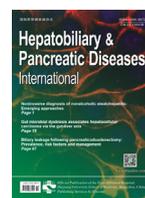




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Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Meta-analysis

Survival after repeat hepatectomy for recurrent colorectal liver metastasis: A review and meta-analysis of prognostic factors

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ARTICLE INFO

Article history:

Received 27 September 2018

Accepted 12 February 2019

Available online 22 February 2019

Keywords:

Colorectal cancer

Metastasectomy

Prognosis

Meta-analysis

ABSTRACT

Background: Frequent recurrent hepatic metastasis after hepatic metastasectomy is a major obstacle in the treatment of colorectal liver metastasis (CRLM). We performed the present systematic review to evaluate the short- and long-term outcomes after repeat hepatectomy for recurrent CRLM and determine factors associated with survival in these patients.

Data sources: An electronic search of PubMed database was undertaken to identify all relevant peer-reviewed papers published in English between January 2000 and July 2018. Hazard ratios (HR) with 95% confidence interval (95% CI) were calculated for prognostic factors of overall survival (OS).

Results: The search yielded 34 studies comprising 3039 patients, with a median overall morbidity of 23% (range 8%–71%), mortality of 0 (range 0–6%), and 5-year OS of 42% (range 17%–73%). Pooled analysis showed that primary T3/T4 stage tumor (HR = 1.94; 95% CI: 1.04–3.63), multiple tumors (HR = 1.49; 95% CI: 1.10–2.01), largest liver lesion ≥ 5 cm (HR = 1.89; 95% CI: 1.11–3.23) and positive surgical margin (HR = 1.80; 95% CI: 1.09–2.97) at initial hepatectomy, and high serum level of carcinoembryonic antigen (HR = 1.87; 95% CI: 1.27–2.74), disease-free interval ≤ 12 months (HR = 1.34; 95% CI: 1.10–1.62), multiple tumors (HR = 1.64; 95% CI: 1.32–2.02), largest liver lesion ≥ 5 cm (HR = 1.85; 95% CI: 1.34–2.56), positive surgical margin (HR = 2.25; 95% CI: 1.39–3.65), presence of bilobar disease (HR = 1.62; 95% CI: 1.19–2.20), and extrahepatic metastases (HR = 1.60; 95% CI: 1.23–2.09) at repeat hepatectomy were significantly associated with poor OS.

Conclusions: Repeat hepatectomy is a safe and effective therapy for recurrent CRLM. Long-term outcome is predicted mainly by factors related to repeat hepatectomy.

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Introduction

Hepatectomy represents a potentially curative treatment for colorectal liver metastases (CRLM), resulting in a 5-year overall survival (OS) rate of 40%–60%. Following resection, more than 60% patients may experience disease recurrence, which is independently associated with a significantly inferior OS [1]. Approximately 30% of recurrent metastases were isolated to the liver. Many centers have demonstrated the therapeutic value of repeat hepatectomy as the main curative option for treating recurrent CRLM [2–11]. Nonetheless, most published reports were conducted in a single institution with a small sample size, thus limiting their external validity and generalizability. The present systematic review was to evaluate the short- and long-term outcomes after repeat hepatectomy for recurrent CRLM and analyze the prognostic factors for OS.

Methods

This systematic review and meta-analysis was carried out in accordance with the Preferred Reporting Items for systematic reviews and meta-analyses statement [12].

Systematic search strategy

An electronic search of PubMed database was undertaken to identify all related peer-review papers published in English between January 2000 and July 2018 with MeSH search terms (colorectal liver metastases; recurrence; repeat hepatectomy; repeat hepatic resection; repeat liver resection; hepatectomy). The reference lists of retrieved articles were reviewed for additional citations.

Criteria for inclusion and exclusion

Only studies reporting the results of 5-year OS or factors that may predict survival of recurrent CRLM patients

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Table 1
The characteristics of the included studies.

Studies	Year	Period of inclusions	Country	IH (n)	IHR after IH	RH (n)	Resectability	M/F ^a	Age ^a (yr) ^b	PC ^a	AD ^a
Suzuki et al. [2]	2001	1980–1999	Japan	96	43%	26	63%	17/9	55	–	–
Petrowsky et al. [3]	2002	1985–2001	Two countries ^c	1362	–	126	–	63/63	62	–	54%
Adam et al. [4]	2003	1984–2000	France	615	–	199	–	–	–	91%	–
Takahashi et al. [5]	2003	1992–2001	Japan	120	40%	22	46%	–	–	–	0
Tanaka et al. [6]	2004	1985–2000	Japan	193	45%	26	30%	–	–	–	48%
Sugawara et al. [7]	2005	1991–2001	Japan	106	54%	27	47%	22/5	59	–	33%
Ishiguro et al. [8]	2006	1985–2004	Japan	–	–	111	–	74/37	59	–	–
Pessaux et al. [9]	2006	1992–2002	France	168	–	42	–	25/17	64	67%	–
Shaw et al. [10]	2006	1987–2005	UK	784	–	66	–	40/26	61	–	–
Yan et al. [11]	2006	1991–2005	Australia	382	–	55	–	31/24	62	–	–
Nishio et al. [14]	2007	1993–2004	UK	540	–	54	–	34/20	61	11%	24%
Sa Cunha et al. [15]	2007	1985–2000	France	311	45%	40	29%	27/13	63	13%	38%
Thelen et al. [16]	2007	1988–2006	Germany	811	–	94	–	–	–	–	36%
Brachet et al. [17]	2009	1992–2007	France	–	–	62	–	39/23	62	61%	61%
de Jong et al. [18]	2009	1982–2008	Four countries ^d	1706	–	246	–	165/81	60	–	66%
Andreou et al. [19]	2011	1993–2009	USA	–	–	43	–	31/12	55	44%	63%
Adair et al. [20]	2012	1993–2010	UK	–	–	195	–	138/57	63	27%	–
Jones et al. [21]	2012	1998–2008	USA	405	37%	52	35%	21/31	56	77%	–
Jönsson et al. [22]	2012	1995–2009	Sweden	240	–	32	–	20/12	64	31%	36%
Rolf et al. [23]	2012	1996–2010	Denmark	–	–	24	–	13/11	52	–	–
Kulik et al. [24]	2013	1994–2010	Germany	1026	–	94	–	60/34	58	–	–
Neeff et al. [25]	2013	1999–2011	Germany	–	–	80	–	56/24	–	88%	–
Wicherts et al. [26]	2013	1990–2010	France	933	–	288	–	190/98	57	56%	68%
Yamazaki et al. [27]	2013	2004–2011	Japan	268	–	37	–	–	67	57%	–
Battula et al. [28]	2014	1998–2011	UK	969	–	53	–	29/24	63	6%	–
Saiura et al. [29]	2014	1999–2008	Japan	287	–	73	–	–	–	–	–
Ali et al. [30]	2015	2001–2013	Italy	116	–	30	–	19/11	62	33%	93%
Lee et al. [31]	2015	1994–2009	Korea	461	–	55	–	36/19	58	–	91%
Hallet et al. [32]	2016	2006–2013	France	2324	30%	447	64%	281/166	61	69%	50%
Denbo et al. [33]	2017	2006–2013	USA	–	–	98	–	63/35	–	93%	–
Dupré et al. [34]	2017	2010–2015	UK	366	–	31	–	24/7	63	42%	–
Fukami et al. [35]	2017	1994–2015	Japan	282	–	62	–	44/18	63	–	40%
Nanji et al. [36]	2017	2002–2009	Canada	1310	–	78	–	53/25	56	60%	63%
Neal et al. [37]	2017	2001–2010	UK	488	47%	71	31%	49/22	–	11%	28%
Total (median, range)					44% (30%–54%)		41% (29%–63%)		61 (52–67)	56% (6%–93%)	49% (0–93%)

