.com/SLA/B333 presents the >1 cm versus 0 to 10 mm comparison regarding 5-year OS. Both comparisons yielded statistically significant protective associations, with similar effect estimates (RR = 0.94, 95% CI: 0.88–0.99 and RR = 0.92, 95% CI: 0.87–0.97, respectively).

## Comparison of the >1 versus <1 mm Margin Width Groups

The results of the meta-analyses regarding the comparison of >1 versus <1 mm margin widths are presented in Table 3. Importantly, a wider resection margin (>1 mm) was significantly associated with improved OS at all examined time points; pooled RR at 1 year = 0.48, 95% CI: 0.29–0.78, pooled RR at 3 years = 0.77, 95% CI: 0.63–0.93, pooled RR at 5 years = 0.80, 95% CI: 0.72–0.88 (Fig. 4), and pooled RR at 10 years = 0.95, 95% CI: 0.92–0.99. No significant associations were detected with respect to DFS, probably due to the small number of eligible study arms and the resulting low statistical power.

## Meta-regression Analysis

Meta-regression analysis assessed the influence of publication year, percentage of males, mean age of the sample, synchronous diagnosis of hepatic metastases (%), administration of neoadjuvant (%) and adjuvant (%) treatment, primary cancer site (%) and mean number of hepatic metastatic lesions, on the observed association between a wider resection margin (>1 cm) and survival (OS and DFS) at 5 years. Importantly, no statistically significant association was detected (Supplemental Table 5, http://links.lww.com/SLA/B333).

