

Gastrectomy Alone or in Combination With Hepatic Resection in the Management of Liver Metastases From Gastric Cancer: A Systematic Review Using an Updated and Cumulative Meta-Analysis

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Abstract

Background: Recent studies have demonstrated that hepatectomy in patients with synchronous hepatic gastric metastases may improve survival in certain patients. This study aimed to evaluate survival benefits of gastrectomy plus hepatectomy versus gastrectomy alone in patients with hepatic gastric metastases.

Methods: Studies were identified by a systematic search of Embase, PubMed, Cochrane Library, and Google Scholar databases. Traditional and cumulative meta-analyses were used to monitor the evidence over time.

Results: Eleven studies which included 861 patients compared gastrectomy plus hepatic resection in 349 patients with gastrectomy alone in 512 patients. Overall significantly better survival rates of 1, 2, 3, and 5 years were demonstrated for patients who underwent gastrectomy plus hepatic resection compared to patients who underwent gastrectomy alone ((hazard ratio (HR) = 0.52 (0.39, 0.69), $P < 0.001$), (HR = 0.85 (0.74, 0.97), $P = 0.01$), (HR = 0.80 (0.72, 0.90), $P = 0.003$), (HR = 0.83 (0.78, 0.90), $P < 0.001$), respectively).

Conclusions: Carefully selected patients with hepatic gastric metastases may benefit from hepatic resection.

Keywords: Hepatic metastases; Gastric adenocarcinoma; Hepatec-

tomy; Gastrectomy

Introduction

Gastric cancer has a poor prognosis and it is the second most common cause of cancer deaths worldwide [1]. At the time of diagnosis, only 30% of the patients are suitable for curative treatment [2]. Synchronous hepatic metastases are diagnosed in 3% to 14% of the patients [3, 4], while metachronous variants appear in 37% of patients after curative gastrectomy [5]. Current evidence recommends supportive therapy and palliative chemotherapy for patients with peritoneal spread and distant metastases [6]. The results of a randomized phase 3 trial conducted in Japan, South Korea and Singapore compared the survival benefits of gastrectomy followed with chemotherapy against chemotherapy alone in patients with advanced cancer and with a single non-curable factor confined either to the peritoneum, liver, or para-aortic lymph nodes (16a1/b2). The result did not demonstrate any survival benefits from the gastrectomy [7]. Therefore, gastrectomy cannot be justified as a treatment option for that group of patients.

Recent meta-analysis demonstrated survival benefits of hepatic resection in cases of hepatic gastric metastases in carefully selected patients [8].

The aim of the present study is to evaluate the survival benefits of the gastrectomy plus hepatectomy (GH) compared with gastrectomy (GA) alone for cases of hepatic metastases from gastric adenocarcinoma using traditional and cumulative meta-analyses.

Materials and Methods

This systematic review and meta-analysis was carried out in accordance with the guidelines set out in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist [9]. The article does not contain any studies with human or animal subjects performed by any of

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Literature search

A systematic literature search of articles published in the last 30 years was performed using the Embase, MEDLINE (PubMed), Cochrane library, and Google Scholar databases, using free text and MeSH search terms (gastric cancer, gastrectomy, hepatic or liver gastric metastases, hepatectomy or liver resection for gastric metastases, stomach neoplasms). A grey literature search of the clinicaltrials.gov website was also performed. References in the retrieved articles were checked manually and further analyzed. Disagreements between authors were resolved by consensus.

Study selection, inclusion and exclusion criteria

Cohort or retrospective studies, and case-matched studies that evaluated the results of the patient undergoing any form of liver resection for liver gastric adenocarcinoma, in the absence of peritoneal metastases were included in the study. All reviews, narrative articles, cohort studies with less than 10 patients, extrahepatic metastases, malignancies other than gastric adenocarcinoma with liver metastases, studies with insufficient data regarding survival outcome after liver resection and non-English language publications were excluded.

Data extraction and outcomes

Two reviewers (PG and KR) independently extracted the following summary data for the included studies: name of authors; number of patients; age; gender; synchronous, metachronous, unilobar, bilobar, solitary and multiple liver metastases; neo-adjuvant and adjuvant therapy; morbidity; median follow-up time; median survival; 1-, 2-, 3-, and 5-year overall survival; and 30-day mortality. Primary outcomes were 1-, 2-, 3-, and 5-year overall survival.