IH: initial hepatectomy; IHR: intrahepatic recurrence; RH: repeat hepatectomy; M: male; F: female; PC: preoperative chemotherapy; AD: adjuvant chemotherapy.

^a Patients underwent RH.

^b Mean or median.

^c Germany and USA.

^d USA, Italy, Switzerland, and Belgium.

undergoing curative-intent resection were considered eligible. Experimental studies, studies reporting outcomes of patients who underwent local ablation (cryotherapy, radiofrequency or microwave ablation) other than surgical resection at the time of first treatment or at recurrence of CRLM, studies reporting outcomes of patients who had a two-stage hepatectomy for initially unresectable CRLM, abstracts, editorials, expert opinions, and studies with fewer than 20 patients were excluded.

Data extraction and quality assessment

Data extraction and critical appraisal were independently performed by two authors. Extracted data included first author, year of publication, study period, sample size, patient demographics, mortality, morbidity, OS, and prognostic factors for OS. For studies in which the 1-, 3- and 5-year OS rates were not given directly, the information was derived from the reported survival graphs. The quality of each study was classified according to the Oxford Centre for Evidence-based Medicine Levels of Evidence, ranging from level 1 to level 5 [13]. Discrepancies between the two reviewers were resolved by discussion and consensus.

Statistical analysis

Data are presented as median (range) unless otherwise stated. The meta-analysis was conducted using Review Manager (RevMan), version 5.3 software (The Cochrane Collaboration, Software Update, Oxford). A random-effects model using the hazard ratios (HR) with

95% confidence interval (95% CI) from univariate analysis or multivariate analysis obtained from each study was calculated for the prognostic factors of OS: a HR > 1 represents worse outcome for the test category versus the reference category. Heterogeneity between studies was assessed with a χ^2 test and I^2 , with significance set at $P < 0.1$.

Results

Fig. 1 shows the process of identifying articles for review. The initial search strategy yielded 2268 studies, of which 34 publications including a total of 3039 patients undergoing repeat hepatectomy met the inclusion criteria and were included for analysis [2–11,14–37]. All studies were retrospective nature and classified as level 4 evidence. Table 1 summarizes the characteristics of the analyzed studies. The median (range) age at time of repeat hepatectomy was 61 (52–67) years with a pooled male/female ratio of 1:0.56. A laparoscopic approach was used in one study with four patients overall [35], and the rest was open surgery.

Table 2 summarizes the surgical outcomes after repeat hepatectomy. The median (range) overall morbidity and mortality were 23% (8%–71%) and 0 (0–6%), respectively. The median follow-up period ranged from 17 to 61 months. Median (range) OS was 38 (19–80) months, with 1-, 3-, and 5-year survival of 91% (70%–98%), 56% (26%–82%), and 42% (17%–73%), respectively.

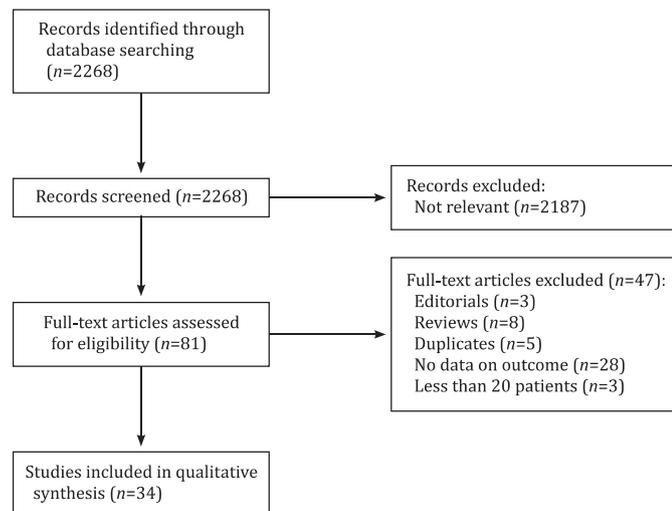
The data regarding third and fourth hepatectomies were limited. Twenty-two articles reported a third hepatectomy involving a total of 361 patients [2,4,5,7–10,14,17–21,24–28,34–37].

Table 2

The surgical outcomes after repeat hepatectomy.

