Original Article

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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 −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 · Colorectal cancer · Liver metastases · Simultaneous resection · 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.

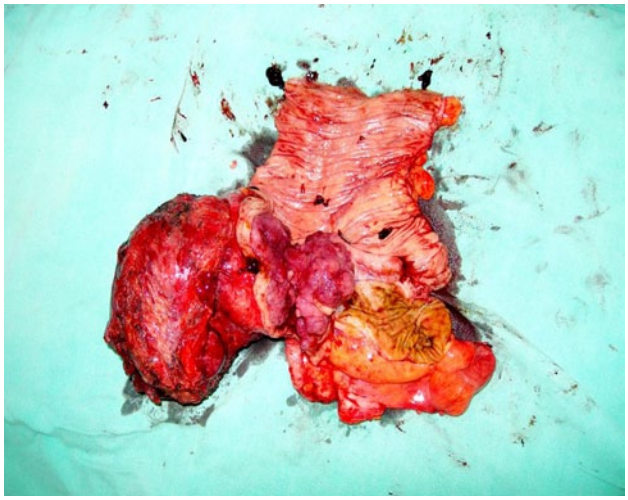

Fig. 1 A mass of approximately 10 × 10 cm at ileocecal junction. Intraoperative frozen section showed adenocarcinoma

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).

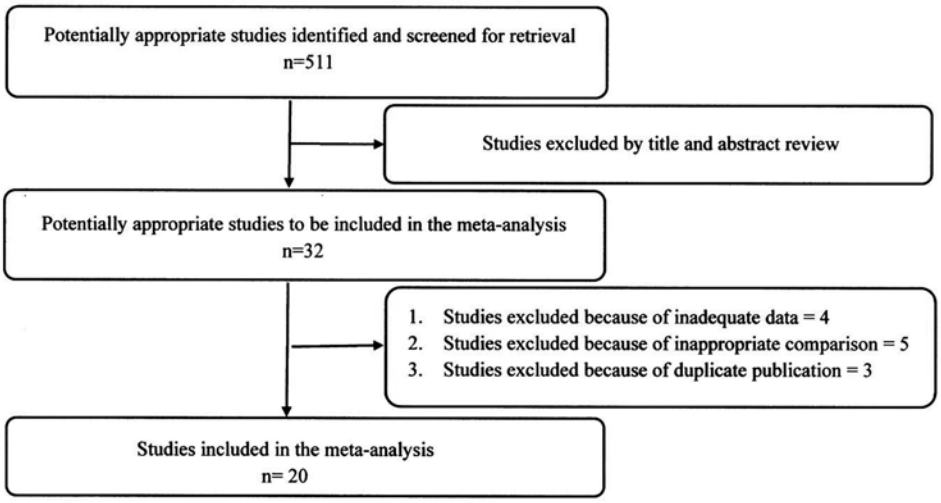

Fig. 2 Flow chart showing result of systematic literature search

Table 1 The key characteristics of the included studies

Year	Author	Country	Study type	Total no. of patients	Simultaneous				Staged				Score
					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*				

