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Surgical treatment of gastric cancer liver metastases: Systematic review and meta-analysis of long-term outcomes and prognostic factors

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ABSTRACT

The prognosis of patients with metastatic gastric cancer remains dismal, with palliative treatment as standard of care. However, encouraging results have been reported for surgical resection of liver only metastatic gastric cancer in carefully selected patients. A systematic review of articles published from 2000 onwards was conducted according to PRISMA guidelines. Twenty-nine studies were included in qualitative and quantitative analysis. Meta-analysis of proportions pointed out 29.1 % 5ySR (I 2 = 39 %). The pooled weighted median of MSTs was 31.1 months. T stage > 2, metastasis greatest dimension ≥ 5 cm, the presence of multiple metastases and bilobar disease resulted among the strongest predictors of mortality. Funnel plots, Egger's tests, and P-curve analyses failed to show significant publication bias. Based on strict selection criteria and robust statistical analyses, our results show that, in very carefully selected patients without extrahepatic disease, surgical resection with curative intent may significantly improve overall survival.

1. Introduction

Gastric cancer is the fifth most frequent neoplasia and the second cause of death for cancer worldwide (Globocan Observatory W, 2019). A substantial proportion of patients are diagnosed with or develop, during the course of the disease, distant metastases, mostly to the liver, peritoneal surface, and extra-regional lymph nodes. Despite a great effort over the years to improve survival of patients with liver metastases, the prognosis remains dismal. According to recent valuable pieces of evidence (Koizumi et al., 2008; Bang et al., 2010; Kang et al., 2017), the current median survival time for GCLM patients treated with systemic chemotherapy waves between 7 and 14 months.

The mainstay of treatment for stage IV disease in patients with good performance status is represented by fluoropyrimidine/platinum-based doublets or triplets palliative chemotherapy(National Comprehensive Cancer Network, 2020; Smyth et al., 2016). Nevertheless, despite the lack of prospective/randomized trials exploring the beneficial effect of surgical resection, recent systematic reviews with meta-analysis have reported encouraging results deriving from this approach (Gavriilidis et al., 2019; Montagnani et al., 2018; Markar et al., 2016). The 5-year survival rate ranges from 10 to 40 % in carefully selected patients.

Currently, according to the treatment algorithms of the principal international guidelines, patients with metastatic disease should not be considered candidates nor for gastrectomy, neither for metastasectomy outside experimental settings (Smyth et al., 2016; De Manzoni et al., 2017). However, according to the Japanese gastric cancer treatment guidelines, hepatectomy may be considered for patients with a small number of metastatic nodules, and not restricted to a solitary tumor,

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provided that there is no other non-curable factor (Japanese Gastric Cancer Association, 2017). A recent Chinese consensus paper underlined the indication of surgical treatments only when R0 resection is intended and achievable (Zhang and Chen, 2020).

Currently, a lack of consensus regarding the optimal treatment strategy for patients suffering from gastric cancer liver only metastases exists. Moreover, other meta-analysis previously published on the topic, considered studies involving patients with extrahepatic disease as well as overlapping series. Therefore, we felt the need to investigate the impact of hepatic resection on survival by applying a rigorous methodology and statistical analysis. Furthermore, the role of prognostic factors has been evaluated as well.

2. Materials and methods

2.1. Search strategy

A systematic review of the English-language literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2009). The study was conducted following the MOOSE recommendations. The Medline, Scopus, Cochrane Library and Web of Sciences databases were screened selecting the time interval from 2000 up to April 9th, 2020 using the keywords "liver metastas* OR hepatic metastas* AND gastric cancer OR cancer of the stomach AND surgery OR surgical resection OR resection OR surgical treatment (Search query: ((liver metastas*) OR (hepatic metastas*)) AND ((gastric cancer) OR (cancer of the stomach)) AND ((surgery) OR (surgical resection) OR (resection) OR (surgical treatment))). Articles without free full text available were searched through the digital library of the University of Milan and through direct contact with authors. Hand-search of bibliographies of included studies and previous reviews on the topic was also performed to include additional relevant studies according to our selection criteria. Two investigators (FB, SP) carried out the literature search independently.

2.2. Inclusion criteria

We included studies reporting 5-year or longer survival rates of gastric cancer patients who developed liver only metastases treated with surgical resection of primary tumor and metastases. Studies including patients undergoing surgery and/or local therapies (Radio Frequency Ablation - RFA, Microwave Coagulation Therapy – MCT) without reporting separate data were excluded. Indication to surgical resection should have been made with radical (R0) intent of primary and metastatic lesions. Studies including patients with metastatic disease to organs other than the liver (e.g. peritoneum) were excluded to avoid selection bias.

A specific population (P), intervention (I), comparator (C), outcome (O), and study design (S) (PICOS) framework was specified to define study eligibility, as recommended. In particular, the following criteria were outlined:

- Population (P): patients with histologically confirmed adenocarcinoma of the stomach and liver only metastases;
- Intervention (I): surgical resection of primary tumor and liver metastasis with curative intent;
- Comparison (C): patients not undergoing surgery or receiving surgical resection without curative intent (this criterion was not mandatory for inclusion of the studies in this review);
- Outcomes (O): survival outcomes of patients treated with surgical resection;
- Study design (S): randomized-controlled or prospective/retrospective cohort studies and case series with more than 10 patients. Studies with insufficient reporting of the PICOS criteria were excluded.