**TABLE 1.** Descriptive Characteristics of Eligible Studies

| Ref. | Study Period | Males (%) | Age (Mean or Median) | Follow-up (mo, Median or Mean) | Synchronous Hepatic Metastases (%) | Neoadjuvant (%) | Adjuvant (%) | Number of Metastases [Median or Mean (Range)] | Location of the Primary Site | Definition of R0/R1 Resection Margins | R0 Patients with Data on Margins | Type of Survival Outcome Studied (in y) | Compared Categories in the Original Study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Angelsen et al[36] | 1998–2010 | 52.5 | 66.1 | 56.4 | 45.5 | 15.8 | 17.4 | 2 (1–12) | NR | † | 193 | OS-10 | 1–4 mm, 5–9 mm, ≥10 mm |
| Are et al[6] | 1991–2003 | 56 | 63 | 42 | 34.8 | 33 | NR | 2.4 (0.1–4.7) | C: 850, R: 169 | ‡ | 907 | OS-3 | 1–10 mm, ≥10 mm |
| Arru et al[39] | 1982–2003 | 57.6 | NR | NR | 38.9 | NR | 59.7 | NR | C: 170, R: 76 | * | 171 | OS-5 | ≥1 cm, <1 cm |
| Bramhall et al[41] | 1989–2001 | 61.3 | 62 | 16 | 24.1 | NR | NR | 1.6 (1–6) | NR | § | 179 | OS-3 | 0.5–4 mm, 5–9 mm, ≥ 10 mm |
| Cady et al[2] | 1990 | NR | 61 | NR | NR | NR | NR | 1 | NR | NR | 94 | DFS-5 | <1 cm, ≥1 cm |
| Elias et al[38] | 1984–1996 | 52.2 | 57.2 | NR | 40.4 | NR | NR | 2 (1–12) | C: 82, R: 54 | † | 196 | OS-5 | <1 cm, ≥1 cm |
| Fernandez et al[42] | 1995–2002 | 56 | 61.1 | 31 | 52 | NR | NR | 1.31 | C: 66, R: 31 | NR | 97 | OS-5<br>DFS-5 | <1 cm, ≥1 cm |
| Fong et al[40] | 1985–1991 | 58 | 62 | 37 | 33.6 | NR | 28 | NR | C: 324, R: 132 | † | 361 | OS-5 | 0.1–1 cm, >1 cm |
| Gayowski et al[28] | 1981–1991 | 63.7 | 60 | 69 | 27.5 | NR | NR | NR | C: 148, R: 56 | † | 187 | OS-1<br>DFS-1 | >1 cm, ≤1 cm |
| Hamady et al[21] | 1987–2010 | 63.9 | 64 | 33 | 49.9 | 49 | NR | 2 (1–20) | NR | † | 2052 | DFS-1,3,5,10 | 1–4.9 mm, 5–9.9 mm, ≥10 mm |
| Herman et al[43] | 2000–2009 | 45 | 59 | 34 | 49 | NR | 46.2 | NR | NR | * | 81 | DFS-1,3,5 | <1 mm, >1 mm |
| Hughes et al[44] | 1948–1988 | 52 | NR | 37 | NR | NR | NR | NR | NR | † | 264 | OS-5<br>DFS-5 | >1 cm, 0.1 cm – ≤1 cm |
| Inoue et al[10] | 1995–2009 | NR | NR | NR | 81.1 | NR | NR | 3.5 (2–13) | C: 74, R: 32 | ‡ | 104 | OS-1,3,5<br>DFS-1,3,5 | ≤ 1 cm, >1 cm // ≤1 mm, 2–9 mm, ≥10 mm |
| Iwatsuki et al[30] | 1981–1996 | 58.4 | 60 | 32 | 29.2 | NR | 66.2 | NR | C: 226, R: 78 | NR | 277 | OS-3,5,10<br>DFS-3,5,10 | >1 cm, ≤1 cm |
| Jamison et al[22] | 1960–1987 | 61.8 | NR | NR | 39.5 | NR | 12.5 | NR | NR | ‡ | 154 | OS-1,5,10 | 0–1 mm, 1–10 mm, ≥10 mm |
| Jatzko et al[33] | 1984–1992 | 74.2 | 65 | 24 | 60.1 | NR | NR | NR | C: 30, R: 36 | NR | 66 | OS-5<br>DFS-5 | ≤1 cm, >1 cm |
| Kato et al[46] | 1992–1996 | 66.8 | 63.5 | 47.2 | 45 | NR | 52.1 | 1 | C: 351, R: 241, C+R: 6 | NR | 445 | OS-3, 5 | <1 cm, ≥1 cm |
| Kokudo et al[47] | 1980–2000 | 55.2 | 59 | 29.1 | 60 | NR | NR | 2.1 (+/− 0.2) | C: 126, R: 57 | * | 183 | OS-1,3,5<br>DFS-1,3,5 | <2 mm, 2–4 mm, 5–9 mm, ≥10 mm |
| Lordan and Karanjia[45] | 1996–2006 | 68 | 68 | 34 | 73.1 | 87.4 | NR | NR | NR | † | 224 | OS-1,3,5 | 1–3 mm, 3–5 mm, 5–10 mm, >10 mm |
| Minagawa et al[29] | 1980–1997 | 62.9 | 59.2 | 28 | NR | NR | NR | 2 (1–17) | C: 137, R: 91 | NR | 145 | OS-3,5,10<br>DFS-3,5,10 | ≥1 cm, <1 cm |
| Muratore et al[48] | 1999–2007 | 60.2 | 62.8 | 39.8 | 49.7 | 37 | 74 | 2.4 (2.1–2.6) | C: 208, R: 106 | † | 259 | OS-3,5<br>RFS-3,5 | ≤ 1 cm, >1 cm |
| Nuzzo et al[9] | 1992–2005 | 56.2 | 61 | 39 | 35.7 | NR | NR | 2 (1–14) | C: 133, R: 52 | * | 176 | OS-5<br>DFS-5 | ≥10 mm, 6–9 mm, 3–5 mm, ≤2 mm |
| Ohlsson et al[49] | 1971–1995 | 54 | NR | 62.4 | 44.1 | NR | 18 | NR | NR | † | 104 | OS-5 | 0.1–1 cm, >1 cm |
| Pawlik et al[37] | 1990–2004 | 38 | 60 | 29 | 41.5 | NR | 60 | 2 (1–11) | C: 395, R: 162 | † | 512 | OS-5 | 1–4 mm, 5–9 mm, ≥1 cm |
| Pawlik (2016, JHU unpublished data) | 2000–2015 | 58.5 | 58 | 28.1 | 57.8 | 55.6 | 65.1 | 2 (1–3) | C: 405, R: 113 | ‡ | 363 | OS-1,3,5,10<br>DFS-1,3,5,10 | <1 vs ≥1 cm // <1 vs ≥1 mm |
| Sadot et al[31] | 1992–2012 | 57 | 61 | 55 | 50 | NR | 93 | NR | NR | ‡ | 2116 | OS-5,10 | 0.1–0.9 mm, 1–9 mm, ≥ 10 mm |
| Scheele et al[20] | 1960–1992 | 52.7 | 59 | NR | 40.6 | NR | NR | NR | C: 189, R: 161 | † | 350 | OS-5<br>DFS-5 | 1–9 mm, ≥10 mm |
| Seifert et al[51] | 1985–1996 | 59.16 | 58.9 | 17 | 50.1 | NR | NR | NR | C: 80, R: 40 | NR | 44 | OS-5 | <1 cm, ≥1 cm |
| Truant et al[11] | 2000–2010 | NR | 62.7 | 43 | 56.8 | 66.9 | 60 | 2.8 | C: 204, R: 69 | † | 214 | OS-5<br>DFS-5 | <10 mm, 10 mm |
| Tsai et al[32] | 1995–2004 | 59.3 | 60.3 | 28.5 | 62.2 | 0 | 100 | 2 | C: 118, R: 37 | NR | 155 | OS-5<br>DFS-5 | ≥1 cm, <1 cm |