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

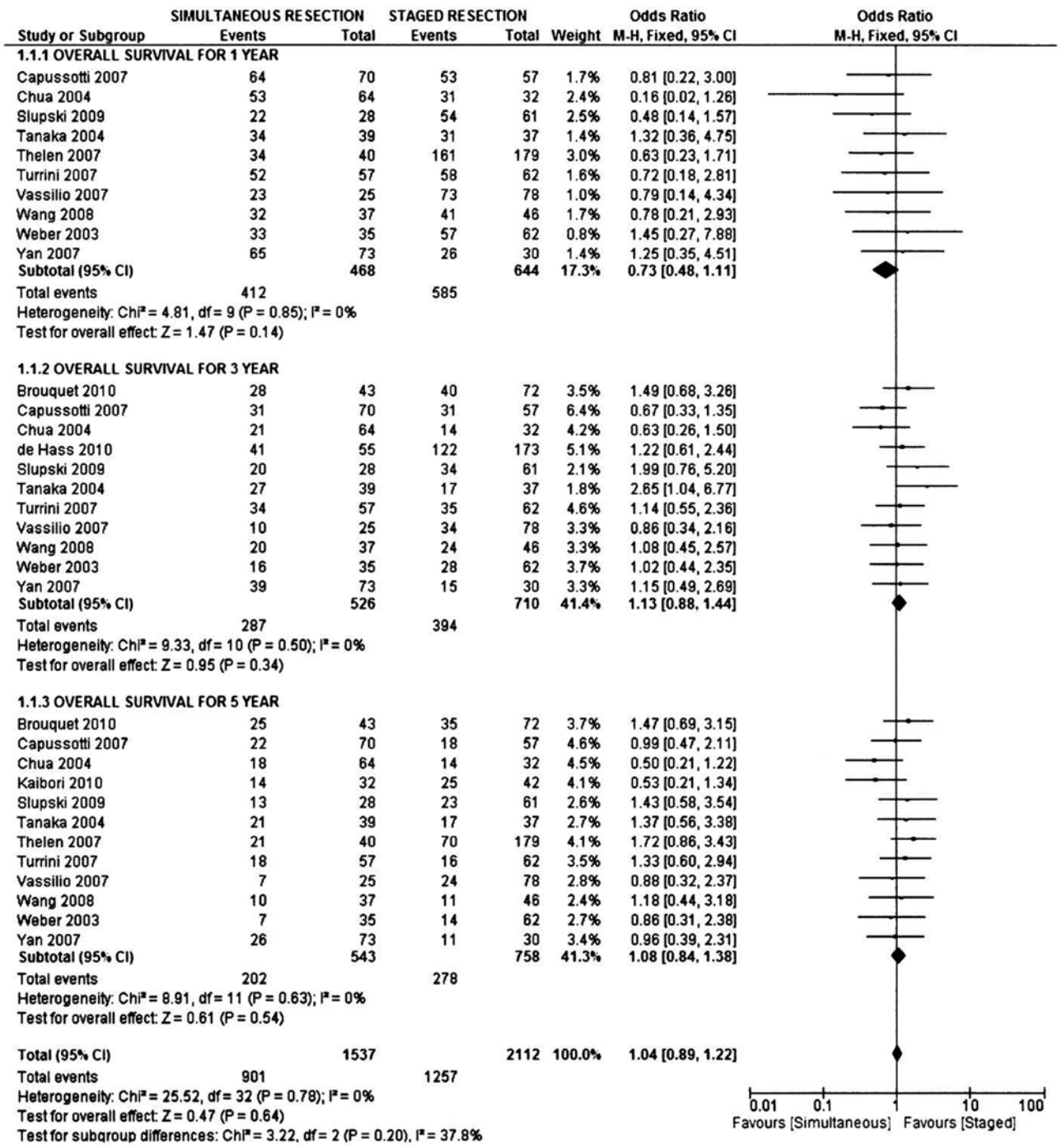

Fig. 3 Forest plot showing the result of the meta-analysis comparing overall survival rate at 1, 3, and 5 years after simultaneous resection versus staged resection for synchronous colorectal liver metastases

