ORIGINAL ARTICLE

Influence of Margins on Disease Free Survival Following Hepatic Resection for Colorectal Metastasis: A Meta-Analysis

Mashaal Dhir · Elizabeth R. Lyden · Lynette M. Smith · Chandrakanth Are

Abstract The aim of our study was to conduct a meta-analysis of reports published on hepatic resection for colorectal liver metastases (CRLM) and determine if a negative margin ≥1 cm confers a disease free survival (DFS) advantage over sub-centimeter negative margins. The 357 initially selected articles were screened to identify 90 articles of interest of which eleven were finally included in the meta-analysis. Patients with positive margins were excluded from the meta-analysis. Meta-analysis was performed using STATA 9.2 statistical software. A total of 1,989 patients with negative margins from the eleven studies were included in the meta-analysis. The 5-year DFS for all patients was 27.9 % (95 % CI 23.5 % to 32.2 %). The 5-year DFS for ≥1 cm negative margin subgroup was 34.4 % (95 % CI 27.97 % to 40.7 %) when compared to 21.0 % (95 % CI 17.4 % to 24.7 %) for <1 cm negative margin subgroup. The odds ratio for ≥1 cm negative margins was found to be 0.552 (95 % CI 0.408 to 0.747, $p<0.001$) when compared to <1 cm negative margins. The results of this meta-analysis demonstrate that in patients undergoing hepatic resection for CRLM, a negative margin ≥1 cm may confer a better DFS compared with a sub-centimeter negative margin.

M. Dhir · C. Are
Department of Surgery, Division of Surgical Oncology,
Eppley Cancer Center, University of Nebraska Medical Center,
Omaha, NE, USA

E. R. Lyden · L. M. Smith
Department of Epidemiology and Biostatistics,
College of Public Health, University of Nebraska Medical Center,
Omaha, NE, USA

C. Are (✉)
Division of Surgical Oncology, Department of Surgery/Genetics,
Cell Biology and Anatomy,
University of Nebraska Medical Center,
Omaha, NE 68198, USA
e-mail: care@unmc.edu

Introduction

Hepatic resection remains a well accepted modality in the treatment of patients with colorectal liver metastases (CRLM) with 5 year overall survival (OS) ranging from 37 % to 58 % [1–4] and 5 year disease free survival (DFS) ranging from 11 % to 50 % [3, 5–14]. Recurrence of the disease after resection still remains a challenge and adversely affects the long term outcomes. Most of the factors associated with recurrence are related to the biology of the disease including primary tumor stage, disease free interval of less than 12 months, preoperative carcinoembryonic antigen (CEA) levels, number & size of metastatic tumors and presence of extra-hepatic disease [2, 15].

Surgical resection margin is also considered to be an additional prognostic factor. Although there is a consensus that positive margins portend a worse DFS as compared to negative margins, the extent of negative margins remains controversial. Several studies have documented a DFS advantage of ≥1 cm negative margins over <1 cm negative margins of resection [5, 8, 10, 13]. Whereas others have concluded that the width of negative margin has no influence on DFS [3, 6, 7, 9–11, 14]. Many authors have argued that tumor biology rather than the extent of surgical margin determines outcomes in these patients and the debate continues. Most of the data is derived either from single institutional studies or from select few multi-institutional studies. In such a scenario a meta-analysis may help provide useful clinical data.

It has been recently shown that in patients undergoing hepatic resection for CRLM a negative margin ≥1 cm confers an OS advantage when compared to sub-centimeter negative margins [16]. The aim of the current study was to

perform a meta-analysis of studies published on CRLM (using surgical resection as a primary mode of treatment) to determine if negative resection margin of ≥1 cm confers a DFS advantage over negative resection margin of <1 cm.

Materials and Methods

Search Strategy and Inclusion/Exclusion Criteria

Articles in PubMed database from 1966 to the present were searched using the key words 1) "Colorectal metastases" AND ["Liver resection" OR "Hepatic resection"] 2) Search 1 AND "margins". The search was restricted to articles published in English language. We identified 357 articles with some overlap between the two categories. A backward search was also performed using cross references from the bibliographies of relevant articles and review articles to ensure a comprehensive search. Figure 1 depicts the search strategy in detail.

The following articles were excluded from the analysis

1. Review articles/Letters
2. Articles analyzing patients with recurrent hepatic metastases only
3. Articles including patients with non colorectal hepatic metastases
4. Articles including patients mainly treated with ablation therapies such as cryotherapy, radiofrequency ablation or chemoembolization
5. Articles comparing patients who underwent resection, to patients who underwent no treatment or non-resectional treatment

In order to select relevant and high quality articles we further sub-stratified our inclusion criteria into absolute and relative inclusion criteria.