**TABLE 1.** (*Continued*)

| Ref. | Study Period | Males (%) | Age (Mean or Median) | Follow-up (mo, Median or Mean) | Synchronous Hepatic Metastases (%) | Neoadjuvant (%) | Adjuvant (%) | Number of Metastases [Median or Mean (Range)] | Location of the Primary Site | Definition of R0/R1 Resection Margins | R0 Patients with Data on Margins | Type of Survival Outcome Studied (in y) | Compared Categories in the Original Study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| van Ooijen et al[34] | 1979–1989 | 60.1 | 57 | NR | 33.1 | NR | NR | NR | C: 70, R: 48 | NR | 82 | DFS-5 | <1 cm, >1 cm |
| Vandeweyer et al[50] | 1992–2007 | 62.5 | 64 | 56.4 | 43.5 | NR | NR | NR | C: 158, R: 103 | ‡ | 233 | OS-1,3,5 DFS-1,3,5 | 0–1 mm, >1–<4 mm, 4–<10 mm, 10 mm // 1–10 mm, >= 10 mm // ≤ 1 mm, >1 mm |
| Wakai et al[35] | 1989–2004 | 71.1 | 64 | 127 | 38.9 | 0 | 67.7 | NR | C: 55, R: 35 | * | 80 | OS-1,3,5,10 DFS-1,3,5,10 | ≥1 cm, <1 cm |
| Yamamoto et al[27] | 1992–1994 | 66.67 | NR | 37.6 | 29.2 | NR | NR | NR | C: 61, R: 34, C + R: 1 | NR | 79 | OS-1 | ≤1 cm, >1 cm |

C indicates colon; DFS, disease-free survival; NR, not reported; OS, overall survival; R, rectum; RFS, recurrence-free survival.
*R1 resection was defined as the presence of tumor cells on the transection line (0 mm).
†R1 resection was defined as the presence of tumor cells <1 mm from the transection line.
‡Separate data were collected regarding both alternative definitions.
§R1 resection was defined as the presence of tumor cells <0.5 mm from the transection line.

## Sensitivity Analyses

Three post hoc sensitivity analyses were conducted. A post hoc sensitivity analysis that retained only the studies in which specific attention was paid to pathology review, confirmed our main finding (improved 5-year OS for patients who underwent a resection with a margin width >1 cm, RR = 0.92, 95% CI: 0.86–0.97) (Supplemental Table 10, http://links.lww.com/SLA/B333). A subgroup analysis including studies published from 2001 onwards replicated the key findings, while a sensitivity analysis excluding data from Johns Hopkins University also did not modify the results (Supplemental Tables 8 and 9, http://links.lww.com/SLA/B333, respectively).

