REVIEW ARTICLE

Surgical resection of hepatic metastasis from gastric cancer: a review and new recommendation in the Japanese gastric cancer treatment guidelines

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Abstract Liver metastases from gastric cancer are rarely indicated for surgery because they are often diagnosed as multiple nodules occupying both lobes and coexist with extrahepatic disease. A literature search identified no clinical trials on hepatectomy for this disease; only retrospective studies of a relatively small number of cases collected over more than a decade, mostly from a single institution, were found. Five-year survival rates from these reports ranged from 0 % to 37 %, and long-term survivors were observed among carefully selected case series. The most commonly reported prognostic factor was the number of metastatic nodules, and patients with a solitary metastasis tended to have superior outcome. Patients diagnosed to have a small number of metastatic nodules by modern imaging tools could be indicated for surgery. Because both intrahepatic and extrahepatic recurrences are common, patients are likely to benefit from perioperative adjuvant chemotherapy, although it is not possible at this time to specify which regimen is the most appropriate.

Keywords Liver metastasis · Hepatectomy · Stage IV gastric cancer · Treatment guidelines

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Introduction

Hepatectomy for liver metastases should only be attempted when cure is the goal because hepatectomy usually does not relieve symptoms. Colorectal liver metastases are widely considered as targets of surgery with intent to cure, because they often present as a liver-only disease [1], which is not always the case with other types of cancer. A prognostic model based on several prognostic factors effectively stratified cancers of various origins into three groups in a comprehensive analysis of various noncolorectal nonendocrine liver metastases treated by hepatectomy in 41 French centers [2]. Gastric cancer metastasis in that report was classified into the intermediate-risk group in which 5-year survival rate was in the range of 15–30 %, with hepatic metastasis from pancreatic cancer, melanoma, and duodenal cancer. The low-risk group with a 5-year survival rate >30 % consisted of metastases from adrenal cancer, ovarian cancer, breast cancer, and renal cancer among others, and a high-risk group with 5-year survival

<15 % consisted of metastases from cancer of the lung, esophagus, head and neck, and gastroesophageal junction.

Gastric cancer is known to be heterogeneous in nature, consisting of cancer cells with varying biological characteristics. Gastric cancer can metastasize through the lymphatic pathway, the hematogenous pathway, and by direct dissemination into the peritoneal cavity from the serosal surface. Moreover, the fate of cancer cells that enter the portal circulation could vary. Hematogenous metastases can occur according to both the seed-and-soil hypothesis and the anatomical/mechanical hypothesis, neither of which needs to be mutually exclusive, and the extent to which either mechanism is operational depends on the tumor under investigation [3]. When gastric cancer cells spread through the hematogenous pathway, its first site of metastasis according to the anatomical/mechanical hypothesis would be the liver, followed by the lung. In addition, several gastric cancers spread along the seed-and-soil route, resulting in various distant metastases in the absence of hepatic metastases [4]. This result is in contrast with colorectal cancer in which the anatomical/mechanical hypothesis would seem more often applicable. The aggressive characteristics and unpredictable nature of gastric cancer cells are the reason that surgical resection of hepatic metastases has not been seriously considered.

However, some might not agree that gastric cancer even with solitary liver metastasis should always be considered as a contraindication for surgical treatment. The Japanese Gastric Cancer Treatment Guidelines recommend only chemotherapy, radiation, palliative surgery, and best supportive care for treatment of Stage IV or metastatic gastric cancer [5]. Recently, the guidelines committee of the Japan Gastric Cancer Association decided to revisit the treatment of potentially resectable M1 disease. A working group was organized to discuss whether any tentative comments could be added to the next version of the guidelines regarding surgical treatment with curative intent of (1) patients with resectable hepatic metastasis, (2) patients who are positive for cytological examination of peritoneal washes, and (3) patients with swollen nodes in the paraaortic region. This article is a summary of the literature search and discussion on gastric cancer hepatic metastasis by the members of the working group for this task.

Literature search

A search for relevant literature was conducted in March 2013 using PubMed and Scopus. Key search terms used included "gastric cancer," "liver metastasis," "hepatectomy," and "surgery" to find articles on hepatectomy for gastric cancer metastasis to the liver that were published in English after 2000. Sixty-eight articles were identified, of which the following were excluded: 15 articles that included either other types of distant metastases or hepatic metastasis from other cancer types with no independent outcome data for gastric cancer metastases, 15 articles with emphasis on treatment modalities other than hepatectomy, 6 articles with fewer than 15 cases, 5 articles on prediction and diagnosis of hepatic metastasis, 4 review articles, 3 articles on irrelevant subjects, and 1 article describing only hepatic metastasis from pT1 stage cancer. Three articles analyzed patients from the same institution, and the most recent report by Takemura et al. [6] was selected and added to a total of 17 articles to be analyzed in the current review [2, 6–21]. Most of the papers were retrospective single-institution analyses of consecutive patients who underwent hepatectomy during a given period, with two exceptions in which patients were recruited from multiple institutions [5, 7]. Wang et al. [8] analyzed only patients with synchronous liver metastases, but all other papers discussed both synchronous and metachronous metastases. Two papers analyzed all patients with hepatic metastasis who underwent gastrectomy, regardless of whether the patients underwent hepatectomy [9, 10]. Data of the patients who went on to receive hepatectomy could be retrieved from these reports for subsequent analyses. A paper by Adam et al. was a comprehensive analysis of noncolorectal nonendocrine liver metastases [2], from which patients with gastric cancer metastases could be retrieved for some of the analyses in this review.