Absolute criteria for inclusion were as follows:

1. Inclusion of margin of resection as a variable in outcome analysis
2. Calculation of percentage 5-year DFS with margin of resection as a variable
3. Sub-categorization of negative margins into sub-centimeter (with or without additional sub-groups) and more than a centimeter sub-groups

Studies should meet at least 70 % (5 out of 7) of the relative criteria which were defined as:

1. Clear statement of study hypothesis
2. Clear statement of the main outcome of the study
3. Description of the demographic characteristics of the study population
4. Description of operative mortality

5. Description of length of follow up
6. Description of percentage of patients who were lost to follow up

Full texts were reviewed for 90 articles. Duplicate publications by the authors on the same dataset i.e. patients operated during the same duration, were excluded [17, 18]. In such cases the most recent publication of the authors was included in the analysis [7, 11].

Data Extraction and Definitions

Estimates of 5-year DFS and the number of patients (including patients in each margin sub-category) were extracted from the studies (texts or tables). Patients with positive margins were excluded from the current meta-analysis and only patients with negative margins were included. Many studies sub-stratified sub-centimeter negative margins into different sub-categories [4, 8, 10]. For these studies, a weighted mean was calculated using the number of patients in each sub-category and the corresponding percentage survival, to compute percentage survival for the whole <1 cm negative margin sub-group. Some studies [3, 5–7] categorized negative margins as "≤1 cm and >1 cm" while others [4, 8–14] used "<1 cm and ≥1 cm" for negative margins. For the purpose of meta-analysis ≤1 cm and <1 cm were treated as "<1 cm" and > 1 cm or ≥1 cm were treated as "≥1 cm". Such sub-categorization was performed due to lack of individual patient data. This will lead to misclassification of some patients with exactly 1 cm margins into "<1 cm sub-category" and will bias our meta-analysis towards good outcome in <1 cm margins. However, it appeared to be the more conservative approach. This approach was chosen as it will increase the power and precision of our meta-analysis by allowing us to include more studies. Meta-analysis was performed using the number of patients with evidence of recurrent disease vs. patients who were disease free at 5-years in the "<1 cm" and "≥ 1 cm" subgroups.

Statistical Methods

Meta-analysis was performed using STATA 9.2 statistical software (StataCorp, 4905 Lakeway drive, College Station, Texas). All data were treated as binary (Disease free vs. evidence of recurrent disease at 5 years, <1 cm vs. ≥1 cm). An estimate of the number of patients who were disease free at 5 years was calculated by multiplying the total number of patients in <1 cm and ≥ 1 cm sub-categories included in the study by the corresponding 5 year DFS estimate. Odds ratios and 95 % confidence intervals computed from the binary data were used for the final meta-analysis. Random effects model was used due to our suspicion of heterogeneity amongst

Fig. 1 Meta-analysis flow
diagram depicting selection
methodology for the eligible
studies
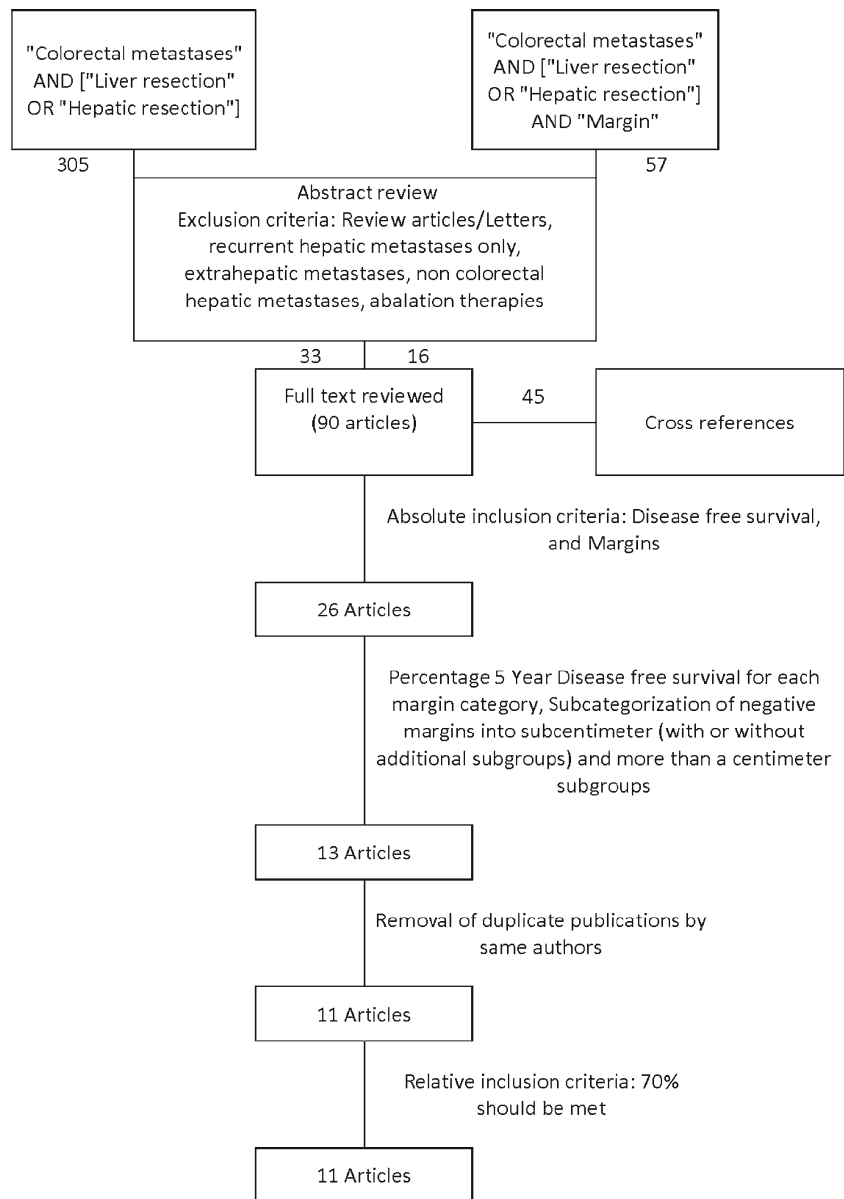
different studies. Heterogeneity was explored using the chi-squared test with a significance level of $p=0.10$. I^2 was calculated to further quantify heterogeneity. Publication bias was explored using funnel plots and symmetry of the funnel plot was analyzed using objective tests such as Egger and Begg tests.

