

Review Article

Clinical modalities for management of gastric cancer hepatic metastasis

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Abstract: The best treatment for gastric cancer hepatic metastasis is still widely debated. Gastric cancer hepatic metastases has long been justified the indication of palliative chemotherapy. Inspired by the good results of the management of colorectal cancer hepatic metastases, surgeons have focused on the curative or palliative treatment of gastric cancer hepatic metastases. The current clinical modalities used for treatment of gastric cancer hepatic metastasis include liver resection, systemic chemotherapy, radiofrequency ablation (RFA), hepatic arterial infusion (HAI), and palliative gastrectomy. This article presents a review of the literature on hepatic resection, RFA, HAI, palliative gastrectomy, and systemic chemotherapy for the treatment of liver metastases in gastric carcinoma, and discusses the indications and long-term results.

Keywords: Gastric cancer, hepatic metastases, liver resection, radiofrequency ablation (RFA), hepatic arterial infusion (HAI), palliative gastrectomy, systemic chemotherapy

Introduction

The gastric cancer is the third leading cause of cancer death in men and the fifth in women with approximately 723,100 deaths per year worldwide [1]. Poor survival is largely attributed to delayed presentation [2]. At the time of diagnosis, 35% of gastric cancer patients have evidence of distant metastases, 31% with peritoneal disease, 14% with liver metastases, and 16% with lung metastases [3]. Its prognosis is poor with a 5-year survival rate less than 30%. This unfortunate prognosis becomes even more compromised if the gastric tumor was associated with liver metastases since the 5-year survival rate does not exceed in this case the 10% and the median survival without any treatment is about 3 to 5 months [4]. Unfortunately this situation is not uncommon as liver metastases are present in 4%-14% of patients with primary gastric cancer [5-8], which is often associated with extrahepatic disease such as peritoneal dissemination, lymph node metastasis, and direct cancer invasion of other organs [8-11].

Clinical approach to gastric cancer patients displaying hepatic metastases at diagnosis is

still debated. Inspired by the good results of the management of colorectal cancer hepatic metastases, surgeons have focused on the curative or palliative treatment of gastric cancer hepatic metastases. The current clinical modalities used for treatment of gastric cancer hepatic metastasis are liver resection [6-9, 12-33], systemic chemotherapy [34], radiofrequency ablation (RFA) [34-37], hepatic arterial infusion (HAI) [38-42], and palliative gastrectomy [43-47].

In this article, we review the current state of knowledge of the clinical strategies to manage gastric cancer hepatic metastasis focus on hepatic resection, systemic chemotherapy, RFA, HAI, and palliative gastrectomy.

Liver resection

The efficacy of resection of liver metastases from gastric cancer has not been established. Encouraged by the results of treatment of liver metastases of colorectal cancers [48, 49], surgeons have focused on the curative treatment of gastric cancer hepatic metastases via liver resection. Numerous studies have investigated the clinical appropriateness, technical feasibility

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Table 1. Liver resection of gastric cancer hepatic metastasis