Assessment of included studies

Two authors (PG, KR) independently assessed the quality of evidence provided by each study using the Oxford Center for Evidence-Based Medicine scoring system [10]. Moreover, the methodological qualities of all retrospective comparative studies were assessed with the validated Newcastle-Ottawa Scale (NOS) [11]; studies that scored ≥ 7 were considered of high quality. NOS is an assessment tool used to measure the quality of retrospective studies included in a systematic review and meta-analysis. Using this tool, each study was assessed using eight parameters, categorized into three groups: first, the selection of the study groups; second, the comparability of the groups; and third, the ascertainment of either the exposure or outcome of interest for case-control studies, respectively. One point was awarded for each quality item. The highest quality

studies were awarded up to nine points [11].

Statistical analysis

Statistical analysis was conducted using Review Manager 5.3 software (Cochrane Collaboration, Oxford, England). Heterogeneity was assessed through the I^2 statistic and cut-off values of 25%, 50%, and 75% were considered low, moderate, and high, respectively [12]. In such cases, both fixed- and random-effects models were produced, and the conclusions compared, with the latter used preferentially in cases where there were discrepancies between the two models. In cases of I^2 values less than 25%, fixed-effects models were used throughout.

Dichotomous variables were analyzed based on odds ratios (ORs) with 95% confidence intervals (CIs). For the analyzed outcomes, the reference categories were selected so that $OR < 1$ favored hepatectomy. Continuous variables were combined based on both the mean difference (MD) and the standardized mean difference (SMD). For studies that did not report the mean and variance for the two groups, these values were estimated from the median, range, and the size of sample where possible, using the technique described by Hozo et al [13].

Analysis of long-term survival was performed by combining the hazard ratios (HRs) and 95% CIs from the included studies. These were rarely reported, and so were estimated using the method described by Parmar et al [14], where this was possible. Studies that reported the numbers at risk were combined with either the quoted survival rates or values read from enlarged plots of the Kaplan-Meier curves to produce the estimates. Where numbers at risk were not quoted, constant censoring over the period of follow-up was assumed in the estimation. The studies were weighted using an inverse variance approach and $HRs < 1$ favored the hepatectomy plus gastrectomy approach.

In all analyses, the significance level was set at $P < 0.05$. Cumulative meta-analysis was conducted using STATA software (version 15, Stata Corp LP, TX, USA).