The aim of this review was to explore the effect of surgical resection of gastric cancer liver metastasis (GCLM) on survival and to identify variables with a prognostic value on OS.

2.3. Systematic review process

Mendeley reference software (Mendeley Ltd, London, UK) was used to identify and remove duplicates among identified records. Overall, 3177 articles were preliminarily identified by the literature search. After exclusion of duplicates, two independent reviewers (SG, MA) screened titles and abstracts of 2495 records. An a priori developed screening form was created to guide study selection. Disagreement was solved by a third party (CC), who supervised the systematic review process. After exclusion of case reports, book chapters, editorials, conference abstracts, pre-clinical studies, previous reviews, and articles not related to the primary endpoint of this review, 69 articles were assessed for eligibility. Finally, 29 studies fulfilling all inclusion criteria were selected for qualitative and quantitative analysis. The flow-chart depicting the overall review process according to PRISMA is shown in Fig. 1.

2.4. Data Extraction and assessment of included studies

Data were extracted independently by two authors (SG, MA). The following summary data for the included studies were retrieved: name of the authors; year of publication; type of study; years of enrollment; ethnicity of the study, age, male/female ratio, T3−4 gastric cancer proportion, N + proportion, unilobar disease proportion, median FUP time, synchronous, metachronous, solitary and multiple liver metastases; type of surgical resection; resection margins; administration of adjuvant chemotherapy; median overall survival (OS); 5-year survival; total number of resected patients and independent predictors of survival outcome. In case of disagreement, a further reviewer (AB) helped resolve the disagreement through discussion.

Two authors (FB, SP) independently assessed the quality of evidence provided by each study using the Oxford Center for Evidence-Based Medicine scoring system (Phillips et al., 1998). The methodological quality of each retrospective comparative study was assessed using the validated Newcastle-Ottawa Scale (NOS) (Wells et al., 2012); studies that scored ≥ 7 were considered of high quality.

2.5. Primary and secondary endpoints

Primary outcomes were represented by 5-year survival rate (5ySR) and median OS for gastric cancer patients and liver only metastases. The impact of: surgical resection compared to other palliative treatments, administration of adjuvant CT, T and N stage, and specific liver metastases related factors (timing and number of metastases, greatest metastasis diameter > 5 cm, presence of bilobar disease and resection margins) were explored to assess their prognostic value on OS. This represented the secondary endpoint.

2.6. Statistical analysis

The primary outcome measures were expressed in terms of Hazard Ratio (HR) and 95 % Confidence Intervals (CI) for overall survival (OS). Meta-analyses of prevalence and medians were developed.

Random effects models based on generic inverse variance method were built in order to assess the impact of heterogeneity on results. Five-year survival rate was calculated as the proportion of patients alive at 5 years. If not reported, the number of survivors was estimated by Kaplan-Meier curves. To evaluate the impact on OS of different prognostic factors, the HRs were retrieved from each manuscript and their standard errors (S.E.) were computed from the reported 95 % confidence intervals (95 % CIs). If not overtly reported, they were estimated using the total number of events and the number of patients in each arm, as suggested by Parmar (Parmar et al., 1998), whenever possible. HR and S.E.

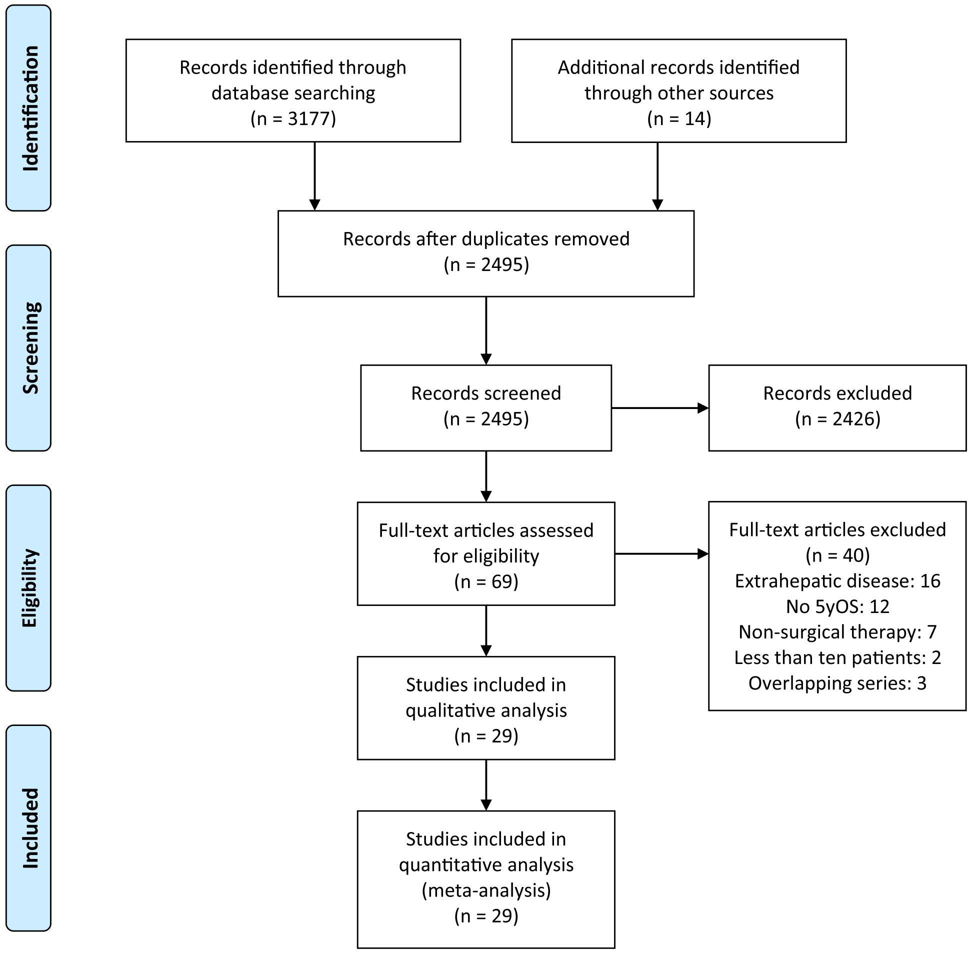

Fig. 1. PRISMA flowchart of selected studies.