Refs	PY	R	Na	P	Pr	CT	S/M	RI	OSR					MST	Be
									1-y	2-ys	3-ys	5-ys	10-ys		
[12]	1994	R	Japan	30	NA	NA	S/M	30/284	NA	NA	NA	NA	NA	NA	NA
[13]	1997	R	Japan	21	CG	NA	S/M	NA	NA	NA	NA	NA	NA	NA	NA
[14]	1998	R	France	11	NA	NA	NA	NA	NA	NA	<30	<20	NA	NA	NA
[15]	2001	R	Japan	40	NA	NA	NA	NA	NA	27	NA	18	11	NA	NA
[16]	2001	R	Japan	17	NA	NA	S/M	NA	47	22	NA	0	NA	NA	NA
[6]	2002	R	Japan	19	CG/PG	NA	S/M	19/807	77	NA	34	34	NA	NA	Y
[17]	2002	R	Austria	15	NA	NA	S/M	NA	NA	NA	NA	NA	NA	8.8	NA
[7]	2003	R	Japan	22	NA	NA	S/M	22/228	73	NA	38	38	NA	NA	Y
[18]	2005	R	Korea	11	NA	NA	S/M	NA	NA	NA	NA	NA	NA	13.0/74.3 ^a	Y
[8]	2007	R	Japan	37	NA	SC	NA	NA	NA	NA	NA	11	NA	31	Y
[9]	2007	R	Japan	42	CG	SC	S/M	42/247	76	NA	48	42	NA	34	Y
[19]	2008	R	Germany	24	CG/PG	NA	S/M	NA	38	NA	16	10	NA	9	Y
[20]	2009	R	Italy	11	CG	NA	M	NA	80.8	30.3	20.2	NA	NA	NA	Y
[21]	2010	R	Japan	16	CG	SC/HAI	S/M	16/63	82.3	NA	46.4	31.7	NA	31.2	Y
[22]	2010	R	Japan	17	CG	SC/HAI	S/M	NA	NA	NA	NA	31.5	NA	34	Y
[23]	2010	R	Korea	14	CG	NA	M	NA	67.0	NA	38.3	NA	NA	11.9	Y
[24]	2012	R	China	30	NA	CG	S	NA	43.3	30.0	16.7	16.7	NA	11.0	Y
[25]	2012	R	Japan	64	CG	NA	S/M	NA	80	NA	50	37	NA	34	Y
[26]	2012	R	Germany	31	CG	SC	S/M	NA	NA	NA	NA	13	NA	NA	Y
[27]	2012	R	Italy	21	CG	NA	S/M	NA	68	NA	31	19	NA	NA	Y
[28]	2013	R	Korea	12	CG	SC	S/M	13/67	65	NA	NA	39	NA	31.0	Y
[29]	2013	R	China	20	NA	CG/SC/HAI	S	20/114	NA	NA	NA	NA	NA	22.3	Y
[30]	2013	R	China	25	NA	CG	S	25/526	96.0	NA	70.4	29.4	NA	NA	Y
[31]	2014	R	China	39	NA	CG	S	NA	56.4	25.6	17.9	10.3	NA	NA	Y
[32]	2014	R	Italy	53	NA	CG/SC	S	53/195	50.4	NA	14.0	9.3	NA	NA	Y
[33]	2015	R	China	35	NA	CG	S	NA	NA	NA	NA	14.3	NA	NA	Y

Abbreviations: Refs, references. PY, published year. R, retrospective study. Na, nation. P, patients enrolled. Pr, pre-treated. CT, combined therapy (regimens). SC, systemic chemotherapy (regimens). HAI, hepatic arterial infusion (regimens). CG, curative gastrectomy. PG, palliative gastrectomy. S/M, synchronous or metachronous hepatic metastasis. RI, resection incidence (patients received liver resection/total patients enrolled). OSR, overall survival rates (%). 1-y, one year. 2-ys, two years. 3-ys, three years. 5-ys, five years. 10-ys, ten years. MST, mean survival time (months). Be, benefits (Y, yes; N, not). NA, not available. ^aMedian survival times of synchronous and metachronous hepatic metastases were 13.0 and 74.3 months, respectively.

ty, safety, and outcomes of liver resection alone or in combination with systemic chemotherapy, HAI and palliative gastrectomy for treatment of gastric cancer hepatic metastasis, these studies are summarized in **Table 1** [6-9, 12-33]. The vast majority of liver metastases from gastric cancer are multiple, bilobar, and often associated with extrahepatic disease, such as peritoneal dissemination, lymph node metastasis, and direct cancer invasion of other organs. Therefore, most of patients with liver metastases are not suitable candidates for hepatic resection, even if only a solitary hepatic metastasis is involved [7]. Selected patients accounting for one-fifth of all cases with liver metastasis

can undergo hepatic resection [8]. The indications for offering liver resection to patients with gastric cancer hepatic metastasis are listed in **Table 2** [6, 15, 18].

Liver resection was rarely applied in gastric cancer hepatic metastasis patients due to its generalized metastases. However, inspired by the exciting achievements by liver resection of colorectal cancer, surgeons are to explore what liver resection brings for metastatic gastric cancer. Studies have reported that liver resection did benefit to the survival of gastric cancer hepatic metastasis patients during the past few years (**Table 1**). Results reported show-

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Table 2. Criteria for offering liver resection to patients with gastric cancer hepatic metastasis

Liver resection criteria
Patients with synchronous metastases who have no peritoneal dissemination or other distant metastases.
Patients with metachronous metastases, but no other recurrent lesion.
Complete resection of hepatic metastases with acceptable postoperative hepatic function.
Regardless of the timing of hepatic resection.
Solitary liver metastasis.

ed that the overall survival rate of gastric cancer hepatic metastasis for 1, 3, and 5-year after macroscopically liver resection (R0 or R1) was 38% to 96%, 14% to 70.4%, and 0% to 42%, respectively, and the median survival time was 8.8 to 34 months (**Table 1**). However, most of these studies had no control arm and limited number of long survivors was regarded as the benefit of liver resection. It has to be noticed that in most of these studies, patients who took resection were highly selected and more favorable population than those who received systemic chemotherapy.