## Evaluation of Quality of Studies and Risk of Bias

An evaluation of the quality of the included studies is presented in Supplemental Table 6, http://links.lww.com/SLA/B333 and Supplemental Figure 6, http://links.lww.com/SLA/B333. As evidenced by the relevant ratings, the quality of eligible studies was mainly compromised by the lack of comparability of factors that may independently influence survival. Importantly, however, the majority of studies met our stated criteria regarding the assessment of outcome and appropriate follow-up. Publication bias was not significant in the analysis examining 5-year survival ($P = 0.894$ and $P = 0.186$ for OS and DFS, respectively, Egger test).

# DISCUSSION

In the current meta-analysis, we demonstrated that an R0 resection with a margin width >1 cm was associated with both improved DFS and OS compared with an R0 resection with narrower margins. Importantly, our findings suggest that while a >1 mm margin is associated with better prognosis than a submillimeter margin, achieving a margin >1 cm may result in even better oncologic outcomes and should be considered if possible. Interestingly, in the case of OS, this observation was independent of the specific definition of R1 employed by each individual study; moreover, potential confounders were accounted for through the meta-regression analysis. Our findings are important because available retrospective studies have produced conflicting results regarding the prognostic implications of margin width, while a randomized trial in this setting is not feasible.[6–11,37,52,53] In particular, the controversies in previous studies and expert recommendations have generally been attributed to limited sample size, failure to adjust for modern chemotherapy regimens, varying definitions of resection margin clearance, and different surgical transection techniques.[31] The current study was largely able to transcend these limitations, through the use of meta-analysis and meta-regression, the total pooled study population consisted of 11,147 patients and the analysis accounted for possible confounders, including chemotherapy; furthermore, both widely used definitions of R1 resection were examined in a subgroup analysis. To enhance the originality of the present study, we also incorporated currently available patient data from Johns Hopkins University reflecting our center's practice; importantly, a sensitivity analysis excluding our data did not affect the results thus emphasizing the robustness of the documented associations.

Although previous meta-analyses have attempted to address the question of optimal margin width, their findings and methodologies were far from uniform. For example, Cucchetti et al[55] in 2012 included 11 studies and a pooled population of 2823 patients in their meta-analysis; around the same time (2011), another meta-analysis included 18 studies and a total of 4821 patients.[54] Although these meta-analyses were, by far, the most comprehensive to date, relatively limited sample sizes and significant discrepancies in the included patient populations rendered the interpretation challenging. Perhaps more importantly, the findings of these 2 studies were also

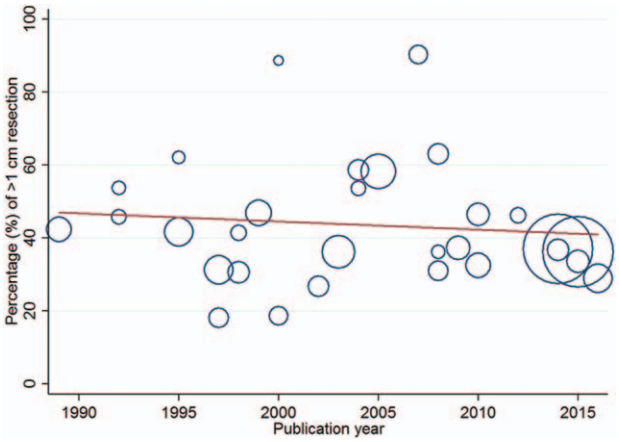


**FIGURE 2.** Percentage of >1 cm resections per publication year.

substantially different. Specifically, while Dhir et al[54] demonstrated that a margin width greater than 1 cm improved prognosis, Cucchetti et al[55] reported that a >1 cm margin width was not associated with improved OS. Much controversy has surrounded these disparate conclusions and their implications; however, the need to revisit the issue of optimal margin width in light of recent developments is not controversial. Six additional relevant studies reporting on a total of 5,797 patients have been published since the time that Dhir et al[54] conducted their meta-analysis[10,11,21,31,36,43]; the 2 largest studies among them concluded that a 1 mm margin is sufficient and that a more extensive clearance does not improve survival, thus directly challenging Dhir et al.[21,31] In the current meta-analysis, every attempt was made to synthesize all relevant information available in the scientific literature at the time of our search; furthermore, previously unpublished data from Johns Hopkins University regarding a large series of 467 patients were also included. The large size of our study population served to increase the power of our analysis, compared with previous studies.

