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Comparison between simultaneous resection and staged resection of synchronous colorectal cancer with resectable liver metastases: a meta-analysis

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Summary

Background Previously, the surgical management of synchronous colorectal liver metastases has been a staged resection. Now, it is shifting toward the simultaneous resection of colorectal primary and liver metastases. The aim of this study is to compare the outcomes between simultaneous resection and staged resection.

Methods The studies were identified searching the database including PubMed, Medline, and Cochrane library. The pooled odds ratios (OR) or weighted mean differences (WMD) with 95% confidence interval (CI) were calculated using either the fixed effect or random effect model.

Results A total of 20 studies were included with 3194 patients: 1137 to simultaneous resection group and 2057 to staged resection group. The overall survival at 1 year (OR=0.73, 95% CI=0.48-1.11, P=0.14), 3 year (OR=1.13, 95% CI=0.88-1.44, P=0.34), and 5 year (OR=1.08, 95% CI=0.84-1.38, P=0.54) and disease-free survival at 1 year (OR=0.77, 95% CI=0.47-1.2, P=0.29), 3 year (OR=0.72, 95% CI=0.44-1.18, P=0.19), and 5 year (OR=0.60, 95% CI=0.34-1.04, P=0.07) showed no significant difference between the two groups. The operative time (WMD=-38.61, 95% CI=-89.26-12.04, P=0.14), and postoperative recurrence (OR=0.86, 95% CI=0.58-1.29, P=0.47) were similar between the two groups. Shorter hospital stay (WMD=5.49, 95% CI=-7.04 to

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Prof. L. Tao, PhD, MS e-mail: lit@medmail.com.cn -3.94, *P*=0.00001) and lower overall complication rate (OR=0.73, 95% CI=0.61-0.87, *P*=0.0004) were observed in simultaneous resection group.

Conclusion In appropriately selected patients, simultaneous resection might be considered as the preferred treatment. Simultaneous resection is safe and efficient in the treatment of these patients with the elimination of second major operation.

Keywords Synchronous \cdot Colorectal cancer \cdot Liver metastases \cdot Simultaneous resection \cdot Staged resection

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide with approximately 1.2 million new cases and 6,08,000 deaths annually [1]. For patients in whom metastatic CRC develops, the liver is by far the most common site of metastases, and almost 50% of these patients have the liver as the only site of metastatic disease [2]. Complete surgical removal of all liver disease has been accepted as the only treatment option offering the chance for cure and long-term survival, with 5-year survival rates of up to 50% [3].

Between 15-25 % of the patients have one or more liver metastases at the time of diagnosis [4]. These are generally referred to as synchronous metastases. The optimal timing of liver surgery for synchronous metastases remains still the topic of debate [5]. Traditionally, a staged approach with initial resection of the primary colorectal tumor followed by hepatic resection 2–3 months later have been recommended [6, 7]. However, several recent series have demonstrated a good result for simultaneous resection of colon and liver tumors [8, 9]. With the recent advances in surgical techniques and anesthesiology of liver resection, simultaneous resection of colorectal primaries and liver metastases can be achieved with a low

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peroperative morbidity rate and mortality rate and saves the patient a second laparotomy. In addition, recent studies have demonstrated the feasibility of synchronous hepatic and colorectal resection with good short-term results [8, 10-16].

The goal of this meta-analysis of published studies was to compare overall survival, disease-free survival, overall complication, mortality, intraoperative blood loss, postoperative recurrence, and length of hospital stay in patients who underwent synchronous resection and staged resection

Methods

Study selection

Electronic search was performed to identify all relevant studies that compared the outcomes following simultaneous resection and staged resection for synchronous colorectal liver metastases (SCLM) from PubMed, Medline, and Cochrane database from 2000 to 2012. The following keywords were used to search the studies: "synchronous," "colorectal cancer," "liver metastases," "simultaneous resection," and "staged resection." All abstracts, studies, and citations scanned were reviewed. No language restriction was made.

Criteria for inclusion

Studies having surgery as either simultaneous or staged in patients with SCLM, studies comparing simultaneous and delayed resections in patients with SCLM, and studies reporting on at least one of these outcomes: overall survival rate at 1, 3, and 5 years, disease-free survival rate at 1, 3, and 5 years, length of hospital stay, postoperative recurrence, intraoperative blood loss, overall complication, and mortality were included in this study.

Criteria for exclusion

Abstracts, letters, editorials, and expert opinions, studies dealing with simultaneous resection or staged resection alone, and studies showing no clarity in the outcome of interest for two different disease types were excluded from the analysis.

Data extraction

The reviewer independently extracted the following data variables from each study: First author, year and country of publication, study population, patient characteristics including age and gender, study design, inclusion and exclusion criteria, quality of study, and the treatment outcomes including overall complication, mortality, intraoperative blood loss, length of hospital stay, recurrence rate, 1-, 3-, and 5-year survival rate, and 1-, 3- and 5-year disease-free survival rate. All relevant text, tables, and figures were reviewed for data extraction.

Statistical analysis

The meta-analysis was performed using RevMan software ver. 5.2. Pooled odds ratios (OR) or weighted mean differences (WMD) with 95% confidence intervals (CI) were calculated for dichotomous outcomes and continuous outcomes, respectively. The fixed-effect model was used when no heterogeneity was detected, which means that there was no variance among studies. If any heterogeneity existed, the random-effect model was used for meta-analysis. Statistical heterogeneity between trials was evaluated by the Cochrane χ^2 -test and was considered significant when P < 0.05. Publication bias was qualitatively evaluated using funnel plots.