Studies	No. of patients	R0 resection	MH	Mortality	Morbidity	Median follow-up (months)	MOS (months)	1-year OS	3-year OS	5-year OS
Suzuki et al. [2]	26	96%	12%	0	27%	–	31	81%	62%	32%
Petrowsky et al. [3]	126	79%	29%	2%	28%	59	37	86%	51%	34%
Adam et al. [4]	199	88%	59%	3%	23%	32	–	88%	54%	35%
Takahashi et al. [5]	22	77%	9%	0	18%	23	23	82%	49%	49%
Tanaka et al. [6]	26	–	–	0	30%	21	32	70%	48%	48%
Sugawara et al. [7]	27	96%	26%	0	22%	43	41	83%	68%	49%
Ishiguro et al. [8]	111	84%	12%	0	14%	43	43	91%	74%	41%
Pessaux et al. [9]	42	–	–	0	14%	–	25	74%	37%	21%
Shaw et al. [10]	66	–	21%	0	18%	32	56	94%	68%	44%
Yan et al. [11]	55	–	–	0	29%	30	53	94%	62%	49%
Nishio et al. [14]	54	46%	15%	6%	19%	–	50	89%	53%	46%
Sa Cunha et al. [15]	40	88%	28%	3%	43%	31	32	93%	55%	31%
Thelen et al. [16]	94	85%	48%	3%	23%	–	27	89%	55%	38%
Brachet et al. [17]	62	95%	24%	0	18%	–	35	–	–	31%
de Jong et al. [18]	246	90%	21%	1%	21%	–	42	91%	52%	33%
Andreou et al. [19]	43	86%	12%	0	12%	33	–	96%	82%	73%
Adair et al. [20]	195	48%	17%	2%	20%	–	25	91%	44%	29%
Jones et al. [21]	52	–	21%	2%	27%	19	19	84%	26%	17%
Jönsson et al. [22]	32	–	–	0	71%	–	–	93%	54%	40%
Rolff et al. [23]	24	92%	–	0	24%	–	–	95%	47%	42%
Kulik et al. [24]	94	94%	16%	0	10%	–	48	–	–	–
Neeff et al. [25]	80	79%	35%	3%	53%	61	60	97%	62%	50%
Wicherts et al. [26]	288	61%	17%	2%	34%	45	44	–	58%	41%
Yamazaki et al. [27]	37	–	–	0	25%	–	–	92%	52%	36%
Battula et al. [28]	53	89%	19%	0	8%	32	45	85%	61%	52%
Saiura et al. [29]	73	–	–	–	–	–	–	95%	75%	67%
Ali et al. [30]	30	77%	40%	0	–	25	–	93%	56%	45%
Lee et al. [31]	55	100%	–	0	11%	39	–	93%	59%	43%
Hallet et al. [32]	447	–	26%	1%	29%	17	–	94%	78%	57%
Denbo et al. [33]	98	88%	22%	–	–	35	35	–	69%	44%
Dupré et al. [34]	31	–	26%	0	39%	36	33	93%	52%	22%
Fukami et al. [35]	62	89%	13%	1%	12%	–	80	98%	80%	57%
Nanji et al. [36]	78	–	31%	6%	–	50	45	91%	57%	45s
Neal et al. [37]	71	62%	17%	1%	21%	–	38	–	53%	22%
Total (median, range)		88% (46%–100%)	21% (9%–59%)	0 (0–6%)	23% (8%–71%)	33 (17–61)	38 (19–80)	91% (70%–98%)	56% (26%–82%)	42% (17%–73%)

MH: major hepatectomy; OS: overall survival; MOS: median OS.

**Fig. 1.** Selection of articles for review.

Data were available on morbidity in six studies with a median (range) value of 26% (19%–33%) [2,4,9,17,18,27]. Data were available on mortality in 18 studies with a median (range) value of 0 (0–8%) [2,4,5,7–10,14,17–19,24–28,34,37]. Data were available on median OS in six studies with a median (range) value of 42 (16–52) months [9,17,18,24,26,37]. Data were available on 5-year survival in six studies with a median (range) value of 35% (24%–45%) [4,9,17,18,26,27].

Twelve articles reported a fourth hepatectomy involving a total of 42 patients [7,9,10,14,17,18,20,24–26,35,37]. There were no peri-operative deaths. Data were available on morbidity in four studies with a median (range) value of 34% (0–50%) [9,17,18,24]. One study reported median OS of 19 months [18]. None of these studies presented data on 1-, 3-, and 5-year survival.

The results of the meta-analysis for prognostic variables after repeat hepatectomy are shown in Table 3.

Four studies [3,16,25,32] including 747 patients reported primary T3/T4 stage tumor as a prognostic factor (HR = 1.94; 95% CI: 1.04–3.63). Heterogeneity between studies was low and not significant ($I^2 = 39%$, $P = 0.18$; Fig. 2A).

Four studies [3,17,24,37] including 353 patients reported multiple tumors at initial hepatectomy as a prognostic factor (HR = 1.49; 95% CI: 1.10–2.01). There was no significant heterogeneity between studies ($I^2 = 0$, $P = 0.93$; Fig. 2B).

Five studies [3,17,19,24,37] including 396 patients reported largest liver lesion ≥ 5 cm at initial hepatectomy as a prognostic factor (HR = 1.89; 95% CI: 1.11–3.23). However, there was significant heterogeneity between studies ($I^2 = 57%$, $P = 0.06$; Fig. 2C), indicating high levels of inconsistency of effect for this outcome.

Five studies [3,17,19,30,37] including 332 patients reported positive surgical margin at initial hepatectomy as a prognostic factor (HR = 1.80; 95% CI: 1.09–2.97). Heterogeneity between studies was moderate and not significant ($I^2 = 15%$, $P = 0.32$; Fig. 3A).

Six studies [14,17,18,26,32,37] including 1168 patients reported high serum level of carcinoembryonic antigen at repeat hepatectomy as a prognostic factor (HR = 1.87; 95% CI: 1.27–2.74). There was no statistical heterogeneity between studies ($I^2 = 5%$, $P = 0.38$; Fig. 3B).

Table 3
Meta-analysis of prognostic factors.