logarithmic transformation was derived to estimate treatment effect. The presence of outliers was investigated, and their effects sizes excluded.

Heterogeneity between studies was quantified by I^2 statistic and Cochran's Q test; cut-off values of 25 %, 50 %, and 75 % were considered as low, moderate, and high, respectively (Higgins et al., 2003). Sensitivity analysis was performed using the leave-one-out method and Baujat plot was built to visually inspect studies overly contributing to heterogeneity.

To investigate the association between potential predictors of 5ySR and effect size differences, mixed effects meta regression models and subgroup analyses were developed. Due to lack of data, the possibility to build multiple meta-regressions was precluded, therefore, the analysis was conducted including the covariates one by one.

Contour-enhanced funnel plots were developed to explore publication bias and Egger's test of the intercept was used to quantify funnel plots asymmetry. Duval & Tweedie's trim-and-fill method was adopted to estimate and adjust for the number and outcomes of missing studies each time Egger's test demonstrated significant asymmetry. P-curve analysis was performed to confirm the results of the aforementioned publication bias assessment.

Statistical analysis was conducted with R statistical software (The Comprehensive R Archive Network – CRAN, ver. 4.0.0 × 64) (R Core Team, 2021), using "meta", "metafor", "metamedian" and "dmetar" packages (Schwarzer et al., 2015; Viechtbauer, 2010; McGrath et al., 2020; Harrer et al., 2019).

3. Results

3.1. Descriptive noncomparative analysis of included studies and primary endpoint

After the literature search, 29 studies were included in the qualitative and quantitative analysis (Makino et al., 2010; Garancini et al., 2012; Miki et al., 2012; Schildberg et al., 2012; Takemura et al., 2012; Baek et al., 2013; Qiu et al., 2013; Kinoshita et al., 2015; Komeda et al., 2015; Wang et al., 2014; Saiura et al., 2002; Liu et al., 2015; Yao et al., 2015; Guner et al., 2016; Tatsubayashi et al., 2017; Li et al., 2017a, b; Ryu et al., 2019; Song et al., 2017; Kawahara et al., 2020; Shirabe et al., 2003; Hirai et al., 2006; Cheon et al., 2008; Koga et al., 2007; Sakamoto et al., 2007; Morise et al., 2008; Tsujimoto et al., 2010; Okano et al., 2002; Ambiru et al., 2001). All of them were retrospective. Most of the excluded studies were deemed not eligible because of extrahepatic disease, non-surgical treatments of hepatic metastases (RFA/MCT) or missing data.

In total, 1132 patients undergoing hepatic resection for GCLM were included in the meta-analysis. Of 29 studies selected only 2 came from Western countries. The median age was 62 years, the male/female ratio was 2.5, the median FUP was 24 months, in 88 % of cases unilobar disease was detected and R0 resection was achieved in 97.4 % of cases. Twenty-two studies reported data about postoperative mortality: 17 of them declared no postoperative mortality, whereas in 5 studies it ranged from 1.5%–6%. Only 14 studies recorded information about postsurgical morbidity ranging from 0 up to 56 %, with a median of 10.9 %. In most of the studies included in our systematic review, indications for surgery encompassed the possibility to achieve curative resection of both primary and metastatic tumor, the absence of extra-hepatic disease, and acceptable liver remnant function. Table 1 summarizes patients' characteristics. A detailed list of surgical indications, as well as other characteristics of included studies, has been added to Table 1 in supplementary materials.

After identification of outliers (Wang et al., 2014), meta-analysis of proportions pointed out 29.1 % 5ySR (95 % CI: 25.4–33.2). I^2 statistics revealed the presence of moderate heterogeneity ($I^2 = 39$ %) (Fig. 2A).

Sensitivity analysis showed that 16 % of heterogeneity was explained by 3 studies (Wang et al., 2014; Ryu et al., 2019; Sakamoto et al., 2007). The results are reported in the Baujat plot (supplemental materials). The weighted median survival time of 22 pooled studies was 31.1 months (95 % CI: 26.2–34).

3.2. Meta-analysis of prognostic factors

Meta regression of 26 studies showed the presence of synchronous metastases was the only variable significantly associated with a reduced 5ySR ($p = 0.032$) even though 37.5 % of heterogeneity is explained by this covariate. On the opposite, although burdened by moderate heterogeneity, increasing age resulted significantly related to improved survival ($p = 0.008$).