Liver resection of gastric cancer hepatic metastasis is reasonable in selected patients [50-52] and the results of liver resection of gastric cancer hepatic metastasis is encouraging (**Table 1**). These results have been verifying by a prospective study "The GYMSSA trial" which compared gastrectomy with metastasectomy and systemic chemotherapy vs. systemic chemotherapy alone [3].

Systemic chemotherapy

Systemic chemotherapy is the standard therapy recommended for Stage IV or metastatic gastric cancer by both the National Comprehensive Cancer Network (NCCN) Guidelines [53] and the Japanese Guidelines [54]. Systemic chemotherapy is a standard treatment approach for patients with gastric cancer hepatic metastasis [55, 56]. Systemic chemotherapy, apart from surgical resection and local control, is an appropriate option with the hope of prolonged survival, though surgical resection has been recently reported to prolong the survival of patients with gastric cancer hepatic metastasis in highly selected subjects [8, 10, 25].

The standard treatment regimen for patients with gastric cancer hepatic metastasis was a matter of debate for a long time. In recent

years, advances in systemic chemotherapy including the introduction of new anticancer agents and the development of multi-agent regimens, has made macroscopic complete resection possible in some patients with gastric cancer hepatic metastasis and led to an increase in overall survival compared to that achieved supportive treatment. As more effective toxic drugs being explored, systemic chemotherapy seems to bring more benefit to patients with gastric cancer hepatic metastasis nowadays [57, 58]. And second-line or even third-line chemotherapy can still result in substantial prolongation of survival when compared to best supportive care if physical performance permits [59]. It has been reported that Her-2 positivity rate was significantly higher in gastric cancer hepatic metastasis [60]. The Trastuzumab for Gastric Cancer (ToGA) trial showed that adding trastuzumab to platinum-based chemotherapy [cisplatin (CDDP) plus capecitabine or 5-fluorouracil] significantly improved survival in first-line treatment for advanced gastric cancer with HER2 overexpression or amplification [61]. Trastuzumab in combination with chemotherapy would be as a new standard option for patients with HER-2 positive gastric cancer hepatic metastasis. In the first-line metastatic setting, a phase II study has evaluated cetuximab in combination with oxaliplatin/leucovorin/5-fluorouracil in metastatic gastric cancer, and reported encouraging objective response rate and median overall survival [62]. Drug resistance is widely regarded as one of the disadvantages of chemotherapy, but new oral targeted drug like Apatinib has brought hope to chemotherapy-refractory patients with gastric cancer hepatic metastasis [63]. More optimistic results were recently reported from a randomized, placebo-controlled study. In a phase III study with ramucirumab, patients with metastatic gastric cancer treated with ramucirumab had significantly longer progress free survival (PFS) and overall survival (OS) times than patients given placebo [64].

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Table 3. Radiofrequency ablation of gastric cancer hepatic metastasis

Refs	PY	P/R	Na	P	Pr	CT	S/M	OSR				OS	PFS	MST	Be	RR
								1-y	2-ys	3-ys	5-ys					
[35]	2009	R	Korea	7	CG	SC	M	NA	NA	NA	NA	NA	NA	10.0	Y	14.3
[36]	2010	R	Korea	20	CG	NA	NA	66.8	NA	40.1	16.1	NA	6.8	30.7	Y	70
[37]	2013	R	China	21	NA	NA	S/M	70	11	5	3	NA	NA	14	Y	19
[34]	2014	P	Korea	44	SC	SC	M	NA	NA	NA	NA	20.9	9.8	NA	Y	NA

Abbreviations: Refs, references. PY, published year. P/R, prospective or retrospective study. Na, nation. P, patients enrolled. Pr, pre-treated. CT, combined therapy (regimens). SC, systemic chemotherapy (regimens). CG, curative gastrectomy. S/M, synchronous or metachronous hepatic metastasis. OSR, overall survival rates (%). 1-y, one year. 2-ys, two years. 3-ys, three years. 5-ys, five years. OS, overall survival (months). PFS, progress-free survival (months). MST, mean survival time (months). Be, benefits (Y, yes; N, not). RR, recurrence rate (%). NA, not available.