Results

After the application of the absolute inclusion criteria, relative inclusion criteria and removal of duplicate publications, 11 studies [3, 5–14] were included in the meta-analysis. Table 1 summarizes the study characteristics of the final 11 studies included in the meta-analysis. All studies were retrospective analyses. A total of 1,989 patients with

negative margins from the eleven studies were included in the meta-analysis with individual studies contributing 58 to 259 patients. Median or mean age for most of the studies was in 50's or 60's with majority reporting a mean or median follow up period of at least 2 years. Table 2 summarizes the different studies, number of patients with data on negative margins and estimates of disease free survival in each individual study. Estimates of the 5-year DFS ranged from 11 % to 28 % for the <1 cm negative margin subgroup and 20 % to 42 % for the ≥1 cm subgroup.

The 5-year DFS for all patients was 27.9 % (95 % CI 23.5 % to 32.2 %). The 5-year DFS for ≥1 cm negative margin subgroup was 34.4 % (95 % CI 27.97 % to 40.7 %) when compared to 21.0 % for <1 cm negative margin subgroup (95 % CI 17.4 % to 24.7 %).

Table 1 Important characteristics of studies included in the meta-analysis

First author	Year	Type of study	Number of patients	Number of patients with data on negative margins	Age	Substratification of margins	Duration of follow up
Muratore et al.	2009	Retrospective, January 1999 to December 2007	314	259	Mean age 62.8 years (95 % CI 61.7–63.9)	Negative <=1 cm, Negative >1 cm	Mean- 39.8 months
Vandeweyer et al.	2009	Retrospective, February 1992 to December 2007	261	194	Median age 64 years	Positive, 0-1 mm, >1 mm-<4, 4-<10 mm, >=10 mm	Median - 4.7 years
Nuzzo et. al	2008	Retrospective study from a Prospective database, January 1992–December 2005	185	174	Mean age 61 years (range 32–81 years)	Positive, Negative (<=2 mm, 3-5 mm, 6-9 mm, >=10 mm)	Mean - 39 months
Wakai et. al.	2008	Retrospective, January 1989–December 2004	90	80	Median age 64 years (range 32–80 years)	0 (Positive), <1 cm, >=1 cm	Median - 127 months
Hamady ZZR et al.	2006	Retrospective, January 1993 and December 2001	293	187	Mean age 61 years (range 38–80 years)	Positive, Negative (=1 mm vs >1 mm, 1–2 mm vs >2 mm, 1–5 mm vs >5 mm, 1–10 mm vs. >10 mm	Minimum −29 months
Kokudo et al.	2002	Retrospective, January1, 1980 to December 31, 2000	194	183	Mean age 59 years (range 35 to 82 years)	Negative <2 mm, 2–4 mm, 5–9 mm and >=10 mm)	Median −29.1 months
Minagawa et. al.	2000	Retrospective 1980 to 1997	235	145	Median age 59.2 years (range 30–80 years)	Unknown, <1 cm, >=1 cm	Median −28 months, mean- 43 months
Iwatsuki et al.	1999	Retrospective, Year 1981 to 1996	305	277	Mean ± S.E. (60±0.6 years) range 26 to 82 years	Positive (involved), >1 cm, <=1 cm	Median - 32 months
Scheele et al.	1995	Retrospective, 1960 to 1992	434	350	Median age 59 years (range 26–91 years)	1–9 mm, >=10 mm	All patients followed up to Nov of 1993. Median duration of follow up not specified
Cady et al.	1992		142	58	Median 61 years (range 31–80 years)	Positive, Negative >=1 cm, Negative < 1 cm, unknown	Minimum − 12 months
van Ooijen et al.	1991	Retrospective, 1979 to 1989	118	82	Median age 57 (range 28–83 years)	Positive, <1 cm, >1 cm	Median - 18 months