Assessment of study quality

Studies for possible inclusion were identified from the abstracts of the searches and selected after reading the full text according to the inclusion criteria. As no randomized studies were found, the quality of the included studies were evaluated according to the Newcastle-Ottawa scale [17]. A quality score rating was determined for each study, with seven or more stars indicating higher quality.

Results

Selection of studies and patients' characteristics

Using the keywords "synchronous," "colorectal cancer," "liver metastases," "simultaneous resection," and "staged resection," the titles and abstracts of 511 primary relevant studies were identified for initial review. According to the inclusion and exclusion criteria, 31 potential studies for full-text review were identified. A total of 12 studies were excluded, among which 4 studies had inadequate data for meta-analysis, 5 studies were excluded due to inappropriate comparison, and 3 studies were about simultaneous resection only. Finally, 20 studies published between 2000 and 2013 were included, which fulfilled the selection criteria. Figure 1 shows the search process (Fig. 2).

As the search strategy could not find randomized control trials (RCTs), none of the included studies were RCTs. The total number of patients of all included studies was 3194 among which 1137 were treated with simultaneous resection and 2057 were treated with staged resection. The key characteristics of the included studies are listed in Table 1.



Fig. 1 A mass of approximately 10 × 10 cm at ileocecal junction. Intraoperative frozen section showed adenocarcinoma

Overall survival rate

Among the 20 studies selected, 13 studies reported on the overall survival. There was no significant difference found between the two groups at 1 year (OR=0.73, 95% CI=0.48-1.11, P=0.14), 3 year (OR=1.13, 95% CI=0.88-1.44, P=0.34), and 5 year (OR=1.08, 95% CI=0.84-1.38, P=0.54) (Fig. 3).

Disease-free survival

Included four studies report on disease-free survival with no significant difference between the two groups at 1 year (OR=0.77, 95%CI=0.47-1.2, P=0.29), 3 year (OR=0.72, 95% CI=0.44-1.18, P=0.19), and 5 year (OR=0.60, 95% CI=0.34-1.04, P=0.07) (Fig. 4).

Operative time

From eight included studies, patients undergoing simultaneous resection experienced a similar operative time compared with those undergoing staged resection (WMD=-38.61, 95% CI=-89.26-12.04, P=0.14) (Fig. 5).

Intraoperative blood loss

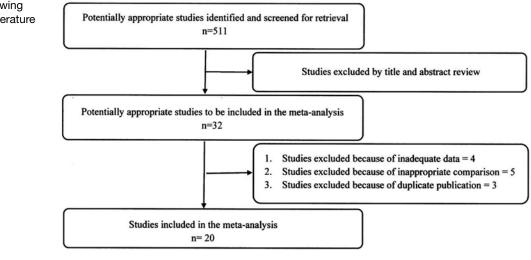
Statistically significant difference was found between the two groups with respect to intraoperative blood loss (WMD=169.85, 95% CI=-327.02 to -12.68, P=0.03). The intraoperative blood loss was decreased in simultaneous resection group (Fig. 6).

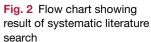
Hospital stay

The postoperative length of hospital stay was shorter in the simultaneous resection group than the staged resection group (WMD=5.49, 95% CI=-7.04 to -3.94, P=0.00001) (Fig. 7).

Overall complication

Postoperative complications were reported in 19 of the included studies. Among them, 1129 patients in simultaneous resection group experienced 408 complications, and 1623 patients having staged resection had 667 complications. The rate of overall complication was significantly lowered in patients undergoing simultaneous resection than those undergoing staged resection (OR=0.73, 95 % CI=0.61-0.87, P=0.0004) (Fig. 8).





Year	Year Author		Study	Total	Simultane	ous			Staged				Score
			type	no. of patients	No. of patients	Age (yrs)	Male	Female	No. of patients	Age (yrs)	Male	Female	
2003	Martin	USA	Retro	240	134	64	69	65	106	61	61	45	*******
2003	Weber	France	Retro	97	35	58	18	17	62	60	31	31	******
2004	Tanaka	Japan	Retro	76	39	65	20	19	37	64	25	12	*******
2006	Capus- sotti	Italy	Retro	79	31	62.4	18	13	48	59.3	27	21	******
2007	Reddy	USA	Retro	610	135	57	84	51	475	58	277	198	******
2007	Turrini	France	Retro	119	57	60	26	31	62	59	28	34	******
2007	Vassilio	Greece	Retro	103	25	63	15	10	78	61	47	31	******
2007	Capus- sotti	Italy	Retro	127	70	64.9	40	30	57	60.8	35	22	******
2007	Thelen	Germany	Retro	219	40	60.5	24	16	179	59.7	96	83	*******
2007	Yan	Australia	Retro	103	73	60	33	40	30	59	15	15	******
2008	Wang	China	Retro	83	37	57	22	15	46	55	31	15	******
2009	Martin	USA	Retro	230	70	58	38	32	160	61	91	69	******
2009	Slupski	Poland	Retro	89	28	59.4	18	10	61	60.2	34	27	*****
2010	Brou- quet	USA	Retro	115	43	58	23	20	72	56	44	28	******
2010	Pool	Nether- land	Retro	37	8	NA	NA	NA	29	NA	NA	NA	*****
2010	Moug	UK	Retro	64	32	69	18	14	32	67	21	11	******
2010	de Hass	France	Retro	228	55	56	28	27	173	58	107	66	******
2010	Kaibori	Japan	Retro	74	32	62.3	17	15	42	65	27	15	******
2010	Luo	China	Retro	405	129	58	76	53	276	60	156	120	******
2004	Chua	USA	Retro	96	64	63	39	25	32	61	18	14	******
	Total			3194	1137				2057				