Radiofrequency ablation (RFA)

Radiofrequency ablation (RFA) is a popular alternative to surgery for tumor ablation due to its safety, availability, and wide applicability to primary or secondary hepatic malignancies [65]. RFA of liver malignancies has been widely accepted as a safe and effective modality for those tumors that cannot be resected because of their number, location, or size relative to liver volume. The complementary role of the RFA is recommended in the palliative treatment of the hepatic metastases of advanced gastric cancer that are difficult to treat surgically [65, 66]. Some surgeons and oncologists evaluated the efficacy of RFA alone or in combination with chemotherapy and curative gastrectomy for the treatment of liver metastasis of gastric cancer, these clinical data are summarized in **Table 3** [34-37].

RFA provides a minimally invasive treatment for liver metastasis and offers patients a short-term survival benefit. RFA has several benefits including both safety and easy accessibility. RFA is less invasive and can be easily repeated when applied in a percutaneous manner. With appropriate selection of patients (excluding large tumor size, certain locations, cases with bile duct obstruction, etc.), RFA is a safe and feasible treatment option, even when multiple RFA treatments are required. Combination of RFA and systemic chemotherapy may be effective treatment modalities for patients with a single, unilobar metachronous gastric cancer hepatic metastasis without extrahepatic metastatic disease [34].

Hepatic arterial infusion (HAI)

Advances in vascular interventional radiology have made it easier to insert a catheter percu-

taneously. Connecting a catheter indwelling in the hepatic artery with a subcutaneously implanted port system facilitates repeated hepatic arterial infusion (HAI) on an outpatient basis. With regard to HAI of chemotherapy, this method takes advantage of the first-pass effects of cytotoxic agents, delivering higher local drug concentration to unresectable liver tumors with minimal systemic side effects [67]. HAI therapy for the local control of hepatic metastatic lesions has commonly been performed in patients with colorectal cancer [68]. However, there have been few studies reporting on the use of HAI to treat a large number of cases of gastric cancer with hepatic metastases. Clinical studies of HAI alone or in combination with chemotherapy and palliative gastrectomy for the treatment of gastric cancer hepatic metastasis is limited, these limited clinical data are summarized in **Table 4** [38-42]. HAI is not a systemic treatment but is an effective treatment for local organ providing a higher concentration to the tumor tissue and a lower one in the rest of the body.

Palliative gastrectomy

Regarding palliative gastrectomy, its defenders argue that this procedure may be beneficial for survival, reducing symptoms, and enhancing the quality of life for patients with advanced stage IV gastric cancer [69-71]. On the other hand, the reduction in tumor mass decreases both metabolic consumption and the secretion of tumor-induced immunosuppressive cytokines [72]. Studies investigated the clinical value of palliative gastrectomy alone or in combination with chemotherapy and liver resection for treatment of gastric cancer hepatic metastasis are summarized in **Table 5** [43-47]. The Criteria for offering palliative gastrectomy to

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Table 4. Hepatic arterial infusion of gastric cancer hepatic metastasis

Refs	PY	P/R	Na	P	Pr	HAI	CT	S/M	1-y OSR	MST	Be	Rs	Ph
[38]	1992	R	Japan	93	PG or SC	①	No	S	NA	11.5	Y	NA	NA
[39]	1992	R	Japan	34	NA	②	No	NA	NA	15	Y	73	NA
[40]	1999	P	Japan	88	NA	③	No	S/M	38.1	10.6	Y	55.6	II
[41]	2005	P	Japan	7	NA	④	RFA	S/M	NA	16.5	Y	71	NA
[42]	2007	R	Japan	18	PG	⑤	No	S/M	NA	19.2	Y	83	NA

Abbreviations: Refs, references. PY, published year. P/R, prospective or retrospective study. Na, nation. P, patients enrolled. Pr, pre-treated. HAI, hepatic arterial infusion (regimens). CT, combined therapy (regimens). SC, systemic chemotherapy (regimens). RFA, radiofrequency ablation. PG, palliative gastrectomy. S/M, synchronous or metachronous hepatic metastasis. OSR, overall survival rates (%). 1-y, one year. MST, mean survival time (months). Be, benefits (Y, yes; N, not). Rs, response rate (%). Ph, phase of clinical trial. NA, not available. ① mitomycin + cisplatin. ② Adriamycin + mitomycin C. ③ 5-fluorouracil + epirubicin + mitomycin C. ④ cisplatin + 5-fluorouracil. ⑤ 5-fluorouracil.