It should also be noted that previous meta-analyses failed to account for the impact of modern chemotherapy regimens on the prognostic implications of margin width.[54] This methodological limitation is important, as it has been postulated that chemotherapy may "sterilize" tumor margins and, in turn, minimize the adverse prognostic effect of a positive or narrow negative margin.[56] In fact, Kok et al[57] questioned the findings of the study by Dhir et al,[54] first because Dhir et al[54] did not take into account the administration of (neo) adjuvant chemotherapy that commonly differs between studies and second because they used odds ratios to quantify the impact of margin width on survival. Of note, in our study, we performed an extensive meta-regression analysis that accounted for the influence of potential confounding factors such as publication year, sex, patient age, synchronous presentation of hepatic metastases, administration of neoadjuvant and adjuvant treatment, primary cancer site, and number of hepatic metastatic lesions. [57] Furthermore, we elected to express our findings in the

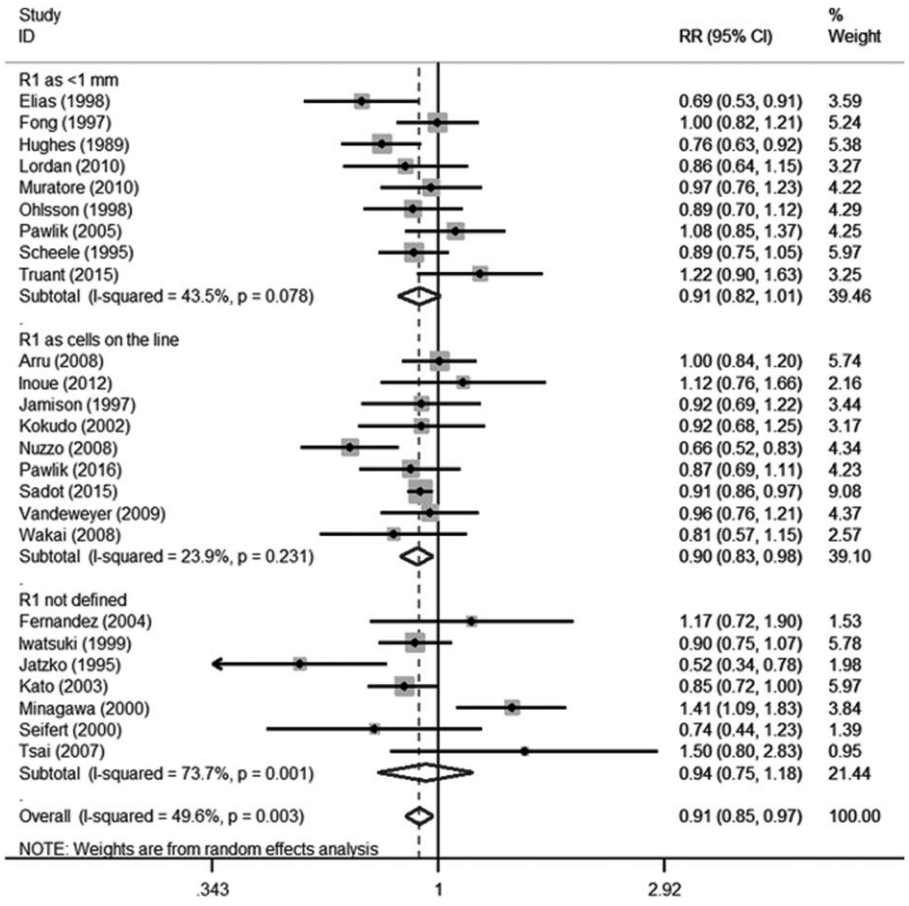


**FIGURE 3.** Five-year overall survival analysis according to margin width (>1 vs <1 cm). Studies that provide data for both definitions of R1 (margin width <1 mm and presence of cells on the transection line) were assigned to the cells on the transection line category.