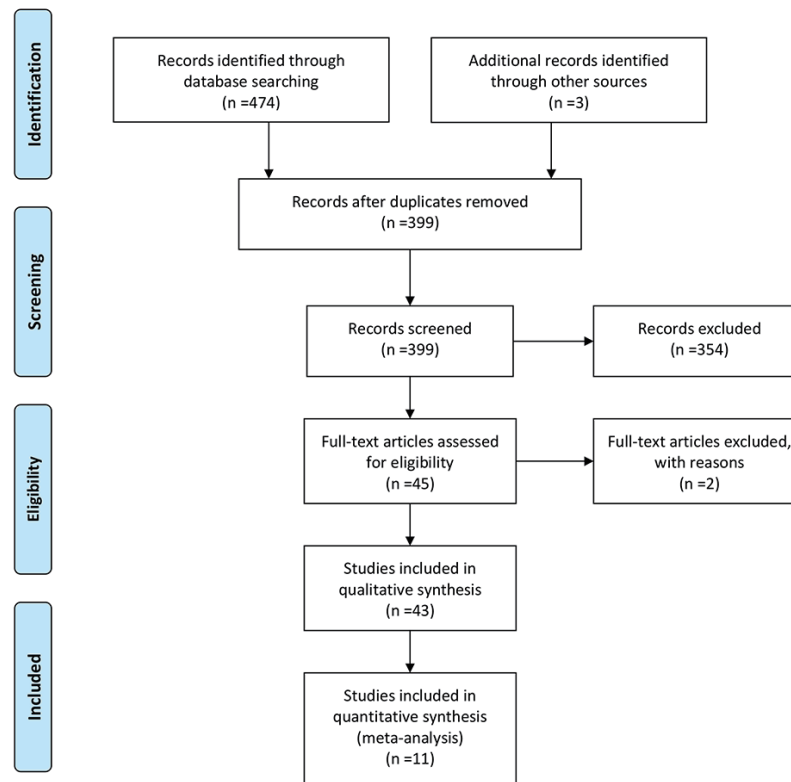
Sensitivity analysis

Analyses of outcomes were conducted using both random-effects and fixed-effects models in order to assess the impact of heterogeneity on the results. Moreover, subgroup analyses of the eastern and western studies were performed. Publication bias was not estimated because less than 10 studies were included in each outcome [15]. Cumulative meta-analysis was performed to detect the accumulation of evidence over time.

Results

Search strategy and included study characteristics

Forty-three studies, which included 1,198 patients, who underwent hepatic resection for hepatic metastases from gastric adenocarcinoma, were selected from a pool of 1,329 studies (Fig. 1) [3, 4, 22, 16-55]. Of these 43 studies, 11 studies comprised



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Figure 1. Flow diagram of the search strategy.

of 861 patients compared gastrectomy plus hepatic resection (349 patients) to gastrectomy without hepatic resection (512 patients). Two studies were excluded because of incomplete reporting of outcomes.

The quality of evidence of all 43 studies were assessed as type 2b using the Oxford Center for Evidence-Based Medicine scoring system.

All 11 studies comparing gastrectomy plus hepatic resection to gastrectomy alone scored more than seven stars in the NOS and were therefore characterized as being of high quality (Supplementary Table 1, www.jocmr.org).

Results of the 43 studies included in qualitative synthesis

The median age of the 1,198 patients who underwent hepatic resection was 64 (25 - 89), the majority of whom were men 752 (63%). Eight percent (8%) of the patients in these various studies underwent neoadjuvant chemotherapy, whereas 48% of them underwent adjuvant chemotherapy. Six hundred and seven (62%) patients underwent resection for synchronous metastases and 376 (38%) for metachronous metastases. Unilateral metastases occurred in 525 (74%) patients and 188 (26%) pa-

tients have bilateral metastases. Five hundred and forty (59%) patients underwent resection for solitary tumors and 377 (41%) for multiple tumors. Minor hepatectomies were performed in 74% of patients. Morbidity was 26% (with a range of 0% to 60%) and the 30-day mortality was 0 (0% to 30%).

The median 1, 2, 3, 5-year survival was 68%, 29.5%, 32% and 27%, respectively with a median survival of 21 (9 - 52) months.

Cumulative meta-analysis

Cumulative meta-analysis demonstrated that there were no studies which indicate the particular impact on the results over time. In the dichotomous variables of synchronous/metachronous and solitary/multiple metastases, turning points on the accumulation of evidence over time were identified. Particularly, in the synchronous/metachronous forest plot, two time periods were depicted. One ranged from 1994 to 2014 when nonsignificant differences were demonstrated and a second period starting from the study of Sinohara et al in 2015 [52] until present when it was demonstrated that significantly less metachronous metastases compared to synchronous cases were