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

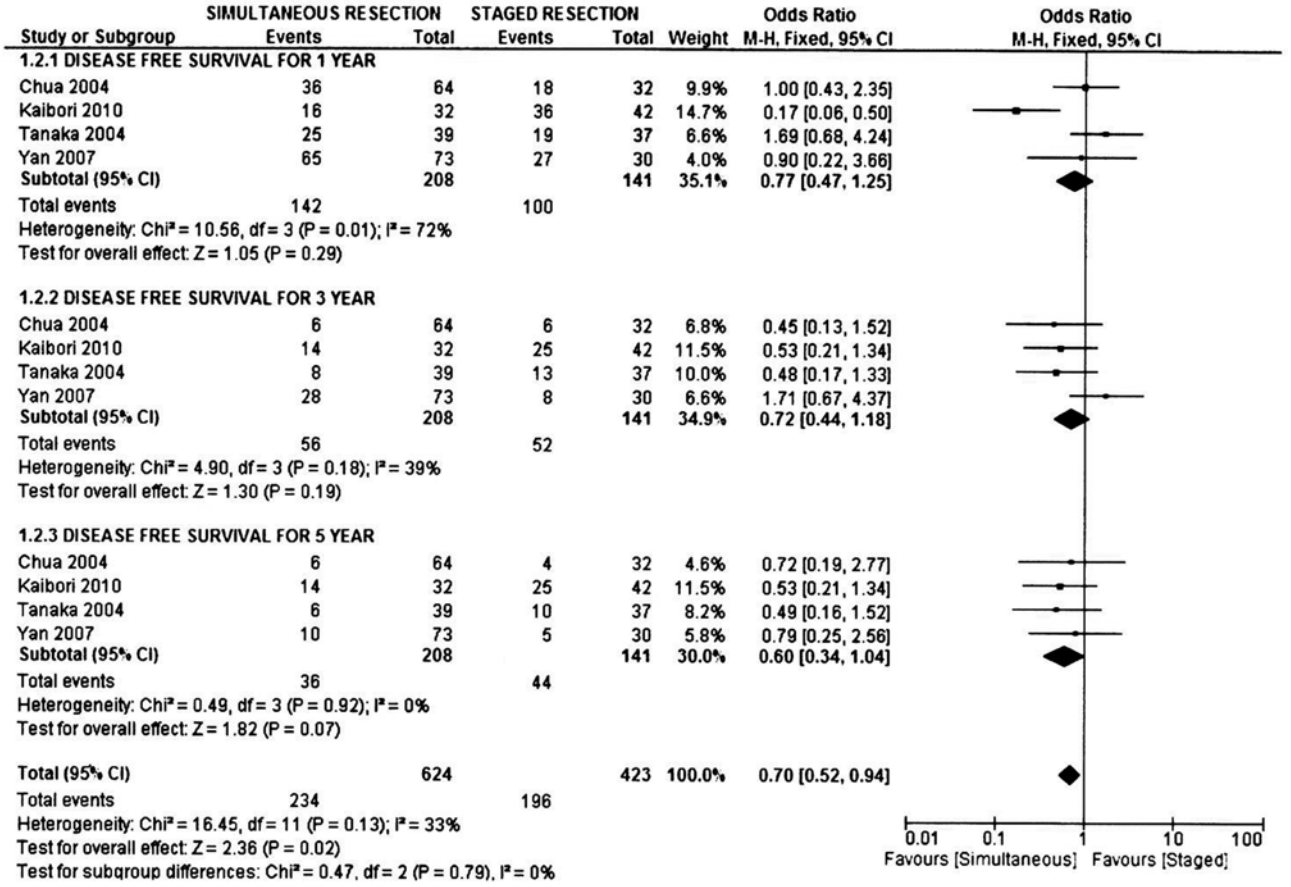

Fig. 4 Forest plot showing the result of the meta-analysis comparing disease-free survival rate at 1, 3, and 5 years after simultaneous resection versus staged resection for synchronous colorectal liver metastases