**TABLE 2.** Results of the Meta-analyses Examining the Association Between Overall and Disease-free Survival (OS, DFS) and Margin Width (>1 vs <1 cm)

| | Overall Survival | | | Disease-free Survival | | |
|---|---|---|---|---|---|---|
| | n* | RR (95% CI) | Heterogeneity $I^2$, *P* | n* | RR (95% CI) | Heterogeneity $I^2$, *P* |
| Total studies | | | | | | |
| 1-y | 9 | 0.87 (0.60–1.27) | 9.9%, 0.353 | 7 | 0.85 (0.70–1.03) | 46.8%, 0.080 |
| 3-y | 12 | **0.86 (0.79–0.95)** | 5.6%, 0.390 | 9 | **0.93 (0.86–1.00)**‡ | 28.0%, 0.196 |
| 5-y | 25 | **0.91 (0.85–0.97)** | 49.6%, 0.003 | 18 | **0.88 (0.81–0.96)** | 73.6%, 0.000 |
| 10-y | 7 | **0.94 (0.88–1.00)**† | 51.5%, 0.054 | 5 | **0.95 (0.91–0.99)** | 0%, 0.410 |
| Studies defining R1 as distance <1 mm from transection line | | | | | | |
| 1-y | 2 | 1.02 (0.56–1.84) | 0%, 0.398 | 3 | **0.83 (0.73–0.95)** | 0%, 0.995 |
| 3-y | 2 | 0.99 (0.62–1.60) | 70.4%, 0.066 | 3 | 0.93 (0.84–1.04) | 36.9%, 0.205 |
| 5-y | 9 | 0.91 (0.82–1.01) | 43.5%, 0.078 | 6 | **0.92 (0.86–0.99)** | 40.4%, 0.136 |
| 10-y | 1 | **0.92 (0.85–0.99)** | nc | 1 | 0.98 (0.92–1.03) | nc |
| Studies defining R1 as tumor cells on the transection line | | | | | | |
| 1-y | 6 | 0.77 (0.44–1.37) | 34.4%, 0.178 | 4 | 0.78 (0.49–1.25) | 72.2%, 0.013 |
| 3-y | 6 | **0.85 (0.75–0.96)** | 0%, 0.674 | 4 | 0.90 (0.76–1.08) | 49.8%, 0.113 |
| 5-y | 9 | **0.90 (0.83–0.98)** | 23.9%, 0.231 | 5 | 0.77 (0.58–1.04) | 88.3%, 0.000 |
| 10-y | 4 | **0.92 (0.89–0.94)** | 0%, 0.587 | 2 | **0.92 (0.85–0.99)** | 0%, 0.438 |
| Studies where R1 definition was not stated | | | | | | |
| 1-y | 1 | 0.44 (0.02–8.08) | nc | 0 | No studies | No studies |
| 3-y | 4 | **0.84 (0.71–0.99)** | 17.4%, 0.304 | 2 | 0.94 (0.79–1.11) | 26.4%, 0.244 |
| 5-y | 7 | 0.94 (0.75–1.18) | 73.7%, 0.001 | 7 | 0.93 (0.82–1.06) | 46.0%, 0.085 |
| 10-y | 2 | 1.08 (0.89–1.32) | 68.4%, 0.075 | 2 | 0.95 (0.82–1.10) | 36.7%, 0.209 |

In studies providing data with both definitions, the analysis defining R1 resection as the presence of tumor cells on the transection line (0 mm) was preferred.
CI indicates confidence interval; nc, not calculable; RR, relative risk.
*Number of study arms.
†$P = 0.050$.
‡$P = 0.042$.
$P < 0.05$ for all bold values, unless otherwise specified.

form of RRs. RRs are more appropriate for cohort studies, such as those included in the present meta-analysis, compared with ORs that mainly pertain to case-control studies.[58] Importantly, the RR is known to be more statistically "conservative" than the odds ratio.

