

Systematic review of partial hepatic resection to treat hepatic metastases in patients with gastric cancer

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Abstract

Objective: To examine overall survival and mortality following hepatic resection in patients with hepatic metastases from gastric cancer.

Methods: EMBASE, PubMed, Web of Science, and Cochrane databases were systematically searched for publications involving more than 10 patients who underwent hepatic resection to treat hepatic metastases from gastric cancer and who did not have peritoneal disease or involvement of other distant organs.

Results: A total of 39 studies were included, involving a median of 21 hepatic resections (range, 10–64). Resection was associated with median 30-day morbidity of 24% (range, 0%–47%) and 30-day mortality of 0% (range, 0%–30%). Median overall survival was 68% at 1 year, 31% at 3 years, and 27% at 5 years. Asian studies reported higher rates than Western studies for overall survival at 1 year (73% vs 59%), 3 years (34% vs 25%), and 5 years (27% vs 17%). Compared with palliative treatment, resection was associated with significantly lower mortality at 1 year (risk ratio [RR] 0.47, $P < 0.001$) and 2 years (RR 0.70, $P < 0.001$).

Conclusion: Patients with hepatic metastases from gastric cancer may benefit from hepatic resection in case of good physical condition, absence of peritoneal dialysis, and optimum liver function with single metastases. More trials are needed to confirm this finding.

Abbreviations: None.

Keywords: gastric cancer, hepatectomy, hepatic metastases, systematic review

1. Introduction

Gastric cancer is the second most frequent cause of cancer-related death in the world.^[1,2] Many patients are diagnosed at an advanced stage of gastric cancer because of late onset and nonspecific symptoms.^[3,4] Surgery is the first-line curative therapy for localized gastric cancer, but it is not officially

recommended for patients with certain complications, such as the 3% to 14% of patients who already have liver metastases when they are initially diagnosed with gastric cancer.^[5,6] Most official guidelines recommend only palliative therapies for such patients in light of their poor prognosis. Palliative chemotherapy has been shown to prolong median overall survival by 4.3 to 12 months relative to best supportive care.^[7]

Despite official recommendations, many clinicians in the West and Asia have been using hepatic resection to treat patients with gastric cancer that has metastasized to the liver. Assessing the rationality of this approach means establishing whether resection significantly improves overall survival beyond palliative treatments. Therefore, we undertook a systematic review of the literature to assess the available evidence on this question.

2. Methods

2.1. Ethics approval

Ethics approval was not needed because the present study was a systematic review.

2.2. Literature search strategy

In July 2016, the most recent online versions of the following databases were searched without language restrictions: PubMed, EMBASE, Web of Science, and Cochrane Library. The following search terms were used to identify single- or parallel-arm studies: “gastric cancer” and “hepatic metastasis” and “hepatic resection” or hepatectomy or “liver resection” or “gastrectomy”. No search filters were imposed. Reference lists in relevant articles were also searched manually to identify additional studies.

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Author contributions: SZ conceived and designed the study. DL, P-CY, and SZ searched the literature and extracted data. DL performed statistical analyses. DL, P-CY, and SZ drafted the manuscript.

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2.3. Inclusion and exclusion criteria

We included in the systematic review full-length research studies that satisfied the following criteria: the study evaluated the efficacy of hepatic resection in patients with hepatic metastases from gastric cancer in the absence of peritoneal metastasis; the study had a randomized control, cohort, or single-arm design; the patient sample was larger than 10; and the study reported sufficient follow-up data to calculate mortality or overall survival rates.

Studies were excluded if they were published in languages other than English; included patients with peritoneal metastasis or metastasis to other organs, such as the spleen or lungs; examined only patients who did not undergo hepatic resection; or involved patients with hepatic metastases from cancers in nongastric organs. Conference abstracts and other forms of summary publication were also excluded. In the case of multiple studies apparently based on the same population, we included only the study with the largest number of participants.