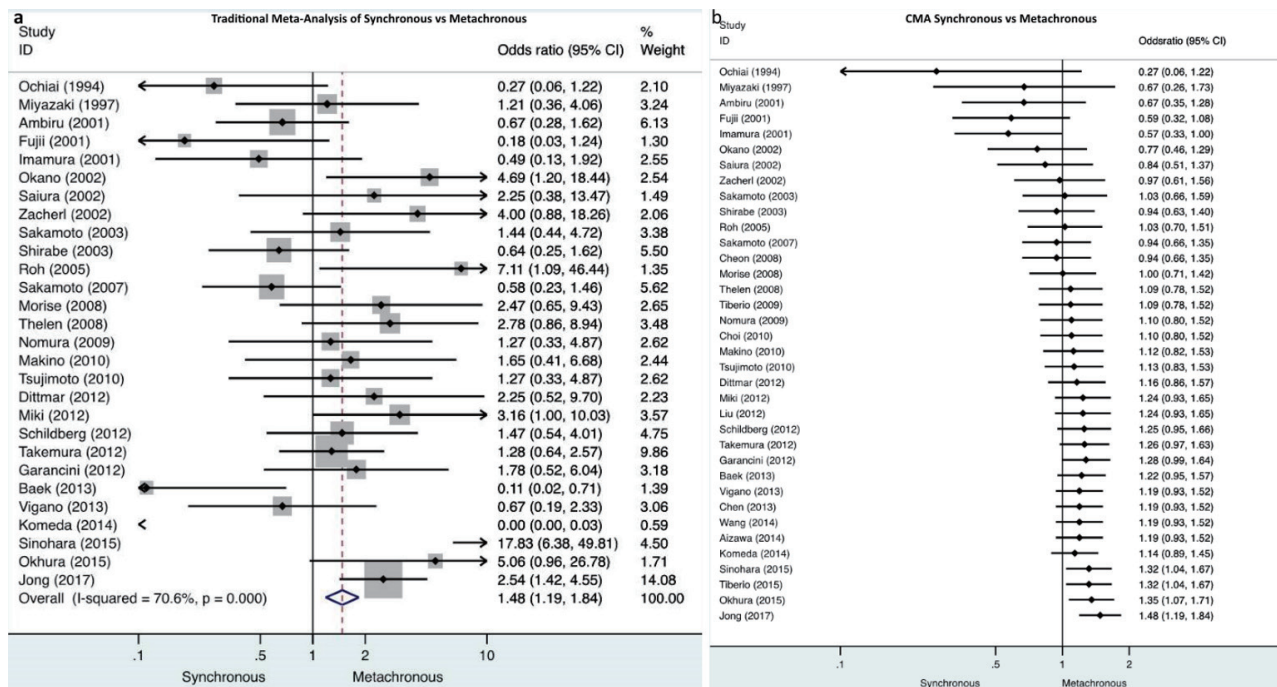


Figure 2. a) Traditional meta-analysis of synchronous/metachronous metastases demonstrates that significantly less metachronous metastases were included compared to synchronous metastases. b) Cumulative meta-analysis of synchronous/metachronous metastases depicts two time periods, one from 1994 to 2014 when nonsignificant differences were demonstrated and a second from 2015 until present when it was demonstrated that significantly less metachronous metastases compared to synchronous cases were included.

included (Fig. 2). Similarly, the time period between 1994 and 2003 is depicted by solitary/multiple forest plots when demonstrably nonsignificant differences exists between solitary and multiple metastases in the included studies. A second period starting in 2003 with the study of Shirabe et al [24] and lasting until present time, demonstrates that significantly less multiple metastases compared to solitary ones were included (Fig. 3).

Meta-analysis of studies comparing GH against GA

Tumor characteristics

There were no significant differences in the proportion of synchronous metastases between the GH and GA groups. Similarly, there were no significant differences in the proportion of metachronous metastases between GH (28%) versus GA (29%) groups. The proportion of patients with unilobar distribution was significantly higher in the GH (58%) than in the GA (25%) groups. There was no significant difference in the proportion of solitary metastases between the GH cohort and GA cohort (Table 1).

Primary outcomes 1-, 2-, 3-, and 5-year overall survival

Patient survival for 1-, 2-, 3-, and 5-year was found to be significantly better in GH cohort compared to the GA group (Ta-

ble 1) (Fig. 4).

Discussion

This updated traditional and cumulative meta-analysis consists of 43 studies which included 1,198 patients with a median age of 64 (25 - 89) years, the majority of whom were men accounting for 63%, compared to 27% who were women. Synchronous metastases cases were 62% and metachronous cases 38%. Unilobar cases were 74% and bilobar 26%. Patients with solitary lesions were 59% while those with multiple lesions were 41%. The 30-day overall mortality was 0% (0-30%) and the median survival period was 21 (9 - 52) months. The 1-, 2-, 3-, and 5-year overall survival was 68% (39-96%), 29.5% (25-50%), 32% (14-70%), and 27% (9-60%), respectively. The updated results of the present study did not show any significant difference when compared with the results of the previous meta-analysis [8].