The proportion of single liver metastases (pooled analysis of 22 studies) showed a trend towards an improved OS, whereas T3−4 and N + tumors (pooled analysis of 24 studies) were related to worse survival outcomes, although these results were not significant. Among variables included in the subgroup analysis of prognostic factors, bilobar disease (HR: 2.46; $p < 0.001$) and metastasis greatest dimension ≥ 5 cm (HR: 1.77; $p < 0.001$) resulted strong predictors of mortality (Fig. 2B-C). Similarly, the presence of synchronous liver metastases resulted in an increased risk of death (HR: 1.08; $p = 0.001$; Fig. 2D) with 23.5 % 5ySR compared to 29.2 % 5ySR of patients suffering from metachronous metastases. Only eight studies reported data about the comparison with other palliative treatments; although burdened by moderate heterogeneity (I^2: 43 %), surgical resection was associated with a significant improvement in overall survival (HR: 0.83; $p < 0.001$; Fig. 2E).

Further results of meta regressions and subgroup analysis of prognostic factors are reported in Table 2.

Forest plots of other prognostic factors are available in supplemental materials.

3.3. Assessment of publication Bias

Egger's test of 5ySR meta-analysis of proportions failed to point out significant asymmetry ($p = 0.256$). P-curve estimates of 15 studies showed a 90 % power of analysis (95 % CI: 78 %–96 %) with a significant right skewness of the curve ($p < 0.001$), underlining a "true" effect size behind our findings. Contour-enhanced funnel plot of publication bias and P-curve analysis plot is shown in Fig. 3.

Further results are reported in supplemental materials.

4. Discussion

Prognosis of stage IV gastric cancer continues to remain dismal. Nevertheless, most studies published from 2000 onwards have highlighted an increasing prognostic benefit for selected patients undergoing surgical resection of GCLM. These results have been confirmed by recent meta-analyses (Gavriilidis et al., 2019; Montagnani et al., 2018; Markar et al., 2016).

However, the majority of available evidences is retrospective and, to date, only one RCT (Al-Batran et al., 2017a) exploring the efficacy of surgical resection in stage IV gastric cancer patients has been published. In particular, results from AIO-FLOT 3 trial pointed out a significant survival benefit of gastric cancer metastatic patients undergoing neoadjuvant chemotherapy followed by surgical resection and post-operative CT. Of note, the study included patients with extrahepatic disease (peritoneal carcinomatosis in almost 7% of patients); furthermore, patients with tumors of the gastro-esophageal junction were enrolled as well.

In our analysis, the studies conducted by Kinoshita (Kinoshita et al., 2015) and Song (Song et al., 2017) were the two most influential and burdened by a low overall heterogeneity contribution. Kinoshita et al. collected data of five cancer centers in Japan enrolling 256 patients with 31.1 % 5yOS. Multivariable Cox regression identified serosal invasion of primary tumor, number of liver metastases ≥ 3 and size of largest hepatic tumor ≥ 5 cm as independent predictors of mortality with no survival beyond 36 months for those with all three factors. More recently, Song et al. analyzed data of 96 patients from 6 institutions in China. The overall survival rate of the cohort (21.7 % at 5 years) was not as encouraging as the one recorded by Kinoshita, but still valuable. Their multivariate analysis pointed out an increased risk of death for patients with multiple liver metastases and T stage ≥ 3.

To date, only (Montagnani et al. (2018) performed an extensive and meticulous analysis of different prognostic factors affecting survival. In their analysis lower T stages, N 0–1 stages, the absence of lymphatic or vascular involvement in the primary cancer, the absence of serosal invasion and negative resection margins were predictors of improved survival. Similarly, the presence of solitary (or less than 3) metastases, unilobar spread of the disease, the diameter of the greatest lesion smaller than 5 cm were all strongly associated to higher OS. Consistently with mainstream views (Qiu et al., 2013; Paoletti et al., 2010; Sun et al., 2009), adjuvant CT demonstrated a protecting effect on prognosis as well.

Our results are consistent with those reported by Montagnani and colleagues. Our meta-analysis of prognostic factors showed that the strongest predictor of mortality was represented by the bilobar distribution of hepatic lesions which was associated with a near 2.5-fold increase in risk of mortality.

The timing of liver disease represents a well-known prognostic factor. In our study, meta regression analysis highlighted how the presence of synchronous liver metastases has a significant harmful effect on survival. In the attempt of identifying more specific variables related to improved survival for both groups, we looked at the studies taking into account only synchronous or metachronous metastases. For the former group, in the papers published by Qiu, Wang and Liu, increasing number of liver metastases, N stage and the presence of lymphovascular invasion were independent predictors of survival. On the other hand, the only study including exclusively metachronous metastases was published by Li in 2017. Cox regression analysis detected surgical resection as the only independent predictor of improved survival. Due to the extremely limited number of studies included in our research about this topic, performing metaregression analysis was not possible.

Among the other variables evaluated, indicators of locally advanced disease (T3−4 and N + tumors) showed a trend towards reduced 5ySR.

Eight studies compared surgical resection to other palliative treatments. The subgroup analysis detected a survival benefit for patients undergoing hepatic resection, with a 20 % reduction in the risk of death overtime. Although this finding relies only on less than one third of the included studies, it can help to elucidate the potential beneficial role of surgery in the treatment of GCLM patients.

Interestingly, increasing age seems to have a protecting effect on survival, as reported in Table 2 (Effect estimate: 0.051; $p = 0.008$). However, because we could not build multiple meta-regression models, these results should be interpreted with caution. This finding could be explained by a more aggressive surgical behavior towards younger patients with higher burden of disease but with longer life expectancy.