Table 1 The key characteristics of the included studies

Postoperative recurrence rate

No significant differences were found between the simultaneous resection group and the staged resection group in terms of postoperative recurrence from the five included studies in our meta-analysis (Fig. 9).

Mortality

No statistically significant difference was found between the simultaneous resection group and staged resection group with respect to postoperative mortality (OR=1.58, 95% CI=0.84-2.96, P=0.16) in our result (Fig. 10).

Discussion

As there were no RCTs found on electronic search strategy, most of the included studies were retrospective studies. Although meta-analysis has traditionally been applied and is best confined to RCT, meta-analysis technique using nonrandomized control trials might be a valid method in some clinical settings in which either the number or the sample size is insufficient. Our study supports simultaneous resection of the SCLM with regard to the intraoperative blood loss and the length of hospital stay, whereas the operative time and postoperative recurrence were similar between the two groups. The overall survival and disease-free survival at 1, 3, and 5 years after resection between the two groups show no significant difference, but the overall complication was significantly lowered in patients with simultaneous resection. The mortality rate in the simultaneous resection group did not statistically differ from that in the staged resection group. As most included studies were retrospective studies, we should interpret the present results carefully.

Many recent studies have shown that simultaneous colorectal resection and hepatectomy is feasible and safe. This meta-analysis concluded that there were no statistically significant differences in overall survival rate, disease-free survival rate, and recurrence rate between simultaneous and delayed resection, but simultaneous resection was associated with shorter hospital stay. From a clinical point of view, these findings seem to be highly significant. Many authors have reported that the advanced stage of primary colorectal tumor, large number and size of hepatic metastases, and synchronous presentation of liver metastases with primary colorectal

Chudu as Cubassus	SIMULTANEOUS RES		STAGED RE SEC		Mainht	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	lotal	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
.1.1 OVERALL SURV							
Capussotti 2007	64	70	53	57	1.7%	0.81 [0.22, 3.00]	
Chua 2004	53	64	31	32	2.4%	0.16 [0.02, 1.26]	
Slupski 2009	22	28	54	61	2.5%	0.48 [0.14, 1.57]	
Tanaka 2004	34	39	31	37	1.4%	1.32 [0.36, 4.75]	
Thelen 2007	34	40	161	179	3.0%	0.63 [0.23, 1.71]	
Turrini 2007	52	57	58	62	1.6%	0.72 [0.18, 2.81]	
/assilio 2007	23	25	73	78	1.0%	0.79 [0.14, 4.34]	
Nang 2008	32	37	41	46	1.7%	0.78 [0.21, 2.93]	
Neber 2003	33	35	57	62	0.8%	1.45 [0.27, 7.88]	
Yan 2007	65	73	26	30	1.4%	1.25 [0.35, 4.51]	
Subtotal (95% CI)		468		644	17.3%	0.73 [0.48, 1.11]	•
Total events	412		585				
Heterogeneity: Chi ² =	4.81, df = 9 (P = 0.85);	² = 0%					
Test for overall effect:	Z = 1.47 (P = 0.14)						
1.1.2 OVERALL SURV	VIVAL FOR 3 YEAR						
Brouquet 2010	28	43	40	72	3.5%	1.49 [0.68, 3.26]	
Capussotti 2007	31	70	31	57	6.4%	0.67 [0.33, 1.35]	
Chua 2004	21	64	14	32	4.2%	0.63 [0.26, 1.50]	
de Hass 2010	41	55	122	173	5.1%	1.22 [0.61, 2.44]	
Slupski 2009	20	28	34	61	2.1%	1.99 [0.76, 5.20]	+
Tanaka 2004	27	39	17	37	1.8%	2.65 [1.04, 6.77]	
Turrini 2007	34	57	35	62	4.6%	1.14 [0.55, 2.36]	
/assilio 2007	10	25	34	78	3.3%	0.86 [0.34, 2.16]	
Nang 2008	20	37	24	46	3.3%	1.08 [0.45, 2.57]	_
Neber 2003	16	35	28	62	3.7%	1.02 [0.44, 2.35]	
Yan 2007	39	73	15	30	3.3%	1.15 [0.49, 2.69]	
Subtotal (95% CI)		526		710	41.4%	1.13 [0.88, 1.44]	•
Total events	287		394				
Heterogeneity: Chi ² =	9.33, df = 10 (P = 0.50)	; I= 0%					
Test for overall effect:	Z = 0.95 (P = 0.34)						
1.1.3 OVERALL SURV							
Brouquet 2010	25	43	35	72	3.7%	1.47 [0.69, 3.15]	-+
Capussotti 2007	22	70	18	57	4.6%	0.99 [0.47, 2.11]	-+-
Chua 2004	18	64	14	32	4.5%	0.50 [0.21, 1.22]	
Kaibori 2010	14	32	25	42	4.1%	0.53 [0.21, 1.34]	
Slupski 2009	13	28	23	61	2.6%	1.43 [0.58, 3.54]	
Tanaka 2004	21	39	17	37	2.7%	1.37 [0.56, 3.38]	-+
Thelen 2007	21	40	70	179	4.1%	1.72 [0.86, 3.43]	+
Turrini 2007	18	57	16	62	3.5%	1.33 [0.60, 2.94]	-+
assilio 2007	7	25	24	78	2.8%	0.88 [0.32, 2.37]	
Nang 2008	10	37	11	46	2.4%	1.18 [0.44, 3.18]	
Neber 2003	7	35	14	62	2.7%	0.86 [0.31, 2.38]	
Yan 2007	26	73	11	30	3.4%	0.96 [0.39, 2.31]	<u> </u>
Subtotal (95% CI)		543		758	41.3%	1.08 [0.84, 1.38]	•
Total events	202		278				
Heterogeneity: Chi ^a = Test for overall effect:	8.91, df = 11 (P = 0.63) Z = 0.61 (P = 0.54)	; ² = 0%					
Total (95% CI)		1537		2112	100.0%	1.04 [0.89, 1.22]	•
Total events	901		1257				
	25 52 df = 32 /P = 0.79	2)· 12 - 0.06				F F	
-leterogeneity: Chi ² =	23.32, 01 - 32 (0.70	y , i = 0 x					0.01 0.1 1 10 1