Interestingly, CMA depicted turning points in the accumulation of evidence over time. The traditional meta-analysis demonstrated that significantly less metachronous metastases were included in the studies; on the contrary the CMA reveals that its effect size was nonsignificant for the period from 1994 to 2014, the second period starts in 2015 until present day and it demonstrates that significantly more synchronous metastases were included compared to metachronous. Similarly, discrepancies between the traditional and CMA were demonstrated in the evaluation of solitary/multiple metastases (Figs. 2, 3). The

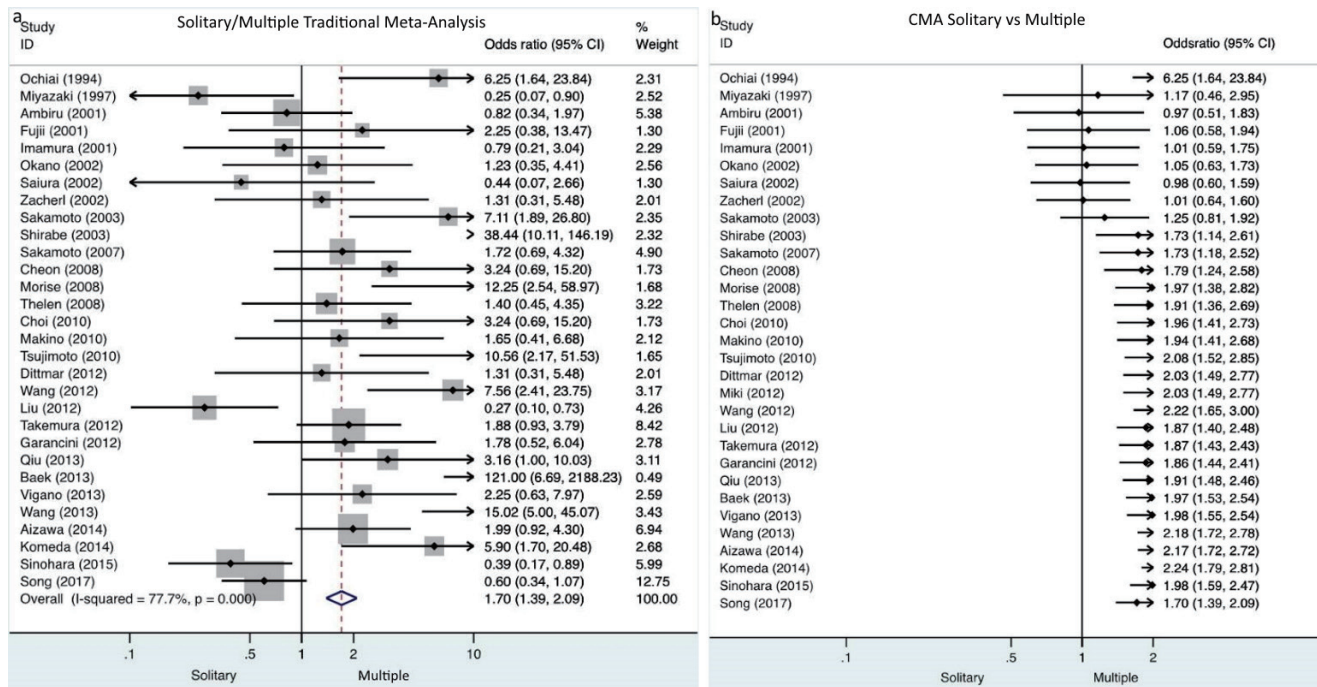


Figure 3. a) Traditional meta-analysis of solitary/multiple metastases demonstrates that significantly less multiple metastases were included compared to solitary metastases. b) Cumulative meta-analysis of solitary/multiple metastases depicts two time periods, one from 1994 to 2003 when nonsignificant differences were demonstrated and a second from 2003 until present when it was demonstrated that significantly less multiple metastases compared to solitary cases were included.