Table 2 Summary of data on disease free survival for studies included in the meta-analysis

First author	Patients with data on negative margins	< 1 cm				≥ 1 cm			
		n	One-year DFS (%)	Three-year DFS (%)	Five-year DFS (%)	n	One-year DFS (%)	Three-year DFS (%)	Five-year DFS (%)
Muratore et al.	259	175	–	30.2	23.5	84	–	37.3	28.2
Vandeweyer et al.	194	107	58	28	20	87	64	41	29
Nuzzo et. al[a]	174	64	–	–	11.4	110	–	–	41.6
Wakai et. al	80	51	–	–	19	29	–	–	40
Hamady ZZR et al.	187	129	–	–	28	58	–	–	31
Kokudo et al.[a]	183	134	62	34.2	24.3	49	78.3	50.1	50.1
Minagawa et. al.	145	118	–	30	24	27	–	27	27
Iwatsuki et al.	277	147	–	30.2	22.5	130	–	38.5	28.9
Scheele et al.	350	204	–	38	28	146	–	46	33
Cady et al.	58	33	–	–	18	25	–	–	50
van Ooijen et al.	82	38	–	–	13	44	–	–	20

[a] For these studies different sub-centimeter sub-categories were pooled to compute percentage survival for "< 1 cm subgroup"

Meta-Analysis and Publication Bias

All Studies

The odds ratio for ≥1 cm negative margins was found to be 0.552 (95 % CI 0.408 to 0.747, $p<0.001$) when compared to <1 cm negative margins (Fig. 2a). A statistically significant improvement in 5 year DFS was seen in patients with negative margins ≥1 cm compared to patient with <1 cm negative margins. There was statistically significant heterogeneity amongst the studies ($p=0.051$) and the contribution of heterogeneity to variation in odds ratio was 45.2 %. Publication bias was tested using Funnel plots (Fig. 2b) and multiple tests including egger test (Coef. = −2.538, Std. Err. = 1.211, $t=-2.1$, $p=0.066$) and begg test (adj. Kendall's score=−23, Std dev.=12.85, $z=-1.79$, $p=0.073$). Although these tests do not rule out publication bias in its entirety, it appears that publication bias in the selected studies is less prominent.

Studies with Sample Size of More Than 100 Patients

A subset analyses for the 8 studies with sample size more than 100 patients was performed (Fig. 3). Again a statistically significant improvement in 5 year DFS was seen in patients with ≥1 cm negative margin compared to <1 cm negative margin (Odds ratio 0.597, 95 % CI 0.427 to 0.837, $p=0.003$). There was a statistically significant heterogeneity amongst the studies ($p=0.040$) and the contribution of heterogeneity to the variation in odds ratio was 52.3 %. Publication bias was tested using egger test (Coef. = −3.183, Std. Err. = 2.144, $t=-1.48$, $p=0.188$) and

begg test (adj. Kendall's score=−10, Std dev.=8.08, $z=-1.24$, $p=0.216$) suggesting that the chances of publication bias were minimal.

Recent Studies Published After Year 2000

Since the meta-analysis included studies spanning over a period of 20 years we elected to perform a subset analyses of studies published in the last 10 years and 5 years respectively, as most of the advances in the surgical techniques and adjuvant therapies have occurred recently (Fig. 4a and b). There were 7 studies [3, 6, 8–10, 12, 13] published in the last 10 years and 5 studies [3, 6, 10, 12, 13] published in the last 5 years. These analyses also revealed a better DFS in patients with ≥1 cm margin compared to <1 cm negative margin and this was found to be statistically significant (Studies in the last 10 years: Odds ratio 0.509, 95 % CI 0.329 to 0.787, $p=0.002$, heterogeneity 56.2 %, heterogeneity $p=0.033$; Studies in the last 5 years: Odds ratio 0.506, 95 % CI 0.294 to 0.872, $p=0.014$, heterogeneity 62.8 %, heterogeneity $p=0.029$).

Discussion

Recurrence is an important deterrent to the long term survival of patients with CRLM who undergo hepatic resection. Several clinic-pathologic factors have been shown to affect DFS but the surgical margins remains one of the unique prognostic factors as it could be influenced by the surgeon and the surgical technique. Some studies have found a DFS