Results and discussion

The median number of patients analyzed among the 17 series was 25 (range, 15–73), spanning a median period of 15 years (range, 5–36). Details such as the indication for surgery, diagnostic modalities used, type of surgery performed, and adjuvant treatments given were diverse and, in addition, could have changed substantially in each institution during the periods studied. Synopses of findings in the 17 papers are summarized in Table 1.

The type of hepatectomy performed was diverse. A greater proportion of patients underwent wedge or nonanatomic resection of the metastatic nodules, and major hepatectomy such as hemihepatectomy was reserved for 23.4 % of the patients (79 of 337). The selection was presumably based on the number, size, and location of the tumors rather than the surgeons' intent to perform anatomic resection for additional resection margin. In cases of colorectal liver metastasis, the preservation of hepatic parenchyma is considered to be of increasing importance in the setting of chemotherapy-associated steatohepatitis and the growing number of patients undergoing repeated metastectomy [22]. Even in gastric cancer metastasis, the most

Table 1 Outcome of the patients with gastric cancer liver metastasis

References	No. of cases	Enrolled	Age (years)	Synchronous metachronous	Synchronous	No. with solitary metastasis	Operative death	Mortality (%)	Morbidity (%)	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	No. of 5-year survivors	MST (months)
Takemura et al. [6]	64	1993–2011	65	34	30	37	0	0	23	84	50	37	27	34
Wang et al. [8]	30	2003–2008	60	30	0	22	0	0		43.3	16.7	16.7	5	11
Schildberg et al. [20]	31	1972–2008	65	17	14		2	6	29	75	25	13	4	14
Garancini et al. [19]	21	1998–2007	64	12	9	12	0	0	19	68	31	19	3	11
Miki et al. [18]	25	1995–2009	72	16	9					73.9	42.8	36.7	9	33.4
Makino et al. [10]	16	1992–2007	65.8	9	7	9	0	0		82.3	46.4	37.1	4	38.3
Tsujimoto et al. [17]	17	1980–2007	66.3	8	8	13	0	0		75	37.5	31.5	5	34
Cheon et al. [9][a]	41	1995–2005	61	30	11	28	1	3		75.3	31.7	20.8	3	17
Thelen et al. [16]	24	1988–2002	64	15	9	13	1	4.2	21	53	22	15	2	10
Morise et al. [15]	18	1989–2004	64	11	7	14	0	0		56.3	27.3	27.3	3	13
Sakamoto et al. [14]	37	1990–2005		16	21	21	0	0	24			11	2	31
Adam et al. [2]	64	1983–2004										27	17	15
Shirabe et al. [7]	36	1979–2001	66	16	20		0	0		64	26	26	4	
Zacherl et al. [13]	15	1980–1999		10	5	8	1	67	47	35.7	14.3	0	0	8.8
Okano et al. [12]	19	1986–1999	69	13	6	10	0	0		77	34	34	3	
Ambiru et al. [11]	40	1975–1999					0	0				18	6	12
Imamura et al. [21]	17	1990–1997		7	10	8	0	0		47	22	0	0	
Total	515					195 (61.1 %)	5	1.1				18.8	97	

MST median survival time

[a] Data include nine patients who were treated by radiofrequency ablation (RFA)

frequent pattern of recurrence was intrahepatic recurrence, observed in 79 % (166 of 209) of all the recurrences reported.

Mortality was 1.1 % (5/426) among the 15 studies in which the data were available, and morbidity ranged from 19 % to 47 % among 6 studies.