Table 1. Outcomes of Interest

Outcome of interest	Number of studies and patients (%; events/total)	Statistical method, estimated effect, 95% CI	P value	I ² (%)
Age	4, 244	MD = -2.40 (-6.13 to 1.34)	0.23	57
Synchronous metastases	4, 206 (54%; 56/104) (51%; 52/102)	OR = 0.42 (0.02 to 8.50)	0.57	89
Metachronous metastases	4, 206 (28%; 29/104) (29%; 30/102)	OR = 1.72 (0.86 to 3.43)	0.12	85
Unilobar metastases	6, 430 (58%; 92/159) (25%; 67/271)	OR = 3.88 (2.43 to 6.19)	< 0.001	0
Bilobar metastases	6, 430 (26%; 41/159) (49%; 133/271)	OR = 0.27 (0.08 to 0.91)	0.04	83
Solitary metastases	5, 320 (52%; 64/124) (36%; 71/196)	OR = 2.98 (0.95 to 9.37)	0.06	70
Multiple metastases	5, 320 (33%; 41/124) (66%; 129/196)	OR = 0.17 (0.04 to 0.80)	0.02	83
1-year OS	9, 637	HR = 0.52 (0.39 to 0.69)	< 0.001	39
2-year OS	4, 397	HR = 0.85 (0.74 to 0.97)	0.01	44
3-year OS	9, 637	HR = 0.80 (0.72 to 0.90)	0.003	58
5-year OS	7, 452	HR = 0.83 (0.78 to 0.90)	< 0.001	0
Subgroup analysis East versus West				
1-year OS East	6, 306	HR = 0.42 (0.28 to 0.65)	< 0.001	34
1-year OS West	3, 331	HR = 0.63 (0.43 to 0.91)	0.01	47
2-year OS West	3, 331	HR = 0.85 (0.71 to 1.01)	0.07	53
2-year OS East	1, 66	HR = 0.80 (0.65 to 1.00)	0.05	0
3-year OS East	6, 306	HR = 0.78 (0.70 to 0.86)	< 0.001	0
3-year OS West	3, 331	HR = 0.85 (0.69 to 1.05)	0.13	67
5-year OS East	5, 272	HR = 0.84 (0.78 to 0.91)	< 0.001	5
5-year OS West	2, 180	HR = 0.80 (0.68 to 0.94)	0.008	0

OS: overall survival; MD: mean difference; HR: hazard ratio; OR: odds ratios.