Fig. 3 Forest plot showing the result of the meta-analysis comparing overall survival rate at 1, 3, and 5 years after simultaneous resection versus staged resection for synchronous colorectal liver metastases

tumor are significantly correlated with poor long-term outcome after hepatectomy [33-37]. However, none of these prognostic factors have been considered as a contraindication to liver resection [36]. SCLM did not influence the survival in the simultaneous resection group. The reported 5-year survival rate after liver resection for patients with SCLM ranges from 20-40% [13, 15, 16]. In addition, with the innovation of surgical techniques and the constant improvement of the comprehensive treatment, more and more recent studies demonstrated that the strategy to simultaneously resect the primary tumor and the synchronous metastases has a similar overall survival rate at 1, 3, and 5 years compared with staged liver resection [8, 11, 15, 16, 37].

Traditionally, staged resection has been considered as the preferable choice in dealing with SCLM. A comprehended increase in perioperative risk with simultaneous resection has traditionally provided the rationale for performing the resection in stages. One of main reasons cited in favor of a staged resection is theoretical improvement

	SIMULTANEOUS RES	ECTION	STAGED RESE	CTION		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.2.1 DISEASE FREE	SURVIVAL FOR 1 YEAR						
Chua 2004	36	64	18	32	9.9%	1.00 [0.43, 2.35]	
Kaibori 2010	16	32	36	42	14.7%	0.17 [0.06, 0.50]	
Tanaka 2004	25	39	19	37	6.6%	1.69 [0.68, 4.24]	+•
Yan 2007	65	73	27	30	4.0%	0.90 [0.22, 3.66]	
Subtotal (95% CI)		208		141	35.1%	0.77 [0.47, 1.25]	•
Total events	142		100				
Heterogeneity: Chi ² =	= 10.56, df = 3 (P = 0.01);	I= 72%					
Test for overall effect	Z = 1.05 (P = 0.29)						
1.2.2 DISEASE FREE	SURVIVAL FOR 3 YEAR						
Chua 2004	6	64	6	32	6.8%	0.45 [0.13, 1.52]	
Kaibori 2010	14	32	25	42	11.5%	0.53 [0.21, 1.34]	
Tanaka 2004	8	39	13	37	10.0%	0.48 [0.17, 1.33]	
Yan 2007	28	73	8	30	6.6%	1.71 [0.67, 4.37]	
Subtotal (95% CI)		208		141	34.9%	0.72 [0.44, 1.18]	•
Total events	56		52				
Heterogeneity: Chi ² =	4.90, df = 3 (P = 0.18); I	= 39%					
Test for overall effect	Z = 1.30 (P = 0.19)						
1.2.3 DISEASE FREE	SURVIVAL FOR 5 YEAR						
Chua 2004	6	64	4	32	4.6%	0.72 [0.19, 2.77]	
Kaibori 2010	14	32	25	42	11.5%	0.53 [0.21, 1.34]	
Tanaka 2004	6	39	10	37	8.2%	0.49 [0.16, 1.52]	
Yan 2007	10	73	5	30	5.8%	0.79 [0.25, 2.56]	
Subtotal (95% CI)		208		141	30.0%	0.60 [0.34, 1.04]	•
Total events	36		44				
Heterogeneity: Chi ² =	0.49, df = 3 (P = 0.92); l	= 0%					
Test for overall effect:	: Z = 1.82 (P = 0.07)						
Fotal (95% CI)		624		423	100.0%	0.70 [0.52, 0.94]	◆
Fotal events	234		196				
Heterogeneity: Chi ² =	16.45, df = 11 (P = 0.13); I ² = 33%					
est for overall effect:	Z = 2.36 (P = 0.02)					5	
est for subgroup diff	ferences: Chi ² = 0.47, df	= 2 (P = 0)	.79), I ² = 0%			Fa	avours [Simultaneous] Favours [Staged]