The current median survival time for GCLM patients waves from 7 to 14 months. In the present systematic review, a total of 29 studies have been included in the meta-analysis of proportions with a 5ySR rate of 29.1 %, and the pooled weighted median of 22 studies highlighted 31.1 months MST. To our knowledge, this is the first meta-analysis reporting such an improved prognosis for patients suffering from GCLM. This

Table 1
Characteristics of included studies.

Author	Year	Country	Years of enrolment	OCLE	NOS	Age	Total resected patients	M/F ratio	T3-T4 (%)	N+ (%)	Unilobar disease (%)	Synchronous/	Solitary/	R0 (%)	Median FUP (months)	Median OS (months)	5ySR (%)	Postop. morbidity (%)	Clavien Dindo	Description	Overall postop. mortality (%)
Ambiru	2000	Japan	1975 - 1999	2b	4	63	40	3	30	75	60	18/22	19/21	40	88	–	18	–	–	–	0
Okano	2002	Japan	1986–1999	4	NA	69	19	2.1	42	53	63	13/6	10/9	100	36	21	34	–	–	–	–
Saiura	2002	Japan	1981 - 1998	4	NA	55	10	2.3	–	20	90	6/4	–	–	–	25	20	–	–	–	–
Schirabe	2003	Japan	1979 - 2001	2b	1	66	36	11	30.5	77.7	–	16/20	–	100	–	–	26	–	–	–	–
Hirai	2006	Japan	1993 - 2004	4	NA	62	14	2.8	–	–	59.6	–	–	–	41	–	41.6	–	–	–	–
Cheon	2007	South Korea	1995 - 2005	2b	5	59	22	4.5	86.4	86.4	21	18/4	18/4	100	15.5	17	22.8	–	–	–	1.72
Koga	2007	Japan	1985 - 2005	2b	4	64	42	2.5	34.1	90.2	–	20/22	29/13	100	16	34	42	–	–	–	4.7
Sakamoto	2007	Japan	1990 - 2005	4	NA	64	37	3.6	32.4	65.9	63.8	16/21	21/16	86.4	–	31	11	24	5.4 % ≥ 3b; 18.6 % ≤ 3a	Colonic perforation, sick sinus syndrome (5.4 %); Bile leakage, pancreatic fistula, wound infections (18.6 %)	0
Morise	2008	Japan	1989 - 2004	4	NA	64	18	8	61.1	83.3	83.3	11/7	14/4	44.4	–	13	27.3	–	–	–	0
Tsujimoto	2009	Japan	1980 - 2007	4	NA	66	17	16	29.4	58.8	–	9/8	13/4	100	29.3	34	31.5	–	–	–	0
Makino	2010	Japan	1992 - 2007	2b	6	66	16	4.25	50	81.2	64.7	9/7	9/7	–	16	31.2	37.1	–	–	–	–
Garancini	2012	Italy	1998 - 2007	4	NA	64	21	3	38	52.3	76.1	12/9	12/9	90.4	20	11	19	19	–	Transient liver failure (4.8 %), bile leakage (4.8 %), pleural effusion (4.8 %), wound infection (4.8 %)	0
Miki	2012	Japan	1995 - 2009	2b	3	72	25	11.5	68	72	80	16/9	18/7	–	–	33.4	36.7	–	–	–	–
Schildberg	2012	Germany	1972 - 2008	4	NA	65	31	1.9	–	–	67.7	17/14	–	74.2	–	–	13	29	23 % ≤ 3a	Surgical complications 23 %; pneumonia 6%	6
Takemura	2012	Japan	1993 - 2011	4	NA	65	64	3.7	23	66	–	34/30	37/27	86	27	34	37	26	1.5 % ≥ 3b	Bleeding (3%; 1.5 % requiring surgery); pancreatic fistula (4.5 %); bile leakage (7.8 %); pleural effusion (6.2 %); abdominal abscess; colitis	0
Baek	2013	Korea	2003 - 2010	4	NA	61	12	11	75	66	–	3/9	11/1	–	12.5	31	39	0*	–	–	0
Qiu	2013	China	1998–2009	4	NA	62	25	7.3	32	84	84	25/0	16/9	100	38	38	29.4	–	–	–	0
Kinoshita	2014	Japan	1990 - 2010	4	NA	65	256	2	80.7	31.4	–	106/150	168/88	89.8	–	31.1	31.1	10.9	≥ 3b	–	1.6
Komeda	2014	Japan	2000 - 2012	4	NA	70	24	7	38	58	–	1/23	17/7	100	–	22.3	40.1	–	–	–	0
Wang	2014	China	1996 - 2008	2b	6	64	39	2	79.4	84.6	79.4	22/31	33/20	–	14	14	10.3	7.7	≤2	Anastomotic leakage (2.5 %); wound infection (5.2 %)	0
Liu	2015	China	1990 - 2009	4	NA	56	35	1.69	82.8	88.5	85.7	39/0	31/8	91.4	41	33	14.3	5.7	≤2	Anastomotic leakage (2.8 %); Bile leakage (2.8 %)	0
Yao	2015	China	2003 - 2010	2b	6	56	31	1.58	–	–	77.4	35/0	27/8	–	–	24	16.7	19.3	≤2	Pneumonia (12.9 %); biliary leakage (6.4 %)	0
Guner	2016	Korea	1998 - 2013	2b	5	61	67	4.6	75	75	88	–	–	70	24	24	30	28	18% ≥ 3b	Hepatic failure (2%) Biloma (3%), Intrabdominal abscess (10%), Anastomotick leakage (2%)	1.5
Tatsubayashi	2016	Japan	2004 - 2014	2b	3	72	28	4.6	71.4	89.9	–	26/42	45/23	–	26	49	32	39.3	≤2		0