2.4. Study identification and data extraction

Studies identified in literature searches were independently screened by 2 authors (DL and P-CY), and discrepancies were arbitrated by a third author (SZ). Two authors (DL and P-CY) independently extracted the following data from included studies using a predefined template: author details, country, recruitment period, study design, median follow-up, sample size, gender, positive and negative findings, and methodological quality. A third author (SZ) checked the extracted data against the original studies. Survival data were taken directly from tables or the text whenever possible; if such data were presented only in graphs, they were extracted by manual interpolation. *P* values associated with intergroup differences in mortality were extracted directly from survival curves, text, or tables wherever possible. The quality of evidence provided by each study was evaluated using the Oxford system for scoring medical evidence levels.^[8]

2.5. Missing data

Meta-analysis was performed on an intention-to-treat basis. To assess attrition bias, we calculated mortality using a “worst-case” approach in which patients with missing data were counted as treatment failures (death). For patients with missing data, we “carried forward” data from the most recent measurement.

2.6. Statistical analysis

Review Manager 5.3 (Cochrane Collaboration) was used to analyze data from included studies. Due to the high likelihood of mortality, risk ratio (RR) with corresponding 95% confidence intervals (95% CIs) were calculated for dichotomous outcomes using the Mantel–Haenszel method. Point estimates of RR were considered statistically significant when $P < 0.05$. Meta-analysis was carried out using a random-effects model if substantial heterogeneity according to an I^2 threshold was found; otherwise, meta-analysis was carried out using a fixed-effects model. If the 2 models gave different results, we reported both results.

3. Results

3.1. Description of studies

Systematically searching several research databases identified 20,390 potentially relevant citations. Screening of titles and abstracts led to a set of 264 studies that were read in full; in the

end, 40 were found to meet inclusion criteria and none of the exclusion criteria.^[5,6,9–46] After removing a duplicate study,^[9] the remaining 39 studies involving 994 patients were included in the final analysis (flow diagram). Eight of them compared the efficacy of hepatic resection to that of other palliative treatments.^[10–17] The quality of evidence in all included studies was Oxford level 2b.

Median sample size was 21 (range, 10–64). Of all included patients, 11% received neoadjuvant chemotherapy, and 55% received adjuvant chemotherapy. Most (71%) underwent minor hepatectomy. Twenty-seven studies (69%) described the indications of hepatic resection for patients with hepatic metastases from gastric cancer. These indications included no signs of peritoneal dissemination or any other organ metastases on preoperative imaging ($n=22$ studies); feasibility of complete tumor resection, including primary gastric cancer and hepatic metastases ($n=15$); preserved liver function on the basis of a panel of serum tests of liver function ($n=9$); adequate physical condition ($n=5$); and appropriate number and distribution of tumors ($n=5$). Only 1 study described complications during or after hepatic resection.^[39]

Patient demographics and characteristics of hepatic metastases from gastric cancer are summarized in Table 1. Among the included patients with detail information, 480 had solitary liver metastasis and 294 had multiple liver metastasis. Nearly half (432) underwent hepatic resection for unilobar hepatic metastasis, while 137 were treated for bilobar hepatic metastases. Just over half (531) underwent hepatic resection for synchronous hepatic metastases, while 312 were treated for metachronous hepatic metastases, that is, metastases occurring >6 months after primary gastrectomy.

3.2. Safety and efficacy

Across all 994 patients, median rates of postoperative complications and mortality at 30 days were, respectively, 24% (range, 0%–47%) and 0% (range, 0%–30%). Median overall survival was 21 months (range, 9–52.3). Median rates of overall survival were 68% at 1 year, 31% at 3 years, and 27% at 5 years. Comparison of studies performed in Asian countries (30 studies, 737 patients) and Western countries (9 studies, 257 patients) indicated that Asian cohorts showed higher median rates of overall survival at 1 year (73% vs 59%), 3 years (34% vs 25%), and 5 years (27% vs 17%).

3.3. Comparison of hepatic resection and palliative treatments

Eight studies compared the efficacy of hepatic resection ($n=196$ patients) and palliative treatments ($n=481$).^[10–17] Median follow-up ranged from 10 to 19 months. Hepatic resection was associated with significantly lower mortality at 1 year (RR 0.47, 95% CI 0.38–0.58, $P < 0.001$) and 2 years (RR 0.70, 95% CI 0.63–0.79, $P < 0.001$; Fig. 1).