Fig. 2 a Meta-analysis of in-
fluence of surgical margin on
disease free survival after he-
patic resection of colorectal
metastases: all 11studies. (Odds
ratios were calculated using the
random effects model. *Large
diamond* at the bottom repre-
sents the overall effect of nega-
tive margins on the disease free
survival. *Small diamonds* em-
bedded in squares represent the
individual study effects with
95 % confidence intervals rep-
resented by the horizontal bars).
b Funnel plot for meta-analysis
of 11 studies depicting one no-
tably outlier study
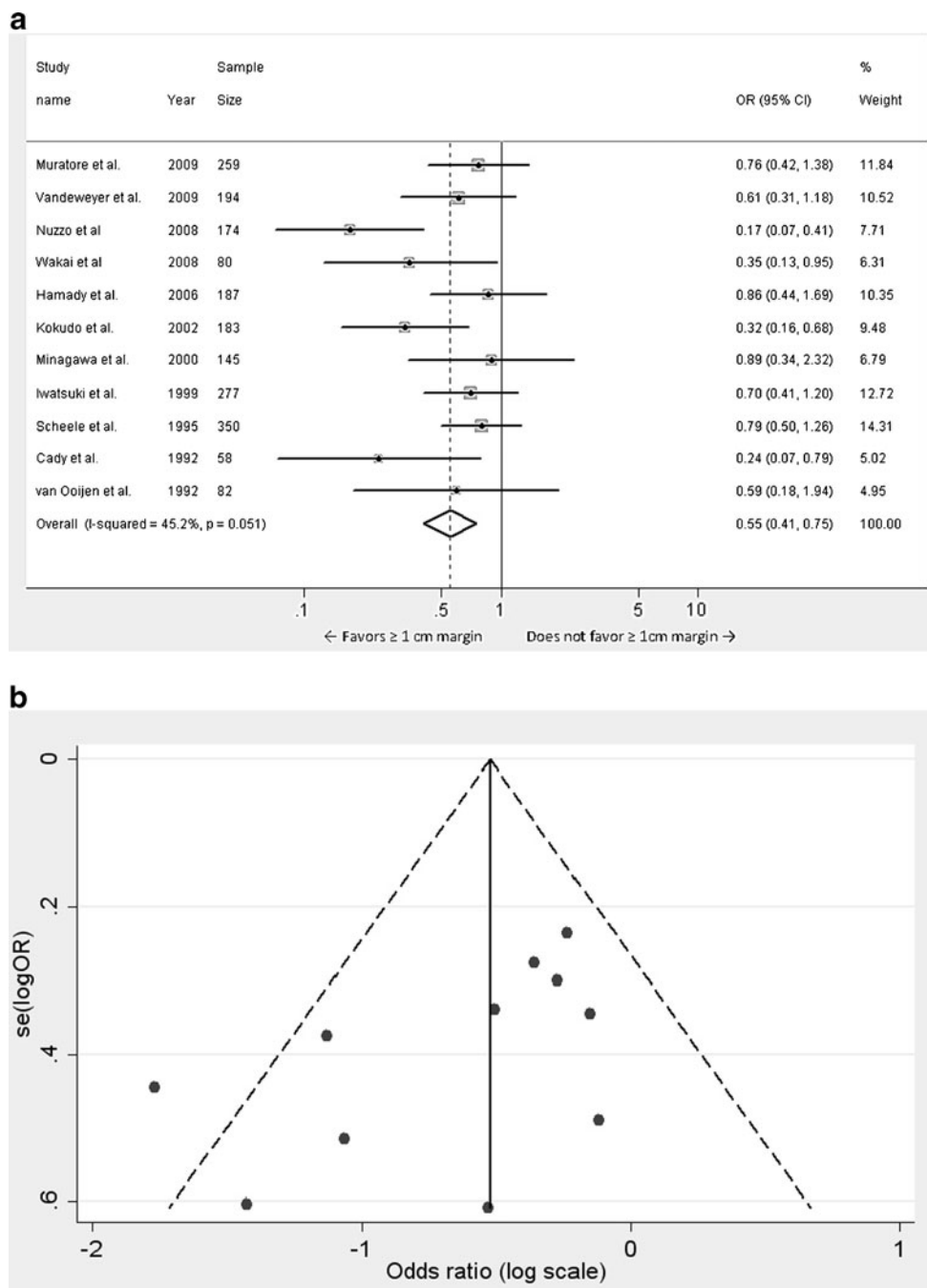
advantage of 1 cm margin [5, 8, 10, 13] whereas other studies have refuted the notion concluding that width of the negative surgical margin does not significantly influence the DFS [3, 6, 7, 9, 11, 12, 14]. However, most of the studies are either small or are from single institutions and therefore an informative conclusion is difficult to derive. Meta-analysis is a statistical tool which synthesizes the effects of smaller studies to estimate the true effect of a clinical inter-vention and provide the best available clinical evidence [19]. The aim of the current meta-analysis was to investigate if negative resection margins of ≥1 cm confer any DFS

advantage over negative resection margins of <1 cm. To our knowledge this is the earliest meta-analysis on the subject with data on a large number of patients.