Variables	No. of studies	No. of patients	HR (95% CI)	P value	I ²
Sex: male/female	6 [3,16,17,30,36,37]	461	1.01 (0.76, 1.34)	0.97	0
Age: old/young	6 [3,16,17,24,36,37]	525	0.85 (0.48, 1.51)	0.59	78%
Primary tumor					
Site: rectum/colon	7 [3,16–18,30,32,37]	1076	1.09 (0.85, 1.39)	0.52	0
Stage:T3–T4/T1–T2	4 [3,16,25,32]	747	1.94 (1.04, 3.63)	0.04	39%
Lymph nodes: positive/negative	6 [3,16,17,30,32,37]	830	1.29 (0.98, 1.71)	0.07	0
Initial hepatectomy					
Serum CEA level: high/low	3 [5,17,37]	155	1.93 (0.88, 4.26)	0.10	32%
Synchronous metastasis: yes/no	7 [3,8,16–18,30,31]	724	1.18 (0.96, 1.46)	0.12	0
No. of liver lesion: >1 /1	4 [3,17,24,37]	353	1.49 (1.10, 2.01)	0.01	0
Largest liver lesion: ≥5/<5 cm	5 [3,17,19,24,37]	396	1.89 (1.11, 3.23)	0.02	57%
Tumor margin: positive/negative	5 [3,17,19,30,37]	332	1.80 (1.09, 2.97)	0.02	15%
Bilobar disease: yes/no	3 [24,30,37]	195	1.29 (0.81, 2.06)	0.29	10%
Anatomical resection: yes/no	2 [17,37]	133	1.52 (0.89, 2.58)	0.13	20%
Major hepatectomy: yes/no	5 [3,16,24,30,37]	415	1.07 (0.79, 1.45)	0.66	0
Adjuvant chemotherapy: no/yes	3 [3,17,37]	259	1.24 (0.88, 1.75)	0.23	0
Repeat hepatectomy					
Serum CEA level: high/low	6 [14,17,18,26,32,37]	1168	1.87 (1.27, 2.74)	0.001	5%
Disease-free interval: ≤12/>12 months	10 [3,7,15,16,24,28,30,32,36,37]	1060	1.34 (1.10, 1.62)	0.003	75%
No. of liver lesion: >1 /1	11 [3,16,17,19,24,30–33,36,37]	1198	1.64 (1.32, 2.03)	<0.001	0
Largest liver lesion: ≥5/<5 cm	7 [3,14,16,20,24,36,37]	712	1.85 (1.34, 2.56)	<0.001	21%
Tumor margin: positive/negative	6 [3,14,16,17,26,37]	695	2.25 (1.39, 3.65)	0.001	51%
Bilobar disease: yes/no	6 [3,16,24,28,30,37]	468	1.62 (1.19, 2.20)	0.002	0
Extrahepatic metastases: yes/no	6 [7,15,18,28,32,37]	884	1.60 (1.23, 2.09)	<0.001	28%
Anatomical resection: yes/no	2 [17,37]	133	1.32 (0.76, 2.29)	0.32	0
Major hepatectomy: yes/no	6 [16,18,24,28,33,37]	656	1.37 (0.95, 1.97)	0.09	45%
Adjuvant chemotherapy: no/yes	4 [3,17,18,37]	505	1.22 (0.87, 1.72)	0.25	0

HR: hazard ratio; CI: confidence interval; OS: overall survival.

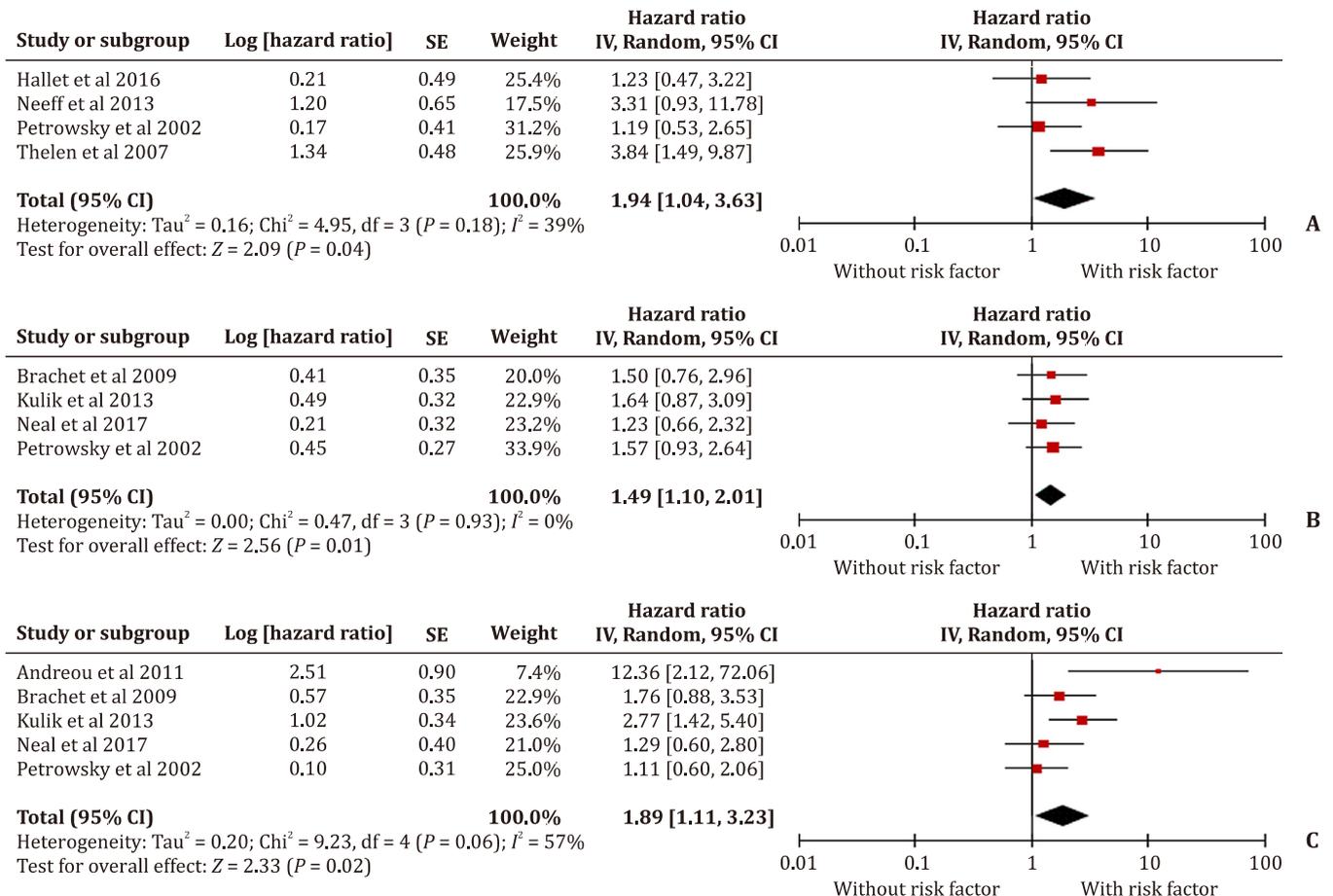


Fig. 2. Forest plot showing effect of T3/T4 primary tumor (A), multiple tumors (B) and largest liver lesion ≥5 cm (C) at initial hepatectomy on overall survival. Square: HR; diamond: pooled HR for all studies.