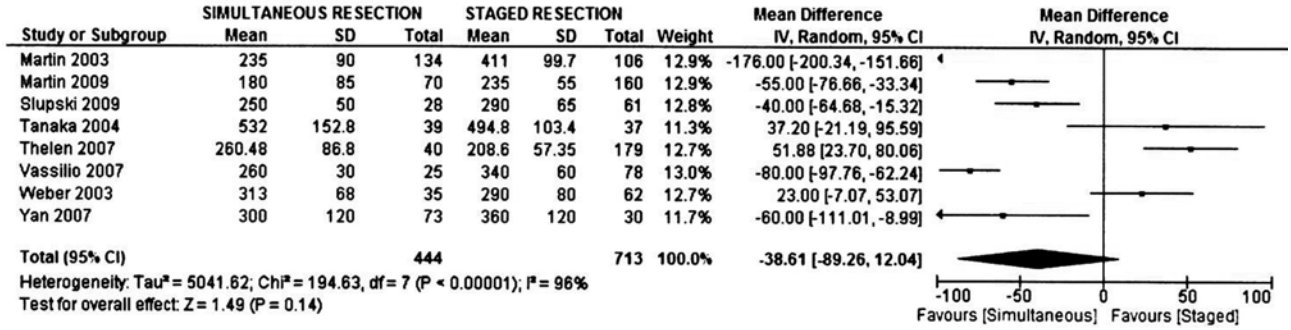

Fig. 5 Forest plot showing the result of the meta-analysis comparing operative time following simultaneous resection versus staged resection for synchronous colorectal liver metastases

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

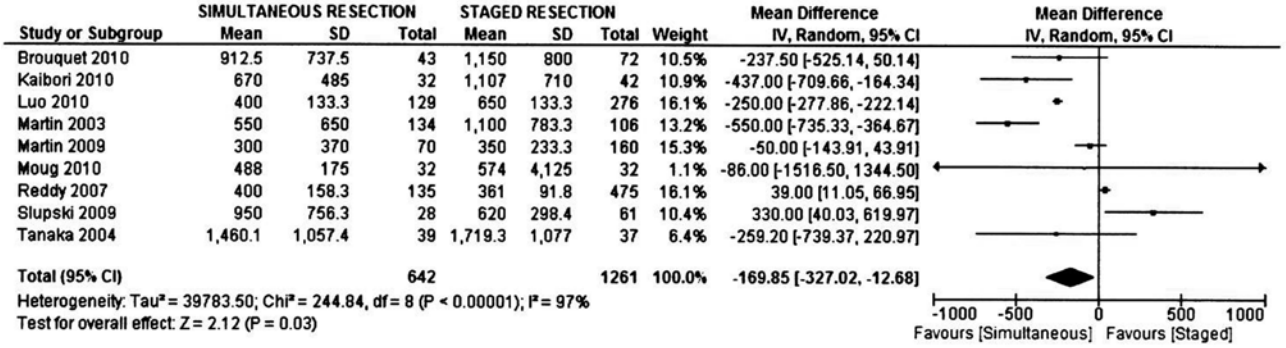

Fig. 6 Forest plot showing the result of the meta-analysis comparing intraoperative blood loss following simultaneous resection versus staged resection for synchronous colorectal liver metastases