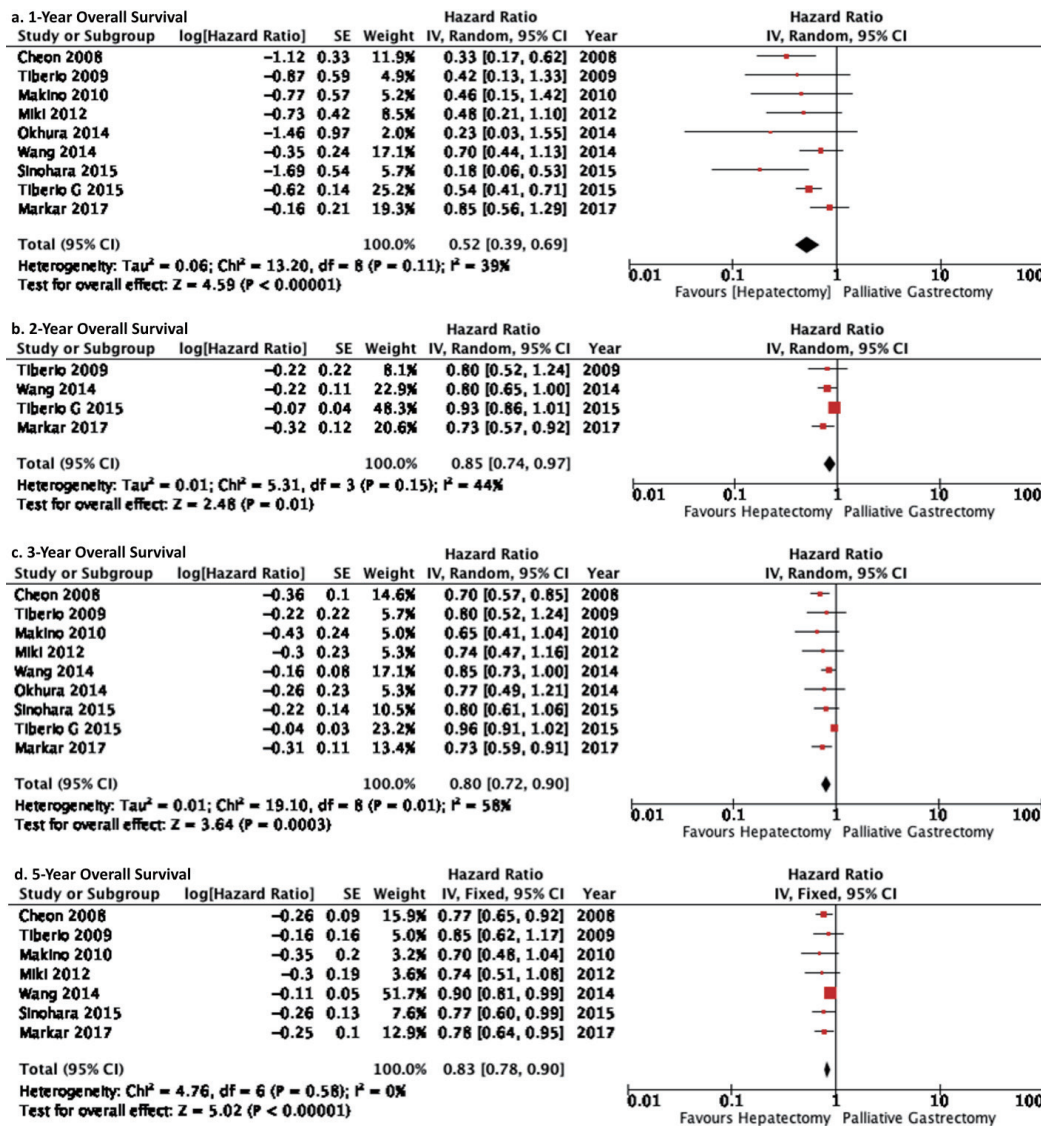


Figure 4. Forest plot depicting 1-, 2-, 3-, 5-year overall survival of gastrectomy plus hepatectomy versus gastrectomy alone. It is depicting that the gastrectomy plus hepatic resection cohort demonstrated significantly better survival benefits compared to gastrectomy alone.

above findings suggest that with the accumulation of evidence and experience, the selection of patients for hepatic resection became more meticulous and careful.

The pair-wise meta-analysis of 11 studies demonstrated that 1-, 2-, 3-, and 5-year overall survival was significantly better in gastrectomy plus hepatectomy cohort compared to gastrectomy alone cohort.

Subgroup analysis demonstrated that there was no evidence of significant difference between Eastern and Western countries in 1-year overall survival (OS); both demonstrated significant results. Interestingly, 2-year OS was marginally nonsignificant in East and West when compared separately. However, this became significant when the two samples were compared together. There was evidence that eastern studies demonstrated significantly better 3-year OS compared to west-

ern studies. There were nonsignificant differences in 5-year OS between East and West; both demonstrated significant results (Table 1). Of note, Markar et al [8] evaluated hepatic resections concomitant and non-concomitant with gastrectomy and reported better survival benefits for the East compared to the West. It is apparent that the cohort of patients who underwent gastrectomy with associated hepatic resection were more carefully selected and this is the reason of similar survival benefits between the East and West.

The results of the present study should be interpreted in the context of its limitations. All the studies were retrospective including small numbers of patients carefully selected without extra-hepatic metastases. Therefore, selection, institutional, national bias, underpowered sample size and smaller oncological burden may have influenced the results. Another caveat of

this study is that very few studies reported detailed morbidity data according to international classifications. Therefore, it was not possible to do meta-analysis of major morbidity.

Conclusions

The results of this study can justify the adjuvant role of hepatic resection for unilobar gastric liver metastases in carefully selected patients.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare they have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

PG contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript and statistical analysis; KJR was involved in analysis and interpretation of data, and drafting the manuscript; NA contributed to acquisition of data, analysis and interpretation of data, and drafting the manuscript; RPS contributed to acquisition of data, analysis and interpretation of data, drafting the manuscript, and study supervision.

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