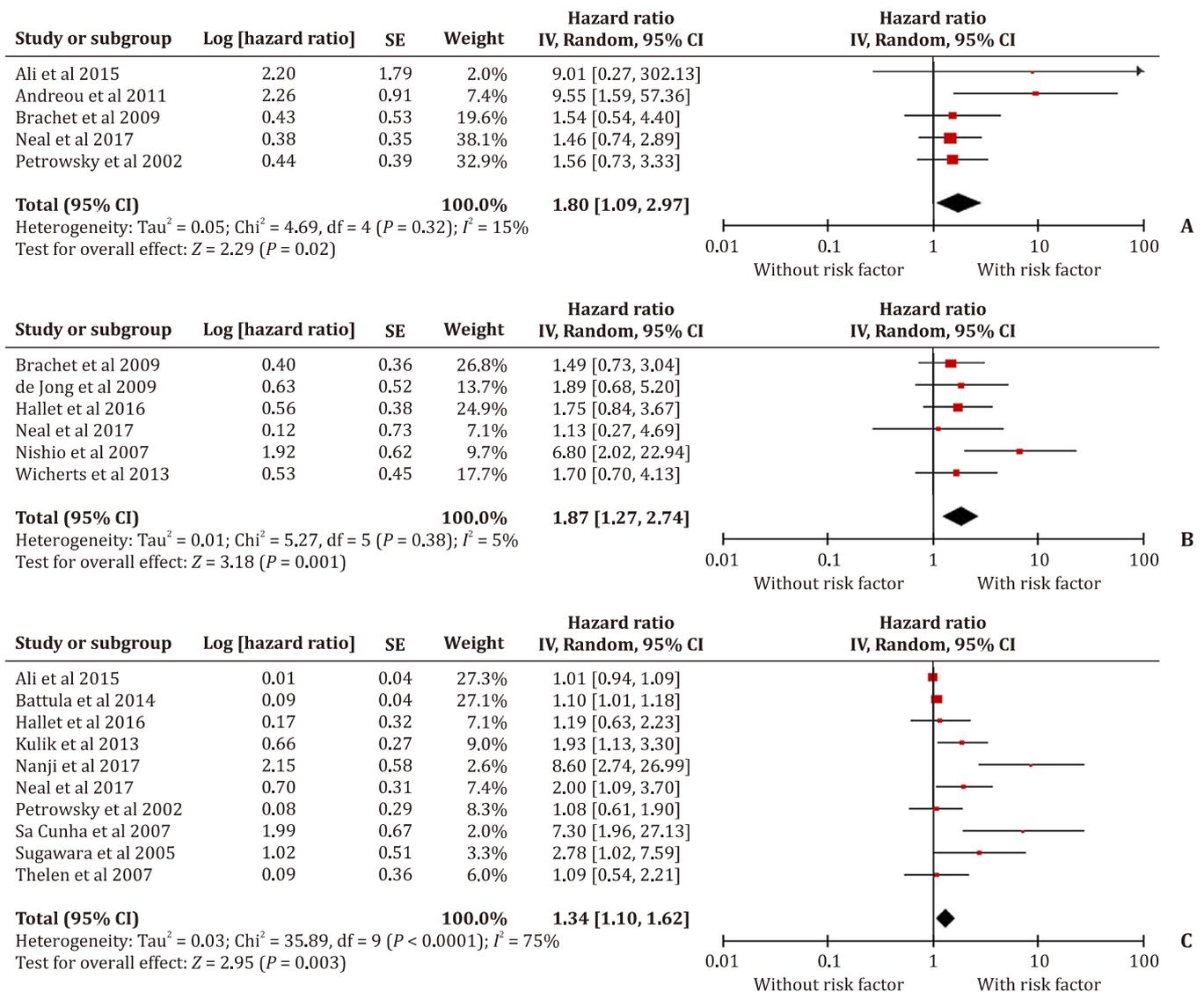


Fig. 3. Forest plot showing effect of positive surgical margin at initial hepatectomy (A), high carcinoembryonic antigen level (B) and disease-free interval ≤ 12 months (C) at repeat hepatectomy on overall survival. Square: HR; diamond: pooled HR for all studies.

Ten studies [3,7,15,16,24,28,30,32,36,37] including 1060 patients reported disease-free interval ≤ 12 months at repeat hepatectomy as a prognostic factor (HR = 1.34; 95% CI: 1.10–1.62). However, there was significant heterogeneity between studies ($I^2 = 75\%$, $P < 0.001$; Fig. 3C), indicating high levels of inconsistency of effect for this outcome.

Eleven studies [3,16,17,19,24,30–33,36,37] including 1198 patients reported multiple tumors at repeat hepatectomy as a prognostic factor (HR = 1.64; 95% CI: 1.32–2.02). There was no statistical heterogeneity between studies ($I^2 = 0$, $P = 0.63$; Fig. 4A).

Seven studies [3,14,16,20,24,36,37] including 712 patients reported largest liver lesion ≥ 5 cm at repeat hepatectomy as a prognostic factor (HR = 1.85; 95% CI: 1.34–2.56). Heterogeneity between studies was low and not significant ($I^2 = 21\%$, $P = 0.27$; Fig. 4B).

Six studies [3,14,16,17,26,37] including 695 patients reported positive surgical margin at repeat hepatectomy as a prognostic factor (HR = 2.25; 95% CI: 1.39–3.65). However, there was significant heterogeneity between studies ($I^2 = 51\%$, $P = 0.07$; Fig. 5A), indicating high levels of inconsistency of effect for this outcome.

Six studies [3,16,24,28,30,37] including 468 patients reported bilobar disease at repeat hepatectomy as a prognostic factor

(HR = 1.62; 95% CI: 1.19–2.20) without statistical heterogeneity between studies ($I^2 = 0$, $P = 0.83$; Fig. 5B).

Six studies [7,15,18,28,32,37] including 884 patients reported extrahepatic metastases at repeat hepatectomy as a prognostic factor (HR = 1.60; 95% CI: 1.23–2.09). Heterogeneity between studies was low and not significant ($I^2 = 28\%$, $P = 0.23$; Fig. 5C).

No other factors were found to be predictive of postoperative prognosis.

Discussion

As the remnant liver is the principal site of recurrence for CRLM, repeat hepatectomy in selected patients may present a rationale strategy to achieve a long-term survival. Lam et al. [38] presented a systematic review of 22 observational studies including 1610 patients on this topic. A significant proportion of studies (23%) included in their review are from pre-2000 studies, which may not reflect modern practice. Our broader search strategy since 2000 was able to include 17 studies [9,20,22,24–37] not previously incorporated in addition to 17 studies [2–8,10,11,14–21]. A strong strength of the present study is the large number of patients.