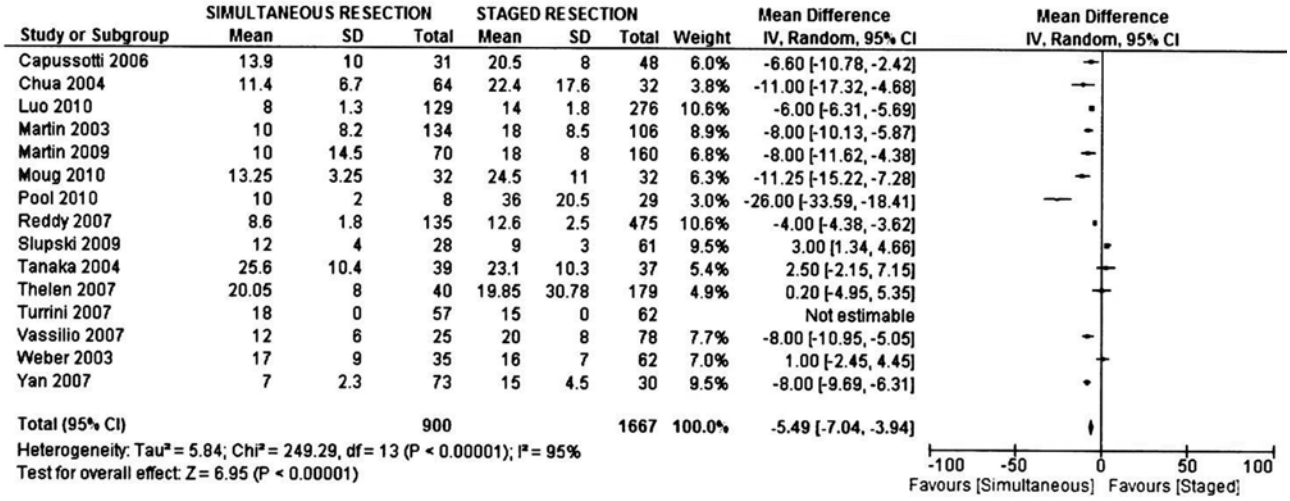

Fig. 7 Forest plot showing the result of the meta-analysis comparing length of hospital stay following simultaneous resection versus staged resection for synchronous colorectal liver metastases

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

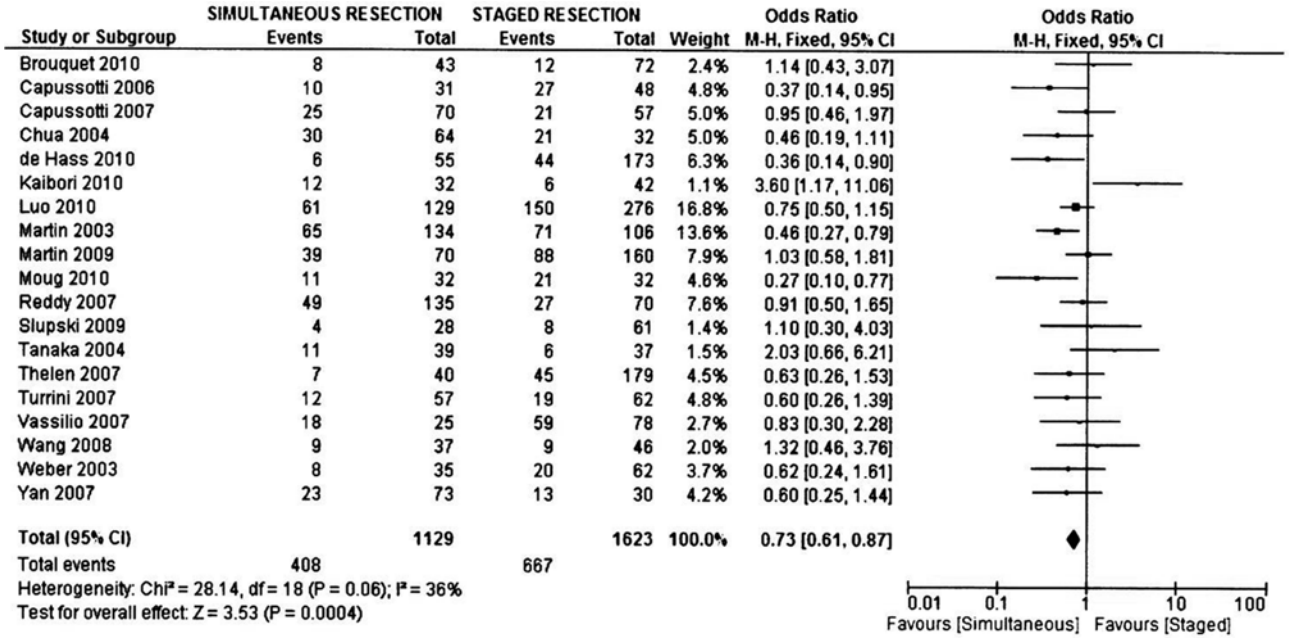

Fig. 8 Forest plot showing the result of the meta-analysis comparing overall complication following simultaneous resection versus staged resection for synchronous colorectal liver metastases