Table 5. Palliative gastrectomy of gastric cancer hepatic metastasis

Refs	PY	P/R	Na	P	Pr	CT	S/M	OSR		OS	PFS	MST	Be
								1-y	2-ys				
[43]	2010	R	China	101	NA	NA	S	NA	NA	NA	NA	NA	N
[44]	2012	R	Korea	25	No	NA	NA	NA	NA	15	NA	NA	Y
[45]	2012	R	China	54	Yes	LR	NA	NA	NA	NA	NA	19.5 ^a /36.8 ^b /19.6 ^c	Y
[46]	2014	R	Korea	14	NA	SC	NA	NA	NA	NA	NA	NA	NA
[47]	2015	P	China	24	SC	SC ^d /LR	S	72	32	20.5	13.0	NA	Y

Abbreviations: Refs, references. PY, published year. P/R, prospective or retrospective study. Na, nation. P, patients enrolled. Pr, pre-treated. CT, combined therapy (regimens). LR, liver resection. SC, systemic chemotherapy (regimens). S/M, synchronous or metachronous hepatic metastasis. OSR, overall survival rates (%). 1-y, one year. 2-ys, two years. OS, overall survival (months). PFS, progress-free survival (months). MST, mean survival time (months). Be, benefits (Y, yes; N, not). NA, not available. ^aTumor located in gastric cardia. ^bTumor located in middle stomach. ^cTumor located in antrum. ^dPaclitaxel plus capecitabine (PX).

Table 6. Criteria for offering palliative gastrectomy to patients with gastric cancer hepatic metastasis

Palliative gastrectomy criteria

Patients with potential life-threatening symptoms such as obstruction, perforation, or bleeding can be eliminated by removing a bulky symptomatic tumor.

Decreasing the tumor load makes the residual tumor more responsive to adjuvant treatment.

Volume and tumor burden reduction diminishes the metabolic demands made on the patient by the tumor.

As the tumor can produce immunosuppressive cytokines, reducing the tumor burden may also have some immunologic benefits.

patients with gastric cancer hepatic metastasis are listed in **Table 6** [72-74].

Studies that find a benefit in terms of survival after palliative gastrectomy, are almost all retrospective and include selection bias in favor of surgical patients (**Table 5**). Only one prospective study evaluating the usefulness of palliative gastrectomy for treatment of gastric cancer hepatic metastasis is reported [47]. For late-stage gastric cancer patients, palliative gastrectomy should be considered for local late-stage, distant lymph node metastasis, and resectable liver metastasis patients. Especially for the patients with liver metastasis, transfer medicine is essential to allow the potentially

curable patients to undergo radical surgery to improve the prognosis. With the improvement of perioperative chemotherapy and surgical skills, the significance of palliative gastrectomy may increase further.

Conclusion

The optimal treatment of gastric cancer with liver metastases without peritoneal dissemination or other distant metastases remains a matter for debate. Surgery for liver metastases arising from gastric cancer is reasonable if a complete resection seems feasible after careful preoperative staging. A hepatic resection should always be considered as an option for

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gastric cancer patients with hepatic metastases. Systemic chemotherapy remains one of the best hopes for a longer survival and an improved quality of life. HAI offers an alternative to surgery in inoperable patients and can be proposed as neoadjuvant treatment to surgery. The interest of RFA and palliative gastrectomy remains unproven. To date a large number of treatment modalities for gastric cancer hepatic metastasis are available, but no current regimes can be regarded as a standard therapy, thus new therapeutic strategies are required to achieve a better clinical efficacy. A randomized study comparing therapeutic outcomes among patients receiving liver resection, systemic chemotherapy alone or in combination with RFA and HAI should be conducted.

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Disclosure of conflict of interest

None.

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