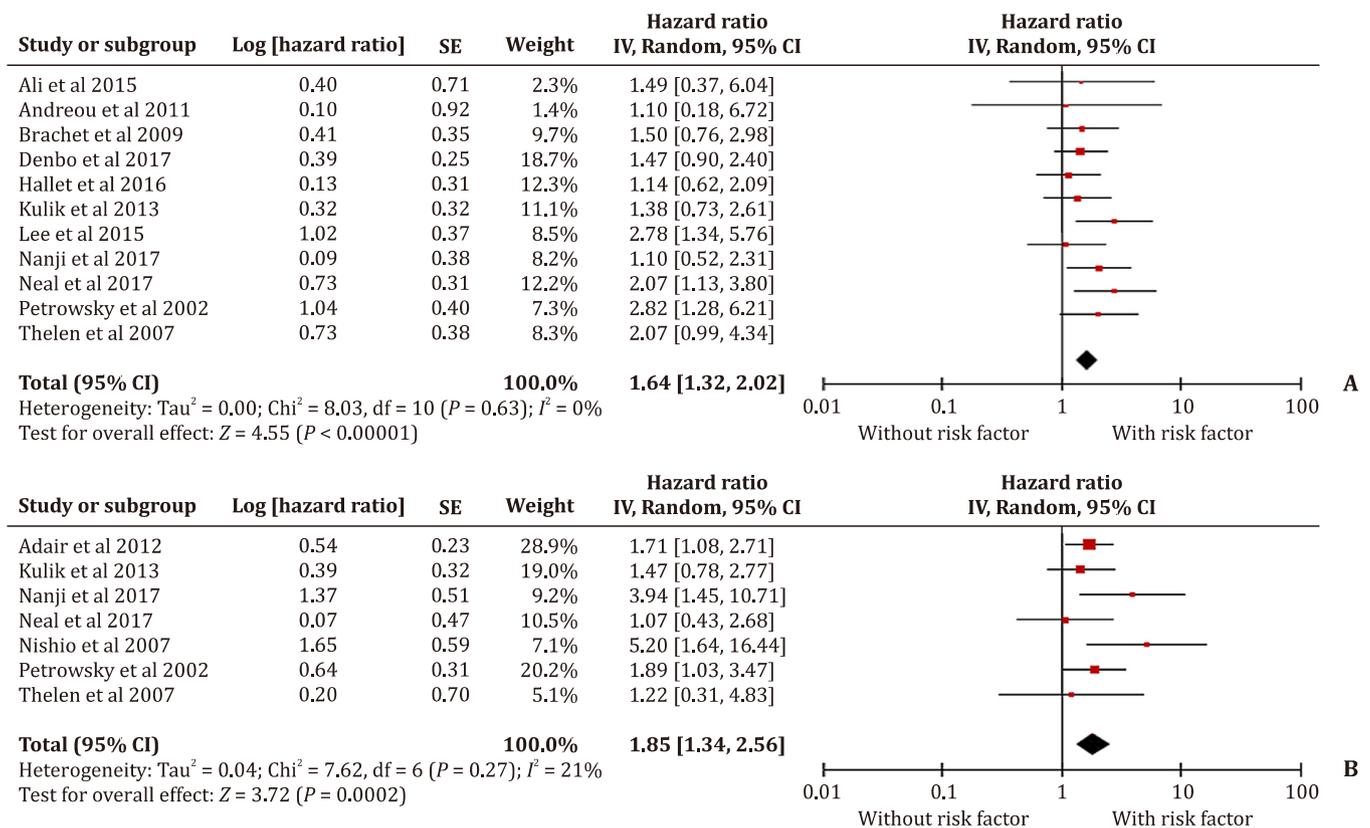


Fig. 4. Forest plot showing effect of multiple tumors (A) and largest liver lesion ≥ 5 cm (B) at repeat hepatectomy on overall survival. Square: HR; diamond: pooled HR for all studies.

Repeat hepatectomy is a considerable surgical challenge because of post-operative adhesions, hypertrophy of the residual liver and modifications in the anatomy due to the previous hepatectomy, all of which constitute major peri-operative concerns and risks. However, the present study showed that repeat hepatectomy could be performed safely with a median morbidity and mortality of 23% and 0, respectively, which are comparable to those obtained for patients undergoing initial hepatectomy [24,37]. The safety of repeat hepatectomy can be guaranteed by careful patient selection, the use of sophisticated surgical techniques, and meticulous peri-operative management.

Excellent long-term outcomes were obtained for patients undergoing repeat hepatectomy, with a median 5-year OS rate of 42%. Significantly, both Saiura et al. [29] and Neal et al. [37] demonstrated that repeat hepatectomy is an independent favorable prognostic factor for patients with CRLM. Together, these data justify the role of repeat hepatectomy for recurrent CRLM. In clinical practice, it is crucial to identify suitable candidates who can benefit from such invasive therapy. The present study showed that factors related to repeat hepatectomy have principal prognostic significance. Of these factors, disease-free interval ≤ 12 months, multiple tumors, and the largest liver lesion ≥ 5 cm are the greatest predictors of short OS. All these three factors can be easily and routinely assessed preoperatively. Developing a scoring index based on these factors would hopefully help better select patients for surgical resection, and further studies are needed to address this important issue.

Remarkably, neither the type (anatomic or nonanatomic) nor the extent (major or minor) of resection at initial or repeat hepatectomy has significant impact on survival. Parenchymal-sparing hepatectomy should therefore be preferred, obviating the need for resection of large amounts of uninvolved parenchyma, if margin-

negative resection is feasible. This practice is supported by the theoretical concept that CRLM rarely harbors micrometastases adjacent to the liver metastasis and the width of a negative surgical margin does not affect the risk of local recurrence or survival [39].

Recently, radiofrequency ablation (RFA) has been used as a regional treatment method to treat primary and metastatic liver tumors. Although RFA has fewer postoperative complications, lower costs, and a shorter length of hospital stay compared with those of hepatectomy, incomplete tumor necrosis and local recurrence remain limitations of the procedure. Generally, RFA is recommended for patients who are not optimal candidates for resection and condemned to palliative chemotherapy, rather than being used as a first-line therapeutic option for recurrent CRLM [40].

Theoretically, adjuvant chemotherapy (AD) is effective in residual micrometastases in the remnant liver. However, survival in patients who underwent repeat hepatectomy was not influenced by AD in our study, probable due to the small sample size, which may render the statistical power insufficiency. Given the well-established benefit of AD in stage II-III colorectal cancer after surgery [41], it seems rational to administer AD for recurrent CRLM using modern regimens.

This review is weakened by the heterogeneity of the included papers, knowing that there were differences in patient selection criteria, surgical skills, peri-operative chemotherapy regimens and follow-up strategies and durations among different centers and institutions. As a result, a test for heterogeneity was significant for several outcomes analyzed. In addition, only articles published in English were included, which may induce publication bias.

In conclusion, repeat hepatectomy is a safe and effective therapy for recurrent CRLM. Factors that related to repeat hepatectomy have principal prognostic significance.