Fig. 4 Forest plot showing the result of the meta-analysis comparing disease-free survival rate at 1, 3, and 5 years after simultaneous resection versus staged resection for synchronous colorectal liver metastases

	SIMULTANE	OUS RESEC	CTION	STAGE	DRESECT	FION		Mean Difference	Mean Di	fference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% Cl
Martin 2003	235	90	134	411	99.7	106	12.9%	-176.00 [-200.34, -151.66]	•	
Martin 2009	180	85	70	235	55	160	12.9%	-55.00 [-76.66, -33.34]		
Slupski 2009	250	50	28	290	65	61	12.8%	-40.00 [-64.68, -15.32]		
Tanaka 2004	532	152.8	39	494.8	103.4	37	11.3%	37.20 [-21.19, 95.59]		
Thelen 2007	260.48	86.8	40	208.6	57.35	179	12.7%	51.88 [23.70, 80.06]		
Vassilio 2007	260	30	25	340	60	78	13.0%	-80.00 [-97.76, -62.24]		
Weber 2003	313	68	35	290	80	62	12.7%	23.00 [-7.07, 53.07]	-	
Yan 2007	300	120	73	360	120	30	11.7%	-60.00 [-111.01, -8.99]	← • — —	
Total (95% CI)			444			713	100.0%	-38.61 [-89.26, 12.04]		-
Heterogeneity: Tau* =	5041.62; Chi	= 194.63, d	f=7 (P <)	0.00001)	I* = 96%			•	<u> </u>	
Test for overall effect:	1							F	-100 -50 avours [Simultaneous]	0 50 100 Favours [Staged]

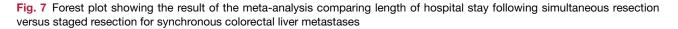
Fig. 5 Forest plot showing the result of the meta-analysis comparing operative time following simultaneous resection versus staged resection for synchronous colorectal liver metastases

in perioperative outcomes. This is supported by the published evidence suggesting that staged resection results in significantly lower morbidity and mortality and thus leading to better long-term outcomes. [6, 38-40]. Recent reports provide an increasing support for performing simultaneous colonic and hepatic resections [15, 16]. Chua et al. [13] from the mayo clinic retrospectively analyzed 96 patients that presented with synchronous CRC and liver metastases. These patients underwent either synchronous or staged resections within the same surgical unit. Postoperative complication rates were similar between groups with no operative mortality. They thus concluded that synchronous resection is safe, effective, and should be the procedure of choice for selected patients in experienced centers. The past decades have seen significant advancements in hepatobiliary surgical training, hepatobiliary techniques, anesthetic management, and overall critical care, which have made hepatic resection safer and increased overall quality of life [24]. Even major liver resections are now done with

	SIMULTAN	EOUS RESEC	CTION	STAGE	RESECT	ION		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% (CI IV, Random, 95% CI
Brouquet 2010	912.5	737.5	43	1,150	800	72	10.5%	-237.50 [-525.14, 50.14	4)+
Kaibori 2010	670	485	32	1,107	710	42	10.9%	-437.00 -709.66, -164.34	4 I
Luo 2010	400	133.3	129	650	133.3	276	16.1%	-250.00 -277.86, -222.14	4 •
Martin 2003	550	650	134	1,100	783.3	106	13.2%	-550.00 [-735.33, -364.67	n ——
Martin 2009	300	370	70	350	233.3	160	15.3%	-50.00 [-143.91, 43.91	ni —+
Moug 2010	488	175	32	574	4,125	32	1.1%	-86.00 [-1516.50, 1344.50	oj ←
Reddy 2007	400	158.3	135	361	91.8	475	16.1%	39.00 [11.05, 66.95	5 •
Slupski 2009	950	756.3	28	620	298.4	61	10.4%	330.00 [40.03, 619.97	n
Tanaka 2004	1,460.1	1,057.4	39	1,719.3	1,077	37	6.4%	-259.20 [-739.37, 220.97	71
Total (95% CI)			642			1261	100.0%	-169.85 [-327.02, -12.68	31
Heterogeneity: Tau ² =	39783.50; C	hi ² = 244.84.	df = 8 (P	< 0.00001): I ² = 979	5		and particular and a sub-	
Test for overall effect:						-			-1000 -500 0 500 1000
									Favours [Simultaneous] Favours [Staged]

Fig. 6 Forest plot showing the result of the meta-analysis comparing intraoperative blood loss following simultaneous resection versus staged resection for synchronous colorectal liver metastases