4. Discussion

Many large prospective studies have verified the benefits of hepatic resection for patients with metastatic tumors from colorectal cancer. In fact, indications for hepatic resection in such patients have been extended to include resectable metastases numbering 4 or more.^[47–50] In contrast, the use of hepatic resection to treat patients with liver metastases from gastric

Table 1
Characteristics of included studies.

Study	Country	Recruitment period	Median follow-up, mo	Sample, n	Median age, y	M/F	Single/multinodular	Uni/bilobar	Synchronous/metachronous
Adam et al	France	1983–2004	31	64	NR	NR	NR	NR	NR
Ambiru et al	Japan	1975–1999	88	40	63	30/10	19/21	24/16	18/22
Aizawa et al	Japan	1997–2010	91	53	66	43/10	31/22	NR	53/0
Beak et al	Korea	2003–2010	13	12	61	11/1	11/1	11/1	3/9
Chen et al	China	2007–2012	10	20	57	12/8	8/12	11/9	20/0
Cheon et al	Korea	1995–2005	16	41	60	34/7	28/13	NR	30/11
Choi et al	Korea	1986–2007	15	14	65	11/3	9/5	11/3	0/14
Dittmar et al	Germany	1995–2009	11	15	57	12/3	8/7	12/3	9/6
Fuji et al	Japan	1979–1999	16	10	58	6/4	6/4	8/2	3/7
Garancini et al	Italy	1998–2007	20	24	64	14/7	12/9	16/5	12/9
Hirai et al	Japan	1993–2004	41	14	NR	NR	NR	NR	NR
Imanura et al	Japan	1990–1997	24	17	NA	15/2	8/9	12/5	7/10
Komeda et al	Japan	2000–2012	NR	24	69	21/3	17/7	NR	1/23
Liu et al	China	1995–2010	38	35	NR	29/6	12/23	12/23	35/0
Makino et al	Japan	1992–2007	NR	16	NA	13/3	9/7	11/5	9/7
Miki et al	Japan	1995–2009	NR	25	72	23/2	18/7	20/5	16/9
Miyazaki et al	Japan	1980–1994	NR	21	63	18/3	7/14	15/6	11/10
Morise et al	Japan	1989–2004	NR	18	64	16/2	14/4	15/3	11/7
Nomura et al	Japan	1991–2005	20	17	66	13/4	NR	NR	9/8
Ochiai et al	Japan	1962–1991	19	21	55	13/8	15/6	NR	13/8
Okano et al	Japan	1986–1999	36	19	69	13/6	10/9	12/7	13/6
Qui et al	China	1998–2009	NR	25	NR	22/3	16/9	21/4	NR
Roh et al	Korea	1988–1996	19	11	61	10/1	11/0	11/0	8/3
Saito et al	Japan	1964–1987	NR	14	59	10/4	NR	12/2	14/0
Saiura et al	Japan	1981–1998	NR	10	60	7/3	4/6	7/3	6/4
Sakamoto et al	Japan	1985–2001	17	22	63	13/9	16/6	17/5	12/10
Sakamoto et al	Japan	1990–2005	NR	37	64	29/8	21/16	30/7	16/21
Schildberg et al	Germany	1972–2008	NR	31	65	20/11	NR	30/1	17/14
Shirabe et al	Japan	1979–2001	NR	36	66	33/3	31/5	NR	16/20
Takemura et al	Japan	1993–2011	27	64	65	49/15	37/27	NR	34/30
Thelen et al	Germany	1988–2002	9	24	64	17/7	13/11	18/6	15/9
Tiberio et al	Italy	1990–2004	19	11	NR	NR	NR	NR	0/11
Tiberio et al	Italy	1997–2011	NR	53	NR	NR	NR	NR	53/0
Tsujimoto et al	Japan	1980–2007	29	17	66	16/1	13/4	17/0	9/8
Ueda et al	Japan	1991–2005	NR	15	NR	NR	NR	NR	NR
Vigano et al	Italy	1997–2008	43	20	61	12/8	15/5	18/2	9/11
Wang et al	China	2003–2008	11	30	60	27/3	22/8	27/3	NR
Wang et al	China	1996–2008	NR	39	64	26/13	31/8	34/5	39/0
Zacherl et al	Australia	1980–1999	NR	15	62	10/5	8/7	NR	10/5

F = female, M = male, NR = not reported.

cancer remains controversial. Retrospective single-arm studies have associated hepatic resection with acceptable long-term overall survival in such patients,^[18–22] but official guidelines recommend only palliative treatments.