Our results show that a negative margin of ≥ 1 cm may have advantage of disease free survival over a sub-centimeter margin of resection. This was further tested using various subgroups such as studies with sample size of > 100, studies from last 10 years and 5 years. The uniformity of this survival benefit across the spectrum of analyses demon-strates robustness of our meta-analysis. A recent study has shown the OS advantage of ≥1 cm negative margins over

Fig. 3 Meta-analysis of influence of surgical margin on disease free survival after hepatic resection of colorectal metastases: studies with sample size of more than 100 patients. (Odds ratios were calculated using the random effects model. *Large diamond* at the bottom represents the overall effect of negative margins on the disease free survival. *Small diamonds* embedded in squares represent the individual study effects with 95 % confidence intervals represented by the horizontal bars)
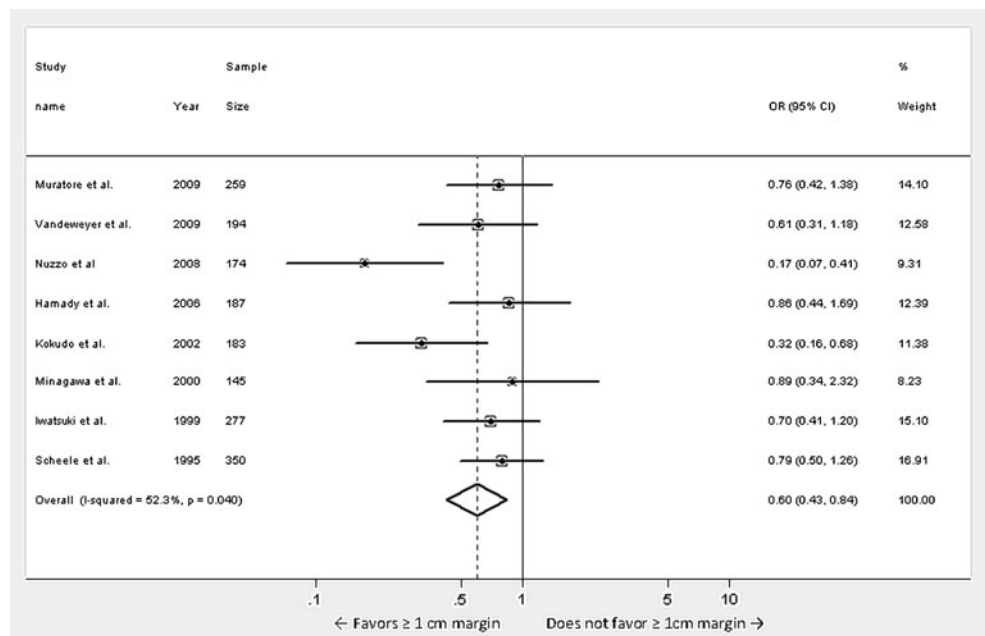
sub-centimeter negative margins [16]. However, the exact reasons for the beneficial effect of margin status on DFS remain unclear. Wakai et al. have previously shown that 95 % of the intra-hepatic micro-metastases occur within 1 cm of the tumor deposits and there are a median of 4 micro-metastases per patient [13]. Therefore a 1 cm margin should help remove 95 % of the micro-metastases. Their results were different from Kokudo et al. who also analyzed the presence of the micro-metastases in the surrounding liver parenchyma using genetic and histologic methods and found micro-metastases to be rare (2 %) [8]. However micro-metastases through the Glisson pedicle were more common (14.3 %) and were located within 5 mm of the tumor edge. Based on these findings and other data the authors recommended a minimum margin of 2 mm (sub-centimeter margin) as an acceptable margin. Although different tumor biology may account for the differences in the findings of Wakai et al. and Kokudo et al. but since both the studies are from the same region a different methodology may better explain the differences in the incidence and location of micrometastases as well as the recommended margins by the authors.

Some authors have hypothesized that if margins truly affect the DFS, most of the recurrences should occur locally at the site of resected tumor. Studies by Muratore et al., Pawlik et al. and Nuzzo et al. have shown that most of the recurrences regardless of the margin width are either extra-hepatic or at other intra-hepatic sites away from the resection end [3, 4, 10]. Interestingly, in the study by Kokudo et al. resection end recurrences although most common in patients with <2 mm surgical margin, were only seen in patients with up to 9 mm surgical margin and no such recurrences were seen in patient with ≥1 cm margin. In spite

of these elegant studies, biological reasons for the beneficial effect of ≥1 cm margin on DFS still remains unclear and are beyond the purview of this analytical article.

Our study has several strengths. The current meta-analysis reflects good methodology. An extensive pubmed search using different relevant terms was performed along with backward search using references from the relevant articles, with well defined inclusion and exclusion criteria to include high quality and relevant studies, elimination of overlapping or duplicate studies, and extensive description of summary measures and results. Additionally, random effects model was used to account for heterogeneity of different studies and several subset analyses were performed to verify the results and rule out publication bias.

In spite of these strengths there are several limitations some of which have been discussed previously [16]. Meta-analysis is only as good as the studies included in it and there is a chance that inspite of our rigorous efforts some relevant studies might have been missed. The meta-analysis approach based on odds ratio is not as accurate as the one based on individual patient data and hazards ratio [20]. Procurement of individual patient data is very difficult and time consuming. Only 4 studies [6, 10, 13, 17] calculated hazard ratios for the margins and only one study had hazard ratios for sub-centimeter and ≥1 cm negative margins [13], making this approach difficult to use. Therefore, odds ratio based approach was found to be the most feasible and used in the current study. This approach although not as accurate as the individual patient data and hazard ratio based approach, has been used previously [21, 22].