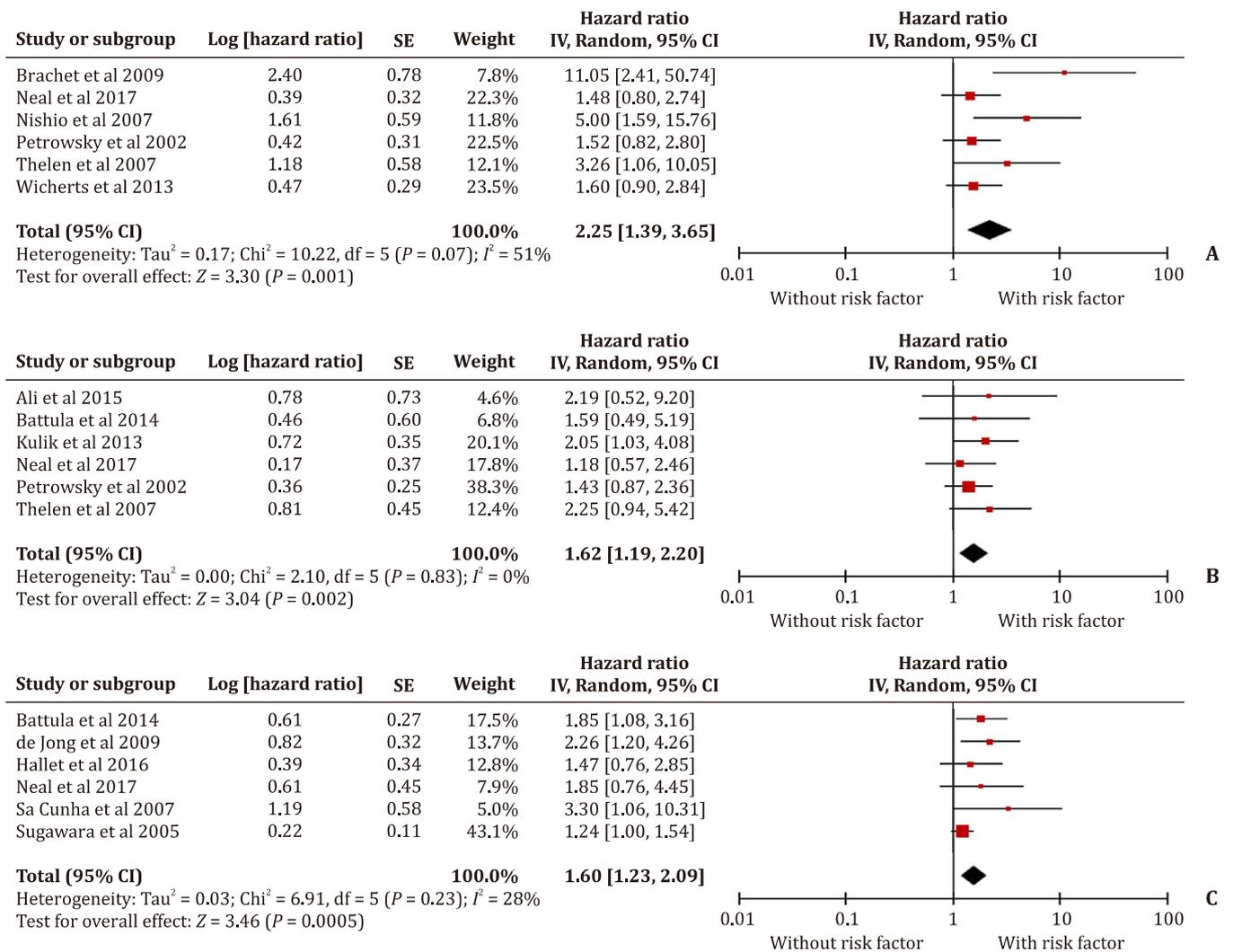


Fig. 5. Forest plot showing effect of positive surgical margin (A), bilobar disease (B) and extrahepatic metastases (C) at repeat hepatectomy on overall survival. Square: HR; diamond: pooled HR for all studies.

Acknowledgments

The author would like to thank Dr. Yan-Fang Zhao (Department of Health Statistics, Second Military Medical University, Shanghai, China) for her critical revision of the statistical analysis section.

Contributors

WSJ and ZYM participated in the design and coordination of the study, carried out the critical appraisal of studies and wrote the manuscript. WSJ, SXY and CZB participated in the literature search, carried out the extraction of data, and assisted in the critical appraisal of included studies. All authors read and approved the final manuscript. ZYM is the guarantor.

Funding

This work was supported by a grant from Foundation of Xiamen Science and Technology Bureau (3502Z20174074).

Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

- [1] Hallet J, Sa Cunha A, Adam R, Goéré D, Bachellier P, Azoulay D, et al. Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg* 2016;103:1366–1376.
- [2] Suzuki S, Sakaguchi T, Yokoi Y, Kurachi K, Okamoto K, Okumura T, et al. Impact of repeat hepatectomy on recurrent colorectal liver metastases. *Surgery* 2001;129:421–428.
- [3] Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann Surg* 2002;235:863–871.
- [4] Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases: the third hepatectomy. *Ann Surg* 2003;238:871–884.
- [5] Takahashi S, Inoue K, Konishi M, Nakagouri T, Kinoshita T. Prognostic factors for poor survival after repeat hepatectomy in patients with colorectal liver metastases. *Surgery* 2003;133:627–634.
- [6] Tanaka K, Shimada H, Ohta M, Togo S, Saitou S, Yamaguchi S, et al. Procedures of choice for resection of primary and recurrent liver metastases from colorectal cancer. *World J Surg* 2004;28:482–487.
- [7] Sugawara G, Isogai M, Kaneoka Y, Suzuki M, Yamaguchi A. Repeat hepatectomy for recurrent colorectal metastases. *Surg Today* 2005;35:282–289.