(*continued on next page*)

Table 1 (*continued*)

																				Anastomotic leakage (7.1 %), Bile leakage / Cholangitis (14.2 %)	
Jiyang Li	2017	China	2001 - 2015	2b	6	54	41	4.1	80.4	87.8	–	15/13	20/8	–	–	70	24.4	–	–	–	0
Li	2017	Taiwan	1996 - 2013	2b	7	62	34	2	–	–	–	14	30/52	–	24.8	26.1	24.5	–	–	–	–
Ryu	2017	Japan	1997 - 2015	4	NA	66	14	2.4	35.2	76.4	–	0/34	–	100	29.4	–	51.3	2.9	≥ 3b	–	0
Song	2017	China	2001 - 2012	4	NA	63	94	3	61.4	59.3	–	15/19	18/16	94.8	33	34	21.7	56	36.5% < 2;	–	0
Kawahara	2020	Japan	2006 - 2016	4	NA	74	20	1.85	25	85	–	59/37	42/54	–	77	42	31.7	0	–	–	0
				2b: 41.4 % 4: 58.6 %		63.8	1132	4.66	52.6	70.7	71.5	561/555	658/415	87.1	32.0	31.1*	29.1**	20.6			0.71

Abbreviations: OCLE: Oxford Center Levels of Evidence; NOS: Newcastle-Ottawa scale; M/F: male/female; - : missing data; NA: Not applicable; FUP: follow-up; CT: Chemotherapy; SR: Survival Rate.

* Result of pooled weighted median.

** Result of pooled weighted proportion.

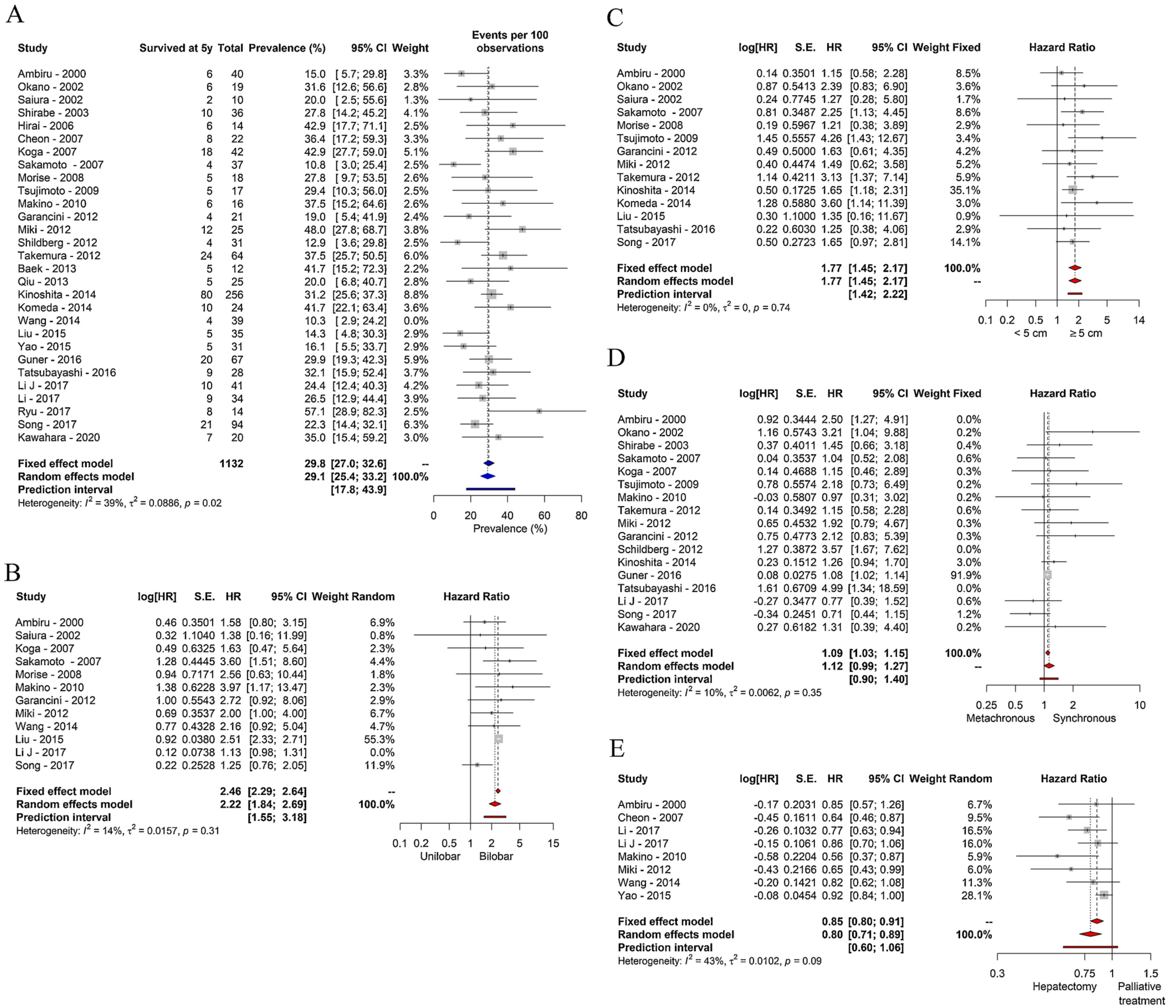

Fig. 2. Forest plot of A) 5y Survival Rate; B) Unilobar vs bilobar disease; C) Metastasis greatest dimension ≥ 5 cm vs < 5 cm; D) Synchronous vs metachronous metastases; E) Surgical resection vs palliation.