	SIMULTANE	OUS RESEC	TION	STAGE	DRESECT	TION		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV. Random, 95% CI
Capussotti 2006	13.9	10	31	20.5	8	48	6.0%	-6.60 [-10.78, -2.42]	-
Chua 2004	11.4	6.7	64	22.4	17.6	32	3.8%	-11.00 [-17.32, -4.68	
Luo 2010	8	1.3	129	14	1.8	276	10.6%	-6.00 [-6.31, -5.69]	•
Martin 2003	10	8.2	134	18	8.5	106	8.9%	-8.00 [-10.13, -5.87]	
Martin 2009	10	14.5	70	18	8	160	6.8%	-8.00 [-11.62, -4.38]	
Moug 2010	13.25	3.25	32	24.5	11	32	6.3%	-11.25 [-15.22, -7.28]	
Pool 2010	10	2	8	36	20.5	29	3.0%	-26.00 [-33.59, -18.41]	
Reddy 2007	8.6	1.8	135	12.6	2.5	475	10.6%	-4.00 [-4.38, -3.62]	
Slupski 2009	12	4	28	9	3	61	9.5%	3.00 [1.34, 4.66]	
Tanaka 2004	25.6	10.4	39	23.1	10.3	37	5.4%	2.50 [-2.15, 7.15]	
Thelen 2007	20.05	8	40	19.85	30.78	179	4.9%	0.20 -4.95, 5.35	
Turrini 2007	18	0	57	15	0	62		Not estimable	
Vassilio 2007	12	6	25	20	8	78	7.7%	-8.00 [-10.95, -5.05]	-
Weber 2003	17	9	35	16	7	62	7.0%	1.00 [-2.45, 4.45]	
Yan 2007	7	2.3	73	15	4.5	30	9.5%	-8.00 [-9.69, -6.31]	
Total (95% CI)			900			1667	100.0%	-5.49 [-7.04, -3.94]	ı •
Heterogeneity: Tau ² =	5.84; Chi ² = 24	9.29, df = 1	3 (P < 0.0	0001); I ²	= 95%				
Test for overall effect:									-100 -50 0 50 10 Favours [Simultaneous] Favours [Staged]



minimal morbidity [41]. It is interesting to note that in this meta-analysis, patients undergoing staged resection had more postoperative complications as compared with those undergoing staged resection. The increase in complications seen in the staged resection group might be explained by the need for two laparotomies and a resulting increase of complications associated with laparotomy.

The acceptance of simultaneous colorectal and liver resection is increasing, at least in patients with right colonic primary and liver metastases that need a minor hepatectomy. But the time of resection of synchronous metastases is still disputed. Many factors should be taken into consideration when making a decision, such as the extent of hepatic resection, the age of patient, and whether the patient has chronic liver disease or not. Simultaneous resection should be avoided in patients aged above 70 years because this increases the likelihood of postoperative mortality [29]. Patients in whom the odds of postoperative hepatic insufficiency are high, such as patients with chronic liver disease, should not be treated with simultaneous procedures. Overall, how to deal with simultaneous CLM is an important research topic correlated to improving the prognosis of patients and the safety of perioperative procedures.

The limitation of this study in particular, the differences between conflicting facts in the disease severity between the two groups, makes the interpretation of any findings difficult. This study can only confirm that in the presence of limited hepatic disease, simultaneous resections result in similar oncological outcomes as staged resections for patients with more extensive metastatic disease. This meta-analysis serves to highlight that most centers elect to perform simultaneous resections only in patients with limited hepatic disease introducing a significant source of bias in comparative studies with the patients in the staged resection group inevitably having more extensive liver disease. This demonstrates the need for prospective studies comparing simultaneous and staged resections, which should avoid bias by comparing similar metastatic burdens between the two groups.

From this meta-analysis of published data, the simultaneous resection of colorectal primary tumor and liver metastases showed no difference between mortality and

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	SIMULTANEOUS RESECTION		STAGED RESE	CTION		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Brouquet 2010	8	43	12	72	2.4%	1.14 [0.43, 3.07]	
Capussotti 2006	10	31	27	48	4.8%	0.37 [0.14, 0.95]	
Capussotti 2007	25	70	21	57	5.0%	0.95 [0.46, 1.97]	
Chua 2004	30	64	21	32	5.0%	0.46 [0.19, 1.11]	
de Hass 2010	6	55	44	173	6.3%	0.36 [0.14, 0.90]	
Kaibori 2010	12	32	6	42	1.1%	3.60 [1.17, 11.06]	
Luo 2010	61	129	150	276	16.8%	0.75 [0.50, 1.15]	
Martin 2003	65	134	71	106	13.6%	0.46 [0.27, 0.79]	
Martin 2009	39	70	88	160	7.9%	1.03 [0.58, 1.81]	
Moug 2010	11	32	21	32	4.6%	0.27 [0.10, 0.77]	
Reddy 2007	49	135	27	70	7.6%	0.91 [0.50, 1.65]	
Slupski 2009	4	28	8	61	1.4%	1.10 [0.30, 4.03]	
Tanaka 2004	11	39	6	37	1.5%	2.03 [0.66, 6.21]	
Thelen 2007	7	40	45	179	4.5%	0.63 [0.26, 1.53]	
Turrini 2007	12	57	19	62	4.8%	0.60 [0.26, 1.39]	
Vassilio 2007	18	25	59	78	2.7%	0.83 [0.30, 2.28]	
Wang 2008	9	37	9	46	2.0%	1.32 [0.46, 3.76]	
Weber 2003	8	35	20	62	3.7%	0.62 [0.24, 1.61]	
Yan 2007	23	73	13	30	4.2%	0.60 [0.25, 1.44]	
Total (95% CI)		1129		1623	100.0%	0.73 [0.61, 0.87]	•
Total events	408		667				
Heterogeneity: Chi ² =	28.14, df = 18 (P = 0.0	6); P= 36%					has the stand
	Z = 3.53 (P = 0.0004)					F	0.01 0.1 1 10 100 avours [Simultaneous] Favours [Staged]