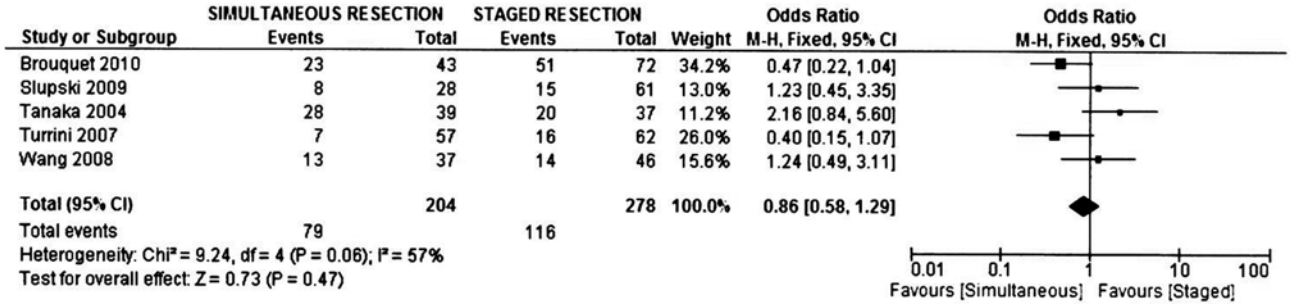

Fig. 9 Forest plot showing the result of the meta-analysis comparing postoperative recurrence following simultaneous resection versus staged resection for synchronous colorectal liver metastases

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.

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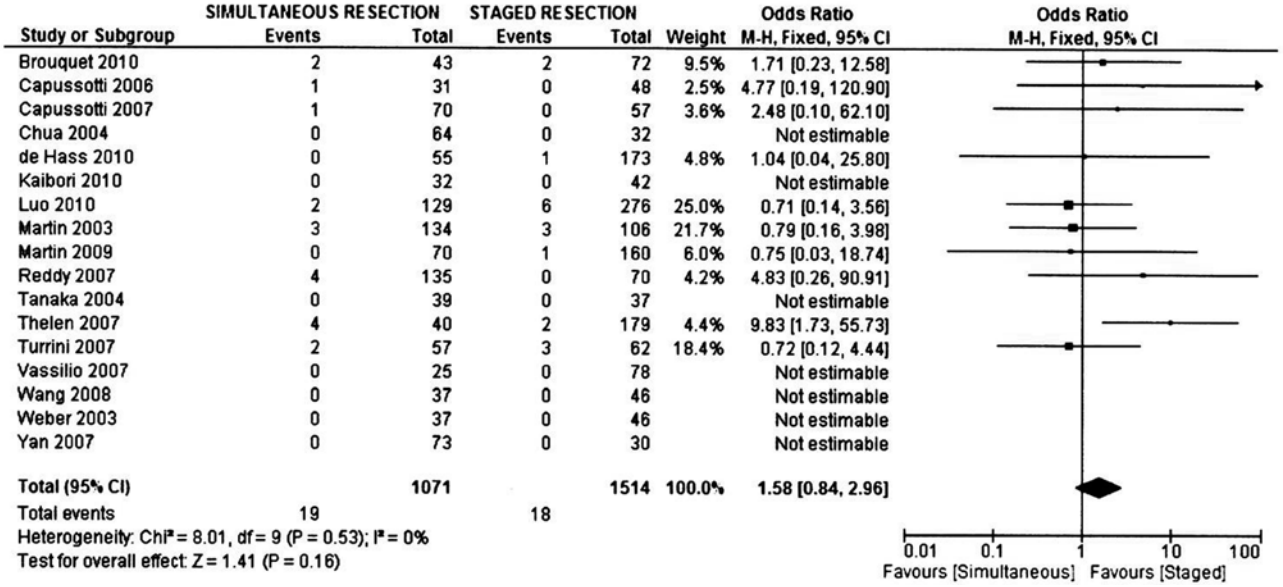

Fig. 10 Forest plot showing the result of the meta-analysis comparing postoperative mortality following simultaneous resection versus staged resection for synchronous colorectal liver metastases

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