Lastly, previous meta-analyses also failed to address the inconsistent nature of existing definitions of microscopically positive margins. Specifically, some studies defined a positive margin as tumor infiltration of the transection line (margin width: 0 mm), while others as the presence of tumor cells within 1 mm of the transection line.[31,59] As such, previous comparisons of the 1 cm versus the <1 cm margin width groups (excluding patients with positive margins), may or may not have included the 0 to 1 mm group depending on the definition used. Given that both definitions are commonly employed (n = 12 vs 7) and that Sadot et al[31] recently demonstrated that a sub – mm (0 to 1 mm) resection margin confers a different prognosis compared with a 0 mm margin, different definitions of R1 may complicate the interpretation of studies comparing R0 to R1, as well as those comparing different margin widths among patients with R0 resection. To this end, this is the first meta-analysis on OS, (and, to our knowledge, the first study in general) to explicitly compare the implications of margin width by employing both widely accepted R1 definitions. Indeed, RRs were similar among studies that defined R1 as the presence of viable cells on the transection margin and studies that defined R1 as the presence of tumor cells within 1 mm from the margin. Perhaps more importantly, we performed an additional subanalysis to directly evaluate the prognostic impact of a 0 to 1 mm margin width. Using data from all studies that included sufficient relevant information as well as unpublished data from JHU, we assigned patients to the <1 and >1 cm groups by employing both R1 definitions (margin width = 0 mm vs margin width <1 mm). Consistent with our overall results, the RR for 5-year OS was shown to be in favor of a >1 cm resection, irrespective of the definition used; RR for >1 cm versus 0–10 mm, 0.92 (0.87 to 0.97) and RR for >1 cm versus 1 to 10 mm, 0.94 (0.88 to 0.99).

**TABLE 3.** Results of the Meta-analyses Examining the Association Between Overall and Disease-free Survival (OS, DFS) and Margin Width (>1 vs <1 mm)

| | Overall Survival | | | Disease-free Survival | | |
|---|---|---|---|---|---|---|
| | n* | RR (95% CI) | Heterogeneity $I^2$, *P* | n* | RR (95% CI) | Heterogeneity $I^2$, *P* |
| Total studies | | | | | | |
| 1-y | 4 | **0.48 (0.29–0.78)** | 0%, 0.443 | 3 | 0.81 (0.62–1.06) | 0%, 0.726 |
| 3-y | 4 | **0.77 (0.63–0.93)** | 24.3%, 0.265 | 3 | 0.92 (0.76–1.13) | 42.8%, 0.174 |
| 5-y | 5 | **0.80 (0.72–0.88)** | 25%, 0.255 | 3 | 0.90 (0.80–1.00)† | 0%, 0.502 |
| 10-y | 3 | **0.95 (0.92–0.99)** | 0%, 0.803 | 1 | 0.97 (0.91–1.04) | nc |

CI indicates confidence interval; nc, not calculable; RR, relative risk.
*Number of study arms.
†$P = 0.056$.
$P < 0.05$ for all bold values, unless otherwise specified.