Fig. 8 Forest plot showing the result of the meta-analysis comparing overall complication following simultaneous resection versus staged resection for synchronous colorectal liver metastases

	SIMULTANEOUS RES	ECTION	STAGED RESE	CTION		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Brouquet 2010	23	43	51	72	34.2%	0.47 [0.22, 1.04	
Slupski 2009	8	28	15	61	13.0%	1.23 [0.45, 3.35	i —
Tanaka 2004	28	39	20	37	11.2%	2.16 (0.84, 5.60	i +
Turrini 2007	7	57	16	62	26.0%	0.40 [0.15, 1.07	i ————————————————————————————————————
Wang 2008	13	37	14	46	15.6%	1.24 [0.49, 3.11	i — •
Total (95% CI)		204		278	100.0%	0.86 [0.58, 1.29]	1 🔺
Total events	79		116				· 1
Heterogeneity: Chi2 =	9.24, df = 4 (P = 0.06);	² = 57%					
Test for overall effect:							0.01 0.1 1 10 100 Favours [Simultaneous] Favours [Staged]

Fig. 9 Forest plot showing the result of the meta-analysis comparing postoperative recurrence following simultaneous resection versus staged resection for synchronous colorectal liver metastases

overall survival, but the disease-free survival rates were similar to staged resection. With the shorter hospital stay and lower morbidity rate, we can conclude that simultaneous resection is safe and efficient and could be considered as the preferred treatment option in appropriately selected patients with resectable SCLM. However, the heterogeneity among the studies remains, and the result of this meta-analysis should be interpreted with caution.

Conflict of interest

All the authors (Sunil Man Bijukchhe, Li Heping, and Li Tao) have no conflict of interest to declare.

References

1. Ferlay J, Shin H, Bray F, et al. GLOBOCAN 2008, Cancer incidence and mortality worldwide, IARC CancerBase. Lyon: International Agency for Research on Cancer; 2010.

- Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, et al. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. J Pathol. 1986;150(3):195–203.
- Scheele J, Altendorf-Hofmann A. Resection of colorectal liver metastases. Langenbeck's archives of surgery. 1999;384(4):313–27.
- 4. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg. 1990;77(11):1241-6.
- 5. Adam R. Colorectal cancer with synchronous liver metastases. Br J Surg. 2007;94(2):129-31.
- Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. 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. 1996;77(7):1254–62.
- 7. Jaeck D, Bachellier P, Weber JC, Mourad M, Walf P, Boudjema K. Surgical treatment of synchronous hepatic metastases of colorectal cancers. Simultaneous or delayed resection? Annales de chirurgie. 1996;50(7):507-12; discussion 13-6.

	SIMULTANEOUS RES	ECTION	STAGED RESE	CTION		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Brouquet 2010	2	43	2	72	9.5%	1.71 [0.23, 12.58]	
Capussotti 2006	1	31	0	48	2.5%		
Capussotti 2007	1	70	0	57	3.6%	2.48 [0.10, 62.10]	
Chua 2004	0	64	0	32		Not estimable	
de Hass 2010	0	55	1	173	4.8%	1.04 [0.04, 25.80]	
Kaibori 2010	0	32	0	42		Not estimable	
Luo 2010	2	129	6	276	25.0%	0.71 [0.14, 3.56]	
Martin 2003	3	134	3	106	21.7%	0.79 [0.16, 3.98]	
Martin 2009	0	70	1	160	6.0%	0.75 [0.03, 18.74]	
Reddy 2007	4	135	0	70	4.2%	4.83 [0.26, 90.91]	
Tanaka 2004	0	39	0	37		Not estimable	
Thelen 2007	4	40	2	179	4.4%	9.83 [1.73, 55.73]	
Turrini 2007	2	57	3	62	18.4%	0.72 [0.12, 4.44]	
Vassilio 2007	0	25	0	78		Not estimable	
Wang 2008	0	37	0	46		Not estimable	
Weber 2003	0	37	0	46		Not estimable	
Yan 2007	0	73	0	30		Not estimable	
Total (95% CI)		1071		1514	100.0%	1.58 [0.84, 2.96]	•
Total events	19		18				-
Heterogeneity: Chi*=	8.01, df = 9 (P = 0.53);	² = 0%					have de la constante de la con
Test for overall effect:						F	0.01 0.1 1 10 100 avours [Simultaneous] Favours [Staged]

Fig. 10 Forest plot showing the result of the meta-analysis comparing postoperative mortality following simultaneous resection versus staged resection for synchronous colorectal liver metastases