Some other systematic review with similar aim has been published.^[51] Only 11 observational studies were included in this review.^[51] The present systematic review of 39 studies involving 994 patients without peritoneal metastasis who underwent hepatic resection to remove hepatic metastases from gastric cancer indicated good median overall survival rates of 68% at 1 year, 31% at 3 years, and 27% at 5 years. Median overall survival time was 21 months, which compares favorably with the 11.3 months reported for patients in a large randomized controlled trial who received combination chemotherapy of epirubicin, oxaliplatin, and capecitabine.^[52] It also compares favorably with the 13.8 months reported for patients who received both trastuzumab and chemotherapy involving the combination of cisplatin with capecitabine or fluorouracil.^[53]

Median overall survival of 11 to 14 months may represent the best-case scenario for patients with hepatic metastases from gastric cancer: a systematic review has concluded that adding targeted therapy to chemotherapy does not prolong overall survival in patients with advanced gastric cancer.^[54] Therefore, our results suggest that hepatic resection is associated with substantially longer median overall survival than chemotherapy with or without targeted therapy. In appropriate patients, hepatic resection may be preferable to chemotherapy.

Careful patient selection is likely to be important for ensuring good prognosis after hepatic resection. Since no official indications exist for patients with liver metastases from gastric cancer, we reviewed the indications reported in 27 included studies. These included the absence of peritoneal or other metastases on preoperative imaging, adequate physical condition, preserved liver function, and feasibility of complete tumor resection. Such indications may also need to include the number of liver metastases, since several studies indicate that overall