The 5-year survival reported from each series ranged from 0 % to 37 % and exceeded 30 % in five series [6, 10, 12, 15, 16]. Median survival time ranged from 9 to 38.8 months. The diversity in outcome may have reflected the diversity in patient selection and strategy taken, including the use of adjuvant therapies. The 5-year survival of all patients analyzed in the current study, calculated by dividing the number of 5-year survivors reported in each article by the total number of patients, was 18.8 % (97 of / 515). Although these series should be considered to represent a well-selected and more favorable population compared with patients with liver metastases who were treated with systemic chemotherapy and had poorer outcome, the 5-year survival rate at 18.8 % obtained cannot be ignored as futile. Gastric cancer with liver metastases has long been considered as a systemic disease with no indication for surgery with curative intent. This point has been made clear, both in the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2013 [23] and in the Japanese Guidelines [5]. However, there are occasions when such metastases are found as clinically resectable disease, and whether these exceptions should still be treated either by palliative chemotherapy or supportive care could be an issue for debate.

Indication for surgery has not been established but could be considered based on analysis of prognostic factors. Independent prognostic factors identified through multivariate analyses were varied, and included the number of metastatic nodules, unilobular distribution, solitary tumor, tumor diameter, and capsular formation regarding hepatic tumors (Table 2). Among these, the "number of metastatic nodules" was considered to be an important factor across several series if "solitary metastasis" was to be included. Among 319 patients with relevant information in the current series, 195 (61.1 %) actually had solitary metastases. One should note, however, that the number of nodules can differ, depending on the type of imaging studies used [24, 25]. Because most institutions needed more than a decade to accumulate 15 patients or more, there should have been much difference in the potential of imaging modalities at the beginning and the end of the study period. In the largest single-institution series, Takemura et al.[6] reported a 5-year survival of 37 %. It may be of note that they currently consider surgery when the number of metastatic nodules was diagnosed as three or fewer, using state-of-the-art imaging tools. As for other prognostic factors, some have found metachronous hepatic metastases to be a sign of favorable prognosis [11, 12, 20] whereas others consider this as irrelevant. In addition, status of the primary tumor such as serosal invasion, lymphatic invasion, and clinical stage were listed as relevant prognostic factors.

It may be worthwhile to mention that the incidence of clinically resectable hepatic metastasis may be lower than what a surgeon expects. Sakamoto et al. [14] reported that they found synchronous liver metastases in 2.2 % of the 5,209 patients who underwent gastrectomy at National Cancer Center, Japan, whereas 1.3 % developed metachronous metastases. About 20 % of these patients underwent hepatectomy for cure. In contrast, 1,013 of 10,259 patients (9.9 %) diagnosed as gastric cancer in the Yonsei University Health System, Korea, had synchronous or metachronous liver metastases [9]. Of these, 58 had metastases confined to the liver and 41 (only 4 % of all patients with liver metastases) underwent surgery with curative intent, which denotes management of both the primary tumor and the liver. The five-year survival rate of these 41 patients was 20.8 %, and the median survival time fell just short of 20 months. In short, 20 % of the patients with liver metastases can be treated surgically in a situation where only patients with potentially resectable disease are referred, a situation possibly encountered at the surgical department in a high-volume cancer center. In contrast, resectable liver metastasis undoubtedly is a rare disease when one attempts to carefully select patients from all gastric cancer patients who visit a hospital.

Indication for the adjuvant therapy given perioperatively was even more varied among the researchers, as no trial-based evidence exists for the population who underwent hepatectomy for gastric cancer metastasis. Takemura et al. [6] took an aggressive approach in which 18 of 73 patients received neoadjuvant chemotherapy and 31 received postoperative chemotherapy, including 5 cases that received arterial infusion (HAIC) postoperatively. In contrast, Sakamoto et al. [14] reported that they delivered chemotherapy only for those who subsequently had recurrences. There is no prospective trial showing the effect of perioperative adjuvant therapies for gastric cancer metastases to the liver. The high incidence of recurrence implies that micrometastases remain in situ after surgery, however. That micrometastases could be managed by modern chemotherapeutic agents has been proven by several adjuvant chemotherapy trials [26–28]. Thus, there is a rationale for perioperative chemotherapy, or even HAIC, given the high incidence of recurrence within the liver. Chemotherapy delivered preoperatively could be useful to identify cancers that do not respond to chemotherapy and progress rapidly and to avoid futile surgery. All five series with 5-year survival >30 % reported details on adjuvant strategies, including neoadjuvant chemotherapy and HAIC. In contrast, none of the patients received chemotherapy until

Table 2 Independent prognostic determinants of the patients with gastric cancer liver metastasis