- 8. Lyass S, Zamir G, Matot I, Goitein D, Eid A, Jurim O. Combined colon and hepatic resection for synchronous colorectal liver metastases. J Surg Oncol. 2001;78(1):17-21.
- Elias D, Detroz B, Lasser P, Plaud B, Jerbi G. Is simultaneous hepatectomy and intestinal anastomosis safe? Am J Surg. 1995;169(2):254-60.
- 10. de Santibanes E, Lassalle FB, McCormack L, Pekolj J, Quintana GO, Vaccaro C, et al. Simultaneous colorectal and hepatic resections for colorectal cancer: postoperative and longterm outcomes. J Am Coll Surg. 2002;195(2):196–202.
- 11. Martin R, Paty P, Fong Y, Grace A, Cohen A, DeMatteo R, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg. 2003;197(2):233-41; discussion 241-2.
- Vassiliou I, Arkadopoulos N, Theodosopoulos T, Fragulidis G, Marinis A, Kondi-Paphiti A, et al. Surgical approaches of resectable synchronous colorectal liver metastases: timing considerations. World J Gastroenterol: WJG. 2007;13(9):1431-4.
- Chua HK, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Colon Rectum. 2004;47(8):1310–6.
- 14. Jaeck D, Bachellier P, Weber JC, Boudjema K, Mustun A, Paris F, et al. Surgical strategy in the treatment of synchronous hepatic metastases of colorectal cancers. Analysis of a series of 59 operated on patients. Chirurgie. 1999;124(3):258-63.
- 15. Weber JC, Bachellier P, Oussoultzoglou E, Jaeck D. Simultaneous resection of colorectal primary tumour and synchronous liver metastases. Br J Surg. 2003;90(8):956-62.
- Tanaka K, Shimada H, Matsuo K, Nagano Y, Endo I, Sekido H, et al. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery. 2004;136(3):650–9.
- Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/ clinical_epidemiology/oxford.htm (2005).

- Brouquet A, Mortenson MM, Vauthey JN, Rodriguez-Bigas MA, Overman MJ, Chang GJ, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? J Am Coll Surg. 2010;210(6):934-41.
- 19. Capussotti L, Ferrero A, Vigano L, Ribero D, Lo Tesoriere R, Polastri R. Major liver resections synchronous with colorectal surgery. Ann Surg Oncol. 2007;14(1):195-201.
- 20. Capussotti L, Vigano' L, Ferrero A, Lo Tesoriere R, Ribero D, Polastri R. Timing of resection of liver metastases synchronous to colorectal tumor: proposal of prognosis-based decisional model. Ann Surg Oncol. 2007;14(3):1143-50.
- 21. de Haas RJ, Adam R, Wicherts DA, Azoulay D, Bismuth H, Vibert E, et al. Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases. Br J Surg. 2010;97(8):1279–89.
- 22. Kaibori M, Iwamoto S, Ishizaki M, Matsui K, Saito T, Yoshioka K, et al. Timing of resection for synchronous liver metastases from colorectal cancer. Dig Dis Sci. 2010;55(11):3262-70.
- 23. Luo Y, Wang L, Chen C, Chen D, Huang M, Huang Y, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastases. J Gastrointest Surg. 2010;14(12):1974–80.
- Martin RC 2nd, Augenstein V, Reuter NP, Scoggins CR, McMasters KM. Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. J Am Coll Surg. 2009;208(5):842–50; discussion 850–2.
- 25. Moug SJ, Smith D, Leen E, Roxburgh C, Horgan PG. Evidence for a synchronous operative approach in the treatment of colorectal cancer with hepatic metastases: a case matched study. Eur J Surg Oncol. 2010;36(4):365-70.
- 26. van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. Br J Surg. 2010;97(3):383–90.
- 27. Reddy SK, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2007;14(12):3481–91.

- Slupski M, Włodarczyk Z, Jasinski M, Masztalerz M, Tujakowski J. Outcomes of simultaneous and delayed resections of synchronous colorectal liver metastases. Can J Surg. 2009;52(6):E241-4.
- 29. Thelen A, Jonas S, Benckert C, Spinelli A, Lopez-Hanninen E, Rudolph B, et al. Simultaneous versus staged liver resection of synchronous liver metastases from colorectal cancer. Int J Colorectal Dis. 2007;22(10):1269–76.
- 30. Turrini O, Viret F, Guiramand J, Lelong B, Bege T, Delpero JR. Strategies for the treatment of synchronous liver metastasis. Eur J Surg Oncol. 2007;33(6):735-40.
- 31. Wang QX, Xu B, Yan JJ, Zhou FG, Yan YQ. Treatment strategy for synchronous liver metastasis from colorectal cancer. Ai zheng. 2008;27(7):748-51.
- Yan TD, Chu F, Black D, King DW, Morris DL. Synchronous resection of colorectal primary cancer and liver metastases. World J Surg. 2007;31(7):1496-501.
- 33. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309-18; discussion 318-21.
- 34. Weber JC, Nakano H, Bachellier P, Oussoultzoglou E, Inoue K, Shimura H, et al. Is a proliferation index of cancer cells a reliable prognostic factor after hepatectomy in patients with colorectal liver metastases? Am J Surg. 2001;182(1):81–8.

- 35. Weber JC, Schneider A, Rohr S, Nakano H, Bachellier P, Mechine A, et al. Analysis of allelic imbalance in patients with colorectal cancer according to stage and presence of synchronous liver metastases. Ann Surg. 2001;234(6):795– 802; discussion 802–3.
- Fong Y, Blumgart LH. Hepatic colorectal metastasis: current status of surgical therapy. Oncology (Williston Park). 1998;12(10):1489-98; discussion 1498-500, 1503.
- Vogt P, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. World J Surg. 1991;15(1):62-7.
- Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg. 2000;231(5):743–51.
- Jenkins LT, Millikan KW, Bines SD, Staren ED, Doolas A. Hepatic resection for metastatic colorectal cancer. Am Surg. 1997;63(7):605-10.
- 40. Scheele J. Hepatectomy for liver metastases. Br J Surg. 1993;80(3):274-6.
- 41. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg. 2002;236(4):397-406; discussion 406-7.