The included studies in the current meta-analyses span over a period of 20 years during which many advances have been made in chemotherapy and resection techniques. We

Fig. 4 a Meta-analysis of influence of surgical margin on disease free survival after hepatic resection of colorectal metastases: studies published after the year 2000. b Meta-analysis of influence of surgical margin on disease free survival after hepatic resection of colorectal metastases: studies published after the year 2005. (Odds ratios were calculated using the random effects model. *Large diamond* at the bottom represents the overall effect of negative margins on the disease free survival. *Small diamonds* embedded in squares represent the individual study effects with 95 % confidence intervals represented by the horizontal bars)
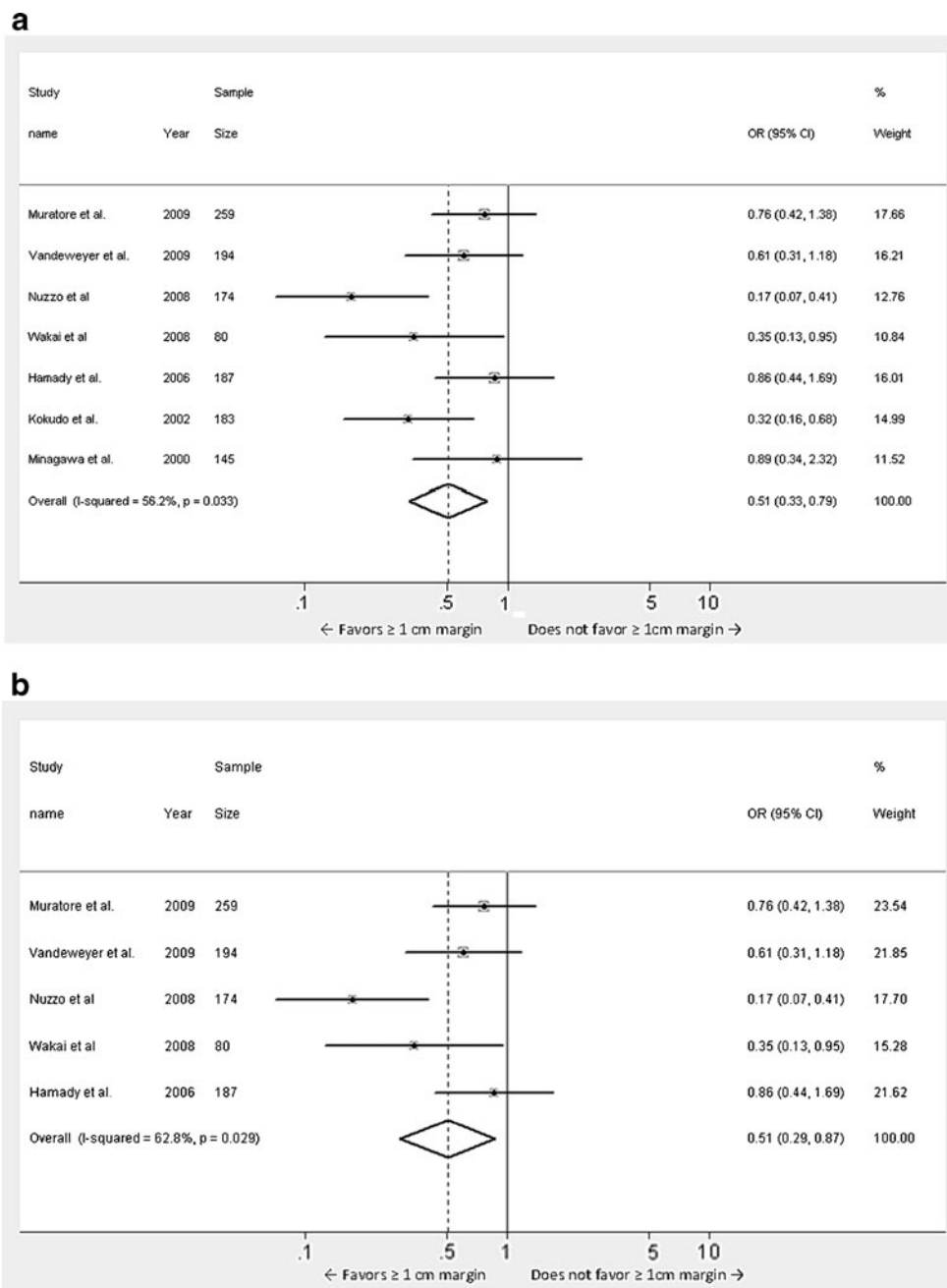
tried to minimize these effects by performing a subset analyses of studies over the last 10 and 5 years however a direct analysis of the effect of these factors have not been performed due to small number of studies and different chemotherapy regimens used. The influence of modern chemotherapy and newer resection techniques will require further studies. In the absence of any randomized controlled trial our meta-analysis may represent a comprehensive analysis of the impact of margins on DFS following hepatic resection for CRLM. The results of our work are reinforced by the simultaneous report by Cucchetti et al. [23]. Although performed independently, the similarity of our results to those of Cucchetti et al. demonstrates the beneficial influence of margins on DFS following hepatic resection for CRLM.