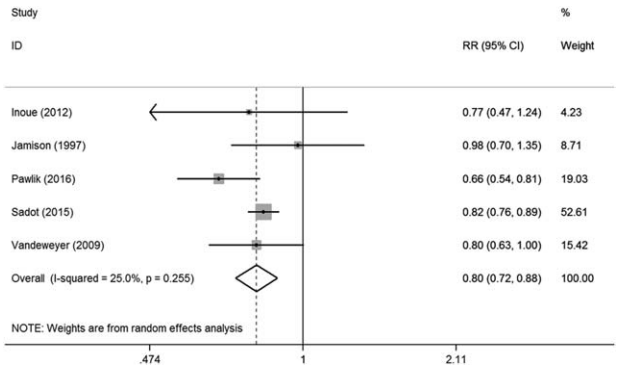


**FIGURE 4.** Five-year overall survival analysis according to margin width (>1 vs <1 mm).

All studies investigating the impact of surgical margin width on long-term outcomes have some intrinsic limitations. In particular, meta-analytic methodology presupposes a relative uniformity in the effects of the studied intervention; nonetheless, there are instances where the effectiveness of an intervention may vary systematically, rather than randomly, as a result of biologic disparities in the treatment population.[60] There is sufficient reason to believe that for our study, the effectiveness of the treatment (surgical margin width) may indeed vary according to patient characteristics (ie, tumor biology) that could not be adjusted for in the meta-regression analysis. In fact, our group previously demonstrated that while a 1 to 4 mm margin width was associated with optimal prognosis in CRLM patients with KRAS wild-type tumors, margin width was not prognostic among patients with KRAS mutated tumors; in fact, a 1 to 4 mm margin width or even a >1 cm margin width was shown to be equivalent to microscopically positive margins in terms of OS.[61,62]

The unrestricted use of several distinct transection methods may also limit the comparability of different studies. In fact, it has been repeatedly reported that certain transection techniques (such as the CUSA and TissueLink) may distort the margin edge by aspirating or ablating a few mm of surrounding hepatic tissue; as such, pathologic assessment may tend to underestimate margin width and overestimate the frequency of R1 resections in such cases.[37] The timing and techniques of the pathologic analysis also vary in practice and should ideally be accounted for in our analysis; however, relevant information from the included studies was largely lacking. Furthermore, it should be noted that the heterogeneity among the included studies ranged from moderate to substantial. The included studies reported on patients treated over a large period of time (approximately 50 years), a fact that enhances the statistical power of the analysis; however, it also contributes to heterogeneity, as paradigm-shifting changes in patient selection, surgical techniques, and systemic therapy have occurred over the examined time period. Ideally, a patient-level analysis concentrating on individuals treated in the modern period could help to answer whether these changes in clinical practice have affected the impact of surgical margin width on survival; however, none of the included studies provided patient-level information and only 2 reported on cohorts that were exclusively treated after 2000. Although a subgroup analysis of studies published from 2001 onwards replicated our key findings, additional research on the prognostic impact of surgical margin in the contemporary era is needed. Another potential limitation of our study is that, similarly to the previously published meta-analysis, there was no contact with authors of studies excluded as a result of inadequate data reporting; on the one hand, this led to a smaller pool of analyzable data that was potentially prone to publication bias, but on the other hand, it avoided the use of unpublished data that may suffer from lack of validity and quality, as they have not undergone peer review.[54] Notably, we were ultimately able to harness sufficient statistical power to detect significant associations. In cases where less than 10 study arms were included in the meta-regression analysis, the results of the latter should be deemed explorative and interpreted with caution

In spite of attempts to explore heterogeneity through sensitivity analyses, we were unable to fully account for its presence. In turn, this might reflect heterogeneity in treatment protocols (surgical techniques and postoperative treatments), as well as the unequal distribution of factors that may modify the impact of surgical margin width in different study populations (eg, tumor biology, bevacizumab administration, response to chemotherapy, etc). Consequently, our findings should be viewed as providing a general recommendation on the ideal margin to be accomplished, when more specific information is not readily available. For example, the response to preoperative bevacizumab or the mutational status of a patient's tumor may not be available in resource-limited settings; under such circumstances, surgeons operate under the same constraints as the present analysis and may, on average, achieve improved outcomes by striving for a margin of >1 cm.

In conclusion, this is an adequately powered meta-analysis, reporting on more than 11,000 patients from 34 studies highlighting the impact of margin width on survival following R0 hepatic resection for CRLM. Furthermore, the inclusion of previously unpublished data from 467 patients who underwent surgery at Johns Hopkins Hospital served to enhance the scope of our analysis. We demonstrated that a margin >1 cm was associated with better OS as well as DFS; these results with regard to OS remained significant irrespective of the R0/R1 definition employed. The association of a >1 mm margin width with improved OS also emerged. Furthermore, possible modifying factors, such as the administration of chemotherapy, did not seem to affect the associations between margin status and survival. Consequently, our results underscore the value of obtaining a >1 cm surgical margin when feasible.

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