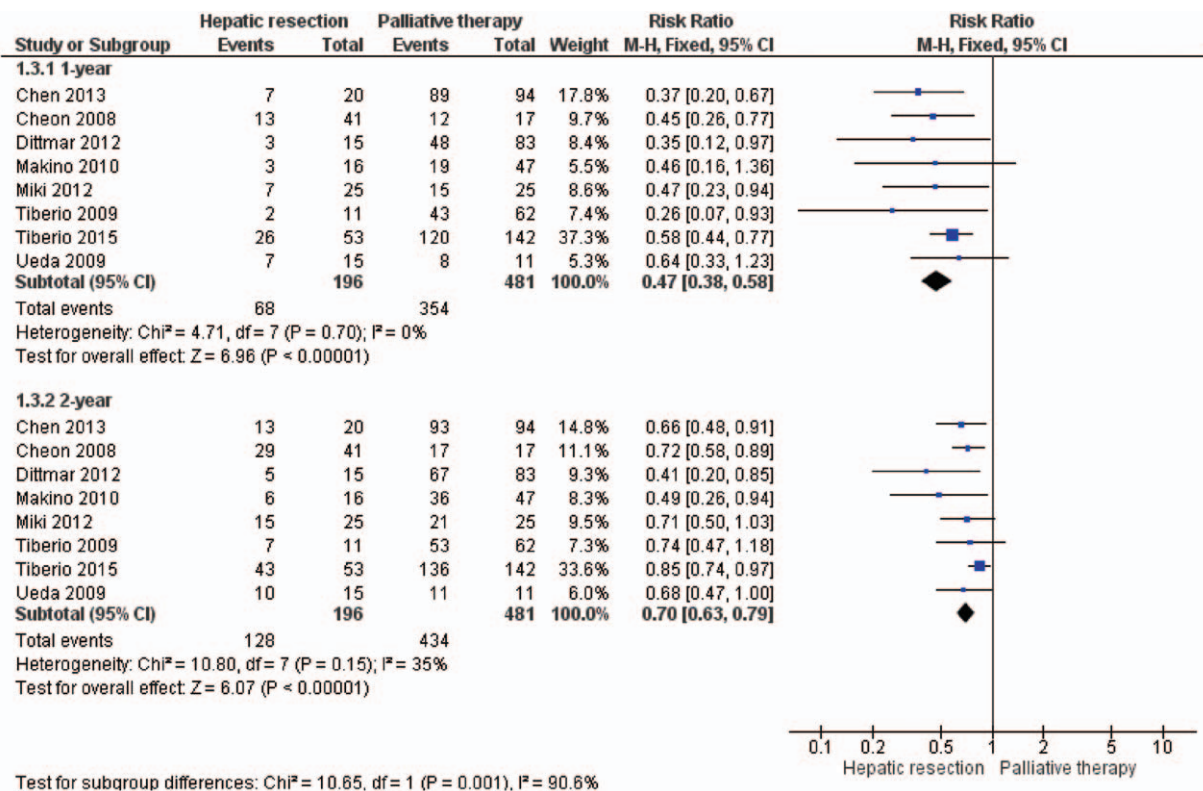


Figure 1. Meta-analysis of mortality at 1 and 2 years after hepatic resection or palliative therapies in patients treated for hepatic metastases from gastric cancer.

survival is higher for patients with solitary metastasis than for those with multiple metastases.^[10,11,19–21] Indications may also need to take into account the same risk factors affecting overall survival after hepatic resection in patients with hepatocellular carcinoma, which include hepatic resection margin, tumor stage of primary cancer, vascular invasion, and lymph node metastasis. Indications for resection may also need to include response to neoadjuvant chemotherapy in those patients who receive it, since prognosis of nonresponders is generally worse than that of responders.^[55,56]

Lymph node ratio may also a risk factor of prognoses among patients with gastric cancer liver metastasis who received combined surgical resection. A retrospective study found that patients with higher lymph node ratio had significantly shorter overall survival and recurrence-free survival than those with lower lymph node ratio.^[57] In the multivariate analyses, higher lymph node ratio and multiple liver metastatic tumors were identified as the independent prognostic factors for both overall survival and recurrence-free survival. Elevated lymph node ratio was significantly associated with advanced pN stage, larger primary tumor size, the presence of microvascular invasion, and neoadjuvant chemotherapy. Therefore, lymph node ratio may be prognostic indicator for patients with gastric cancer liver metastasis treated by synchronous surgical resection.

Clinicians should consider the potential disadvantages of hepatic resection relative to other suitable treatments. Resection may postpone initiation of chemotherapy and reduce the patient's ability to tolerate it. It may also affect patient quality of life, since additional resection surgery can affect patients' nutritional and general physical condition.

Patients were included in the present systematic review only if they had no peritoneal dissemination or metastasis to other distal

organs. The prognosis of patients with positive peritoneal cytology or peritoneal metastasis is extremely poor, and hepatic resection does not appear to offer them any survival benefit.^[58,59] The unsuitability of hepatic resection for patients with peritoneal dissemination may reflect differences in patterns of tumor recurrence in liver and peritoneum.^[60]

Though hepatic resection is associated with better overall survival than other palliative therapies for liver tumors (including primary and metastatic tumor),^[61–65] some other palliative treatment, such as transarterial chemoembolization, may be a potential option for those unsuitable for hepatic resection.^[66–69] Suciu et al^[70] reported a case with multifocal liver metastases from rectal cancer. They found a significant shrinkage of multifocal liver metastases and long-term overall survival after transarterial chemoembolization. Future studies can investigate the role of transarterial chemoembolization for patients with gastric cancer liver metastasis.

The findings of this systematic review should be interpreted with caution. None of the included studies was randomized; patients were carefully selected to undergo hepatic resection. The types and frequency of postoperative complications remain unclear because all but one of the studies failed to report such data. Most patients (71%) underwent minor rather than major hepatectomy. Heterogeneity in surgical technique and skill may also affect patient prognosis. We were unable to perform meta-regression analyses to identify risk factors for mortality because most studies did not report necessary data.

Despite these limitations, this systematic review provides comprehensive evidence that hepatic resection is associated with lower mortality and longer median overall survival than palliative treatments for selected patients with hepatic metastases from gastric cancer. If our findings can be verified and extended in

further large trials with adequate follow-up, they make a strong argument for changing current clinical practices and official guidelines to bring them into line with the evidence base. Moreover, future studies should be prospective and ideally randomized.

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