In conclusion, results of our meta-analysis demonstrate that there may be a DFS advantage of ≥1 cm negative margins over subcentimeter negative margins in patients undergoing hepatic resection for CRLM. Striving to achieve ≥1 cm margin should not preclude resection or compromise the safety of operation, as subcentimeter margins are also associated with a favorable disease fee survival. Since randomized controlled trial may not be feasible, this meta-analysis may represent a comprehensive analysis of the

influence of margins on disease free survival following hepatic resection for CRLM.

References

1. Are C, Gonen M, Zazzali K, Dematteo RP, Jarnagin WR, Fong Y, Blumgart LH, D'Angelica M (2007) The impact of margins on outcome after hepatic resection for colorectal metastasis. Ann Surg 246(2):295–300

2. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230(3):309–318, discussion 318–321

3. Muratore A, Ribero D, Zimmitti G, Mellano A, Langella S, Capussotti L (2010) Resection margin and recurrence-free survival after liver resection of colorectal metastases. Ann Surg Oncol 17 (5):1324–1329

4. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A, Mentha G, Capussotti L, Vauthey JN (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 241(5):715–722, discussion 722–714

5. Cady B, Jenkins RL, Steele GD Jr, Lewis WD, Stone MD, McDermott WV, Jessup JM, Bothe A, Lalor P, Lovett EJ, Lavin P, Linehan DC (1998) Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. Ann Surg 227 (4):566–571

6. Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP (2006) Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1 cm rule. Eur J Surg Oncol 32(5):557–563

7. Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, Geller DA, Gayowski TJ, Fung JJ, Starzl TE (1999) Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 189(3):291–299

8. Kokudo N, Miki Y, Sugai S, Yanagisawa A, Kato Y, Sakamoto Y, Yamamoto J, Yamaguchi T, Muto T, Makuuchi M (2002) Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 137(7):833–840

9. Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura H (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231(4):487–499

10. Nuzzo G, Giuliante F, Ardito F, Vellone M, Giovannini I, Federico B, Vecchio FM (2008) Influence of surgical margin on type of recurrence after liver resection for colorectal metastases: a single-center experience. Surgery 143(3):384–393

11. Scheele J, Stang R, Altendorf-Hofmann A, Paul M (1995) Resection of colorectal liver metastases. World J Surg 19(1):59–71

12. Vandeweyer D, Neo EL, Chen JW, Maddern GJ, Wilson TG, Padbury RT (2009) Influence of resection margin on survival in hepatic resections for colorectal liver metastases. HPB (Oxford) 11 (6):499–504

13. Wakai T, Shirai Y, Sakata J, Valera VA, Korita PV, Akazawa K, Ajioka Y, Hatakeyama K (2008) Appraisal of 1 cm hepatectomy margins for intrahepatic micrometastases in patients with colorectal carcinoma liver metastasis. Ann Surg Oncol 15(9):2472–2481

14. van Ooijen B, Wiggers T, Meijer S, van der Heijde MN, Slooff MJ, van de Velde CJ, Obertop H, Gouma DJ, Bruggink ED, Lange JF et al (1992) Hepatic resections for colorectal metastases in The Netherlands. A multiinstitutional 10-year study. Cancer 70(1):28–34

15. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 77(7):1254–1262

16. Dhir M, Lyden ER, Wang A, Smith LM, Ullrich F, Are C (2011) Influence of margins on overall survival following hepatic resection for colorectal liver metastasis: a meta-analysis. Ann Surg 254 (2):234–242

17. Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, Starzl TE (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 116(4):703–710, discussion 710–701

18. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP (1991) Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 110(1):13–29

19. Mosteller F, Colditz GA (1996) Understanding research synthesis (meta-analysis). Annu Rev Public Health 17:1–23

20. Michiels S, Piedbois P, Burdett S, Syz N, Stewart L, Pignon JP (2005) Meta-analysis when only the median survival times are known: a comparison with individual patient data results. Int J Technol Assess Health Care 21(1):119–125

21. Gurusamy KS, Imber C, Davidson BR (2008) Management of the hepatic lymph nodes during resection of liver metastases from colorectal cancer: a systematic review. HPB Surg 2008:684150

22. Zhou Y, Zhao Y, Li B, Xu D, Yin Z, Xie F, Yang J (2010) Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. BMC Gastroenterol 10(1):78

23. Cucchetti A, Ercolani G, Cescon M, Bigonzi E, Peri E, Ravaioli M, Pinna AD (2012) Impact of subcentimeter margin on outcome after hepatic resection for colorectal metastases: a meta-regression approach. Surgery. doi:10.1016/j.surg.2011.12.009