result can be attributed to the careful exclusion of studies taking into account patients with extrahepatic disease. However, it is worth to underline some considerations. A scrupulous preoperative diagnostic is essential to carefully select patients with liver only metastases. In this setting, positron emission tomography (PET) represents the most useful diagnostic tool to increase the accuracy of clinical staging and it should be performed systematically preoperatively (Kinkel et al., 2002).

Macroscopic peritoneal carcinomatosis or positive peritoneal cytology are considered among the poorest prognostic factors for stage IV gastric cancer patients (Fukuchi et al., 2015; Lee et al., 2012; Hultman et al., 2017). Due to its significantly detrimental impact on survival, celomatic dissemination should be systematically ruled out. To achieve this target, and therefore to maximize the possibility of curative resection, staging laparoscopy, providing remarkable sensitivity and specificity (85 % and 100 % respectively (Ramos et al., 2016)), should be always considered as a complementary diagnostic tool along with CeCT scan.

A recent manuscript published by Luo et al. comprehensively analyzed a consistent body of literature to propose a new classification of GCLM patients with a tailored treatment approach based on location and load of metastatic disease (Luo et al., 2019). In their proposed algorithm, patients with unilobar, ≤ 3 in number and < 5 cm metastases are deemed potentially resectable and, therefore, eligible for preoperative CT, curative (R0) gastric and hepatic surgical resection followed by postoperative CT.

In February 2020, the Chinese consensus on diagnosis and treatment of gastric cancer with liver metastases presented a similar classification system based on the likelihood of a surgical treatment being successful (Zhang and Chen, 2020). According to the Chinese classification, for Type I patients (resectable), neoadjuvant CT followed by surgical resection/RFA is recommended.

In light of the aforementioned pieces of evidence and our results, we think ideal surgical candidates are represented by patients suffering from unilobar, single or < 3 lesions, metachronous, liver only metastases. Other characteristics associated to a favorable prognosis, and therefore useful to select these patients, are T ≤ 2 and N ≤ 1 stages of the primary tumor. Considering the low postoperative mortality, we think these selected patients may benefit from a surgical approach, even though the overall postoperative morbidity can reach significantly high rates.

Table 2
Results of meta regressions and subgroup analysis of prognostic factors.

Meta regression analysis						
Variable	Number of studies	Estimate	S.E.	*p*	R2 (%)	Test for residual heterogeneity
Year of publication	29	−0.0013	0.0195	0.948	0	0.0166
Number of patients	29	−0.0001	0.0016	0.948	0	0.0167
Median age	29	0.051	0.0193	0.008	46.13	0.118
Proportion of T3−4 tumors	24	−0.0036	0.0044	0.418	0	0.031
Proportion of N+ patients	24	−0.0004	0.006	0.95	0	0.0249
Proportion of solitary metastases	22	1.0104	0.8258	0.221	11.54	0.08
Proportion of synchronous metastases	26	−0.8077	0.3754	0.032	37.5	0.1545

Subgroup analysis of prognostic factors								
Variable	Number of studies	5ySR (%)	HR	95 % CI Lower	Upper	*p*	I2 (%)	*p* (Cochrane Q test)
Surgical resection	9	27.8	0.83	0.76	0.91	< 0.001	42.4	0.084
pT > 2	8	16.5	1.81	1.2	2.74	0.004	25.6	0.225
pN > 1	9	23.5	1.75	1.43	2.15	< 0.001	0	0.816
Positive resection margins	7	11	1.59	1.14	2.2	0.005	44.3	0.095
Metastasis greatest dimension ≥ 5 cm	14	13.1	1.77	1.45	2.17	< 0.001	0	0.736
> 3 metastases	4	NA*	2.57	1.8	3.88	<0.001	4.3	0.371
Multiple metastases	19	13.3	1.7	1.39	2.08	< 0.001	28.1	0.129
Bilobar metastases	11	13	2.46	2.28	2.64	< 0.001	13.8	0.312
Synchronous metastases	17	23.5	1.08	1.03	1.14	0.001	9.5	0.348
Post-operative CT	12	31.9	0.8	0.65	0.99	0.04	23.3	0.214

* NA: not applicable. Only 2 studies provided complete date to compute 5ySR.