	Indication for inclusion in the case series	Factors independently showing favorable prognosis
Takemura et al. [6]	All hepatectomy cases	No serosal invasion, diameter <5 cm
Wang et al. [8]	Hepatectomy cases of synchronous metastasis	Solitary liver tumor, absence of peritoneal metastasis
Schildberg et al. [20]	All hepatectomy cases	Solitary liver tumor, synchronous metastasis
Garancini et al. [19]	All hepatectomy cases	Solitary liver tumor, RO resection, capsule formation
Miki et al. [8]	All cases with hepatic metastasis	Stage of the primary cancer
Makino et al. [10]	All cases with hepatic metastasis who underwent gastrectomy	Unilobular distribution
Tsujimoto et al. [17]	All hepatectomy cases	Diameter <6 cm, D2 dissection
Cheon et al. [9]	All cases with hepatic metastasis who underwent laparotomy with curative intent	Smaller number of metastases
Thelen et al. [16]	All hepatectomy cases	Negative resection margin
Morise et al. [15]	All hepatectomy cases	
Sakamoto et al. [14]	All hepatectomy cases	Unilobular distribution, diameter <4 cm
Adam et al. [2]	All hepatectomy cases of noncolorectal nonneuroendocrine hepatic metastasis	
Shirabe et al. [7]	All hepatectomy cases who underwent RO resection	Number of metastases <3, no lymphatic or venous invasion of the primary tumor
Zacherl et al. [13]	All hepatectomy cases	
Okano et al. [12]	All hepatectomy cases	Solitary liver tumor, synchronous metastasis, well-differentiated phenotype, capsule formation
Ambiru et al. [11]	All hepatectomy cases	Synchronous metastasis
Imamura et al. [21]	All hepatectomy cases of gastric and colorectal liver metastasis	No extrahepatic metastasis

recurrence in another series by Sakamoto et al., who reported their 5-year survival at 11 % as unsatisfactory. These facts imply the relevance of perioperative chemotherapy, although outcomes obtained from retrospective case series should be interpreted with caution. Evidence at a higher level will not be available for the time being because the chances of conducting a decently designed trial to generate evidence for adjuvant therapies in a disease as rare as resectable gastric liver metastases would be sparse.

Systemic chemotherapy, HAIC, and radiofrequency ablation (RFA) are among other treatment modalities for gastric cancer metastasis to the liver. No prospective trial investigating systemic chemotherapy specified in hepatic metastases has been reported, with the exception of one small pilot study involving 8 patients [29]. In recent phase III trials of first-line chemotherapy against advanced/metastatic gastric cancer, median survival time ranged from 11 to 15 months [30–34]; 5-year survivors were rarely observed. In a report that integrated 643 patients enrolled in five separate prospective trials performed by the Japan Clinical Oncology Group, the 5-year survival rate of patients with metastasis confined to the liver and treated with systemic chemotherapy alone was 1.7 % [35].

Presumably, this series does not include patients with a relatively small cancer burden for whom indication for surgery was seriously considered, and comparison of survival data with those of highly selected patients who underwent surgical resection of the metastases needs to be interpreted with caution. Nevertheless, it remains impractical to hope to cure patients with gastric cancer metastases to the liver by systemic chemotherapy.

The rationale for HAIC is in high intrahepatic drug concentration in relationship to the systemic concentration [36]. A response rate >50 % has been reported that led to good local control [36, 37]. However, good local control did not necessarily lead to prolonged survival in cases of gastric cancer, in which extrahepatic metastases often emerge even during the course of successful liver-oriented treatment. In addition, an inadequately placed or malfunctioning catheter prevents efficient drug delivery [38]. Thus, catheter-related events such as occlusion, dislocation, and infection could result in interruption or termination of the treatment, even when the tumors are responding.

RFA has been attempted to treat selected patients with hepatic metastasis. The indication for RFA would include (1) liver-only disease; (2) size of the largest tumor less than

5 cm in diameter; and (3) location of tumor not adjacent to major vessels. RFA can be conducted either percutaneously under ultrasonic imaging guidance, laparoscopically, or by the open surgery approach. Reports on RFA applied to treat gastric cancer metastases to the liver remain scarce. Kim et al. [39] treated 20 patients by RFA or RFA and gastrectomy in case of synchronous metastases, achieving a median survival time of 30.7 months, whereas the experience by Kim et al. with 7 patients was more disappointing, with a median survival time of 11 months [40]. There is another report of 7 patients treated by HAIC followed by RFA who achieved a median survival time of 16.5 months [41]. This strategy was meant to select the patients so that RFA would only be delivered after confirming that new intrahepatic or systemic lesions do not develop during the HAIC. The chances of conducting a hepatectomy-versus-RFA trial for gastric cancer metastasis to the liver would seem unlikely. So far, the only clue of whether to perform hepatectomy or RFA comes from a meta-analysis of retrospective comparisons for colorectal liver metastases in which hepatectomy was significantly superior, even when conditions were limited to tumors >3 cm and solitary tumors [42]. Further prospective studies are needed to establish the position of RFA as an option for treatment of gastric liver metastases.

Conclusions

This working group reached the conclusion that hepatectomy could be considered in carefully selected cases of gastric cancer liver metastasis. The abstract of this article will appear in the forthcoming version of the Japanese gastric cancer treatment guidelines.

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