- [8] Ishiguro S, Akasu T, Fujimoto Y, Yamamoto J, Sakamoto Y, Sano T, et al. Second hepatectomy for recurrent colorectal liver metastasis: analysis of preoperative prognostic factors. *Ann Surg Oncol* 2006;13:1579–1587.
- [9] Pessaux P, Lermite E, Brehant O, Tuech JJ, Lorimier G, Arnaud JP. Repeat hepatectomy for recurrent colorectal liver metastases. *J Surg Oncol* 2006;93:1–7.
- [10] Shaw IM, Rees M, Welsh FK, Bygrave S, John TG. Repeat hepatic resection for recurrent colorectal liver metastases is associated with favourable long-term survival. *Br J Surg* 2006;93:457–464.
- [11] Yan TD, Lian KQ, Chang D, Morris DL. Management of intrahepatic recurrence after curative treatment of colorectal liver metastases. *Br J Surg* 2006;93:854–859.
- [12] Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISMA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- [13] Phillips R, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al. Oxford centre for evidence-based medicine – levels of evidence (march 2009). <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/> [Accessed 20 July 2018].
- [14] Nishio H, Hamady ZZ, Malik HZ, Fenwick S, Rajendra Prasad K, Toogood GJ, et al. Outcome following repeat liver resection for colorectal liver metastases. *Eur J Surg Oncol* 2007;33:729–734.
- [15] Sa Cunha A, Laurent C, Rault A, Couderc P, Rullier E, Saric J. A second liver resection due to recurrent colorectal liver metastases. *Arch Surg* 2007;142:1144–1150.
- [16] Thelen A, Jonas S, Benckert C, Schumacher G, Lopez-Hänninen E, Rudolph B, et al. Repeat liver resection for recurrent liver metastases from colorectal cancer. *Eur J Surg Oncol* 2007;33:324–328.
- [17] Brachet D, Lermite E, Rouquette A, Lorimier G, Hamy A, Arnaud JP. Prognostic factors of survival in repeat liver resection for recurrent colorectal metastases: review of sixty-two cases treated at a single institution. *Dis Colon Rectum* 2009;52:475–483.
- [18] de Jong MC, Mayo SC, Pulitano C, Lanella S, Ribero D, Strub J, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. *J Gastrointest Surg* 2009;13:2141–2151.
- [19] Andreou A, Brouquet A, Abdalla EK, Aloia TA, Curley SA, Vauthey JN. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. *HPB (Oxford)* 2011;13:774–782.
- [20] Adair RA, Young AL, Cockbain AJ, Malde D, Prasad KR, Lodge JP, et al. Repeat hepatic resection for colorectal liver metastases. *Br J Surg* 2012;99:1278–1283.
- [21] Jones NB, McNally ME, Malhotra L, Abdel-Misih S, Martin EW, Bloomston M, et al. Repeat hepatectomy for metastatic colorectal cancer is safe but marginally effective. *Ann Surg Oncol* 2012;19:2224–2229.
- [22] Jönsson K, Gröndahl G, Salö M, Tingstedt B, Andersson R. Repeated liver resection for colorectal liver metastases: a comparison with primary liver resections concerning perioperative and long-term outcome. *Gastroenterol Res Pract* 2012;2012:568214.
- [23] Rolff HC, Calatayud D, Larsen PN, Wettergren A. Good results after repeated resection for colorectal liver metastases. *Dan Med J* 2012;59:A4373.
- [24] Kulik U, Bektas H, Klempnauer J, Lehner F. Repeat liver resection for colorectal metastases. *Br J Surg* 2013;100:926–932.
- [25] Neef HP, Drognitz O, Holzner P, Klock A, Bronsert P, Hopt UT, et al. Outcome after repeat resection of liver metastases from colorectal cancer. *Int J Colorectal Dis* 2013;28:1135–1141.
- [26] Wicherts DA, de Haas RJ, Salloum C, Andreani P, Pascal G, Sotirov D, et al. Repeat hepatectomy for recurrent colorectal metastases. *Br J Surg* 2013;100:808–818.
- [27] Yamazaki S, Takayama T, Okada S, Iwama A, Midorikawa Y, Moriguchi M, et al. Good candidates for a third liver resection of colorectal metastasis. *World J Surg* 2013;37:847–853.
- [28] Battula N, Tsapralis D, Mayer D, Isaac J, Muiesan P, Sutcliffe RP, et al. Repeat liver resection for recurrent colorectal metastases: a single-centre, 13-year experience. *HPB (Oxford)* 2014;16:157–163.
- [29] Saiura A, Yamamoto J, Koga R, Takahashi Y, Takahashi M, Inoue Y, et al. Favorable outcome after repeat resection for colorectal liver metastases. *Ann Surg Oncol* 2014;21:4293–4299.
- [30] Ali MA, Di Sandro S, Lauterio A, Concone G, Mangoni I, Ferla F, et al. Repeat hepatectomy for recurrent colorectal liver metastases: is it worth the challenge? *J Gastrointest Surg* 2015;19:2192–2198.
- [31] Lee H, Choi SH, Cho YB, Yun SH, Kim HC, Lee WY, et al. Repeat hepatic resection in patients with colorectal liver metastases. *World J Gastroenterol* 2015;21:2124–2130.
- [32] Hallet J, Cunha AS, Adam R, Goéré D, Azoulay D, Mabrut JY, et al. Outcomes of re-hepatectomy for colorectal liver metastases: a contemporary multi-institutional analysis from the French Surgical Association Database. *Ann Surg Oncol* 2016;23:894–903.
- [33] Denbo JW, Yamashita S, Passot G, Egger M, Chun YS, Kopetz SE, et al. RAS mutation is associated with decreased survival in patients undergoing repeat hepatectomy for colorectal liver metastases. *J Gastrointest Surg* 2017;21:68–77.
- [34] Dupré A, Jones RP, Diaz-Nieto R, Fenwick SW, Poston GJ, Malik HZ. Curative-intent treatment of recurrent colorectal liver metastases: a comparison between ablation and resection. *Eur J Surg Oncol* 2017;43:1901–1907.
- [35] Fukami Y, Kaneoka Y, Maeda A, Takayama Y, Onoe S. Postoperative complications following aggressive repeat hepatectomy for colorectal liver metastasis have adverse oncological outcomes. *Surg Today* 2017;47:99–107.
- [36] Nanji S, Tsang ME, Wei X, Booth CM. Outcomes after repeat hepatic resection for recurrent metastatic colorectal cancer: a population-based study. *Am J Surg* 2017;213:1053–1059.
- [37] Neal CP, Nana GR, Jones M, Cairns V, Ngu W, Isherwood J, et al. Repeat hepatectomy is independently associated with favorable long-term outcome in patients with colorectal liver metastases. *Cancer Med* 2017;6:331–338.
- [38] Lam VW, Pang T, Laurence JM, Johnston E, Hollands MJ, Pleass HC, et al. A systematic review of repeat hepatectomy for recurrent colorectal liver metastases. *J Gastrointest Surg* 2013;17:1312–1321.
- [39] Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. *Ann Surg* 2016;263:146–152.
- [40] Hof J, Wertenbroek MW, Peeters PM, Widder J, Sieders E, de Jong KP. Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. *Br J Surg* 2016;103:1055–1062.
- [41] Quasar Collaborative Group, Gray A, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007;370:2020–2029.