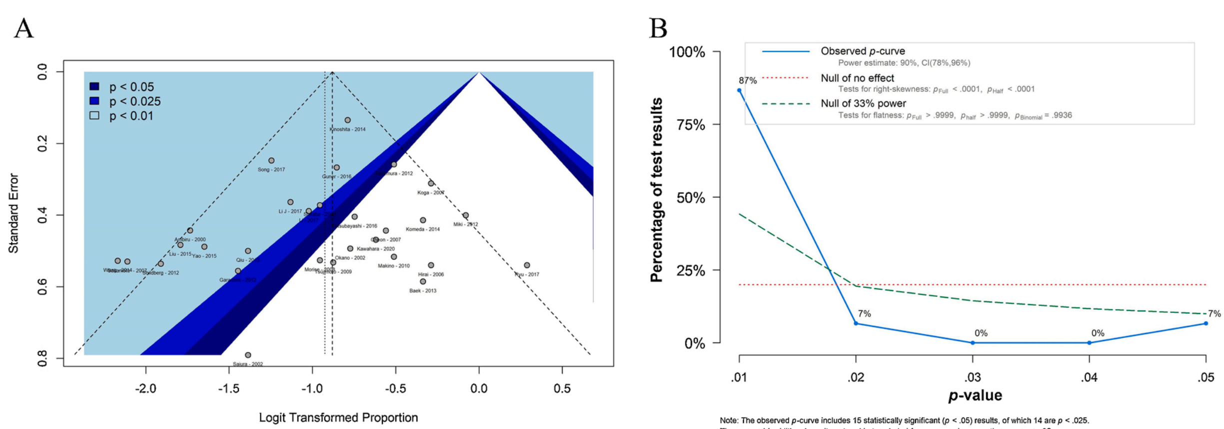

Fig. 3. Assessment of publication bias - A) Contour-enhanced funnel plot; B) P-curve analysis plot.

However, due to the poor quality of the studies included in the present metanalysis, we cannot draw conclusions about the role of surgery independently from chemotherapy. The role of neoadjuvant CT in the multimodal treatment of these patients has been demonstrated essential to improve survival outcome (Al-Batran et al., 2017a; Yoshikawa et al., 2009; Ceniceros et al., 2018). Unfortunately, only seven studies included in the present meta-analysis reported data about the proportion of patients undergoing preoperative CT and just three explored its impact on prognosis. Komeda et al. reported no differences in survival when comparing neoadjuvant CT to upfront resection. Of note, in this study the near totality of patients (23 out of 24) suffered from metachronous metastases and almost half of them received preoperative CT. In the study published by Takemura et al. preoperative CT was administered in 28 % of cases but no details about the indication nor the proportion of synchronous and metachronous patients undergoing neoadjuvant CT was mentioned. Therefore, it could be argued that preoperative CT candidates were selected based on a heavier load of disease.

Recent quality evidence (Dank et al., 2008; Van Cutsem et al., 2006; Shah et al., 2015) suggest that metastatic patients with good performance status benefit from aggressive systemic therapy regimens (FLOT, DCF, FOLFIRI) as a first line treatment, with promising results in overall and disease-free survival. Therefore, we believe that upfront surgical resection should not be offered, even in presence of resectable liver only metastasis and regardless of the timing of metastatic disease (synchronous vs metachronous).

Our findings need to be confirmed in a large prospective controlled study. Hopefully, the results of the AIO-FLOT 5 trial will clarify the role of perioperative chemotherapy in metastatic gastric cancer patients (Al-Batran et al., 2017b).

Looking at some other systematic reviews and meta-analysis previously published on the topic, we noticed the inclusion of studies involving patients with extrahepatic disease as well as overlapping series and esophagogastric junction tumors. Therefore, we felt the need to conduct a methodologically rigorous research, including exclusively studies with liver only metastases, trying to clarify the role of surgery in the treatment of GCLM. Besides, we added two further studies recently published (Ryu et al., 2019; Kawahara et al., 2020). Another key-point of our research is represented by the statistical analysis: the identification of outliers and the assessment of publication bias through contour-enhanced funnel plots and p-curve analysis, allowed us to select only studies truly contributing to the effect estimate.

Nevertheless, some limitations are worth to be mentioned. First, the significant amount of missing data in the selected studies hindered the possibility to develop any multiple meta-regression model. This kind of analysis would have allowed the identification of independent predictors of 5y survival. Second, in spite of 29 studies originally included in the quantitative analysis, the analysis of prognostic factors is based only on a limited number of reports. Furthermore, the selection bias that burdens all retrospective studies is non negligible: all papers included in our meta-analysis reported survival outcomes of surgically treated patients without providing, in most cases, the number and the characteristics of patients excluded from surgery. The inclusion of patients adequately fit for surgery, with liver only and, in most cases, limited burden of disease can have contributed to the goodness of our results.

5. Conclusions

The results of our study show a potential survival benefit for a carefully selected subset of patients suffering from gastric cancer liver only metastases undergoing surgical resection. In light of the various issues that still need to find an answer discussed in the present paper, and the limitations of our study, we suggest a cautious interpretation of our findings. A case-by-case multidisciplinary team discussion is strongly encouraged to offer these patients a chance of long-term survival, especially in the presence of favorable prognostic factors.

Compliance with ethical standards

Human rights statement: This study is a meta-analysis on the published literatures and does not contain any studies with human or animal subjects.

Informed consent: No individual patient data were used for the analysis, which should exempt this study from the requirement of obtaining informed consents.

CRediT authorship contribution statement

Stefano Granieri: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Michele Altomare:** Data curation, Investigation, Validation, Writing - review & editing. **Federica Bruno:** Data curation, Investigation, Validation, Writing - review & editing. **Sissi Paleino:** Data curation, Investigation, Validation, Writing - review & editing. **Alessandro Bonomi:** Data curation, Investigation, Validation, Writing - original draft, Writing - review & editing. **Alessandro Germini:** Supervision, Validation, Visualization. **Antonio Facciorusso:** Supervision, Validation, Visualization, Writing - review & editing. **Daniele Fagnani:** Supervision, Validation. **Giorgio Bovo:** Supervision, Validation. **Christian Cotsoglou:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2021.103313.

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