Outcomes for patients following hepatic resection of metastatic tumors from gastric cancer

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Abstract

Purpose Although several studies have reported the efficacy of hepatic resection for the long-term survival of patients with gastric cancer metastases, the optimal treatment remains to be determined.

Methods Seventeen patients underwent a hepatic resection for gastric cancer metastases at the National Defense Medical College Hospital. We retrospectively analyzed the clinical outcomes of surgical resection and identified factors associated with prognosis for patients who underwent hepatectomy for gastric cancer metastases.

Results In 17 patients, the accumulated 5-year survival rate after hepatic resection was 31.5% and the median survival time was 34 months. Univariate and multivariate analyses showed that gastric tumors less than 6.0 cm and D2 lymphadenectomy were the most important predictors of survival. The five patients who survived more than 5 years after hepatic resection had a D2 lymphadenectomy, modest lymphatic invasion, primary gastric tumors less than 6.0 cm, and a solitary liver metastasis.

Conclusion Although recent progress in adjuvant therapy should be the key to a good prognosis, we believe that surgical resection may bring some hope of long-term survival for judiciously selected patients with hepatic metastases from gastric cancer.

Keywords Gastric cancer · Hepatectomy · Liver metastasis · Prognosis

Introduction

Gastric cancer recurs in various patterns including peritoneal dissemination, lymph node metastases, and hepatic metastases. In some patients, hepatic metastases are present at the time of diagnosis (synchronous metastases), but more frequently, they represent the evolution of the disease after curative gastrectomy (metachronous metastases). Because recurrence usually occurs in a combination of patterns including peritoneal dissemination, lung metastases, and lymph node metastases, only a few patients with hepatic metastases from gastric cancer are candidates for hepatic resection [1, 2].

The efficacy of operative resection for hepatic metastases from colorectal cancer has been established [3, 4], and it carries a 5-year survival rate of 30–50% [5–7]. However, the clinicopathologic characteristics of long-term gastric cancer survivors are not well known, and the efficacy of hepatic resection for metastases from gastric cancer remains elusive [8–10].

In this study, we retrospectively analyzed results and the outcomes of patients who had received surgical resection of hepatic metastases from gastric cancer to determine the actual targets of surgical intervention.

Materials and methods

Patients

Seventeen patients underwent hepatic resection for metastatic tumors from gastric cancer at the National Defense Medical College Hospital from 1980 to 2007. There were 1,417 gastrectomies and 195 hepatectomies performed for metastatic tumors during this period. Adequate amounts of

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Table 1 Demographic data of patients with hepatectomy for metastasis from gastric cancer

	Patients characteristics
Number	17
Age at gastrectomy	66.3 $\pm$ 2.1
Gender (M:F)	16:1
Remnant stomach	
Yes	4
No	13
Location	
U	7
M	5
L	5
Macroscopic type	
0	2
1	3
2	8
3	4
4	0
Depth	
T1, T2	12
T3, T4	5
Maximal size of gastric cancer (cm)	5.7 $\pm$ 0.4
Maximal size of metastatic liver tumor (cm)	4.8 $\pm$ 0.9
Lymphadenectomy	
D1	7
D2	10
Histology	
Intestinal	12
Diffuse	5
Peritoneal metastasis	
Yes	0
No	17
Lymph node metastasis	
N0	7
N1	5
N2	5
Venous invasion	
v0, v1	8
v2, v3	9
Lymphatic invasion	
ly0, ly1	9
ly2, ly3	8
Number of liver metastasis	
1	13
2	2
3	2
Liver resection	
Anatomical	11
Nonanatomical	6

Table 1 continued

	Patients characteristics
Adjuvant therapy after hepatectomy	
Yes	14
Systemic chemotherapy	10
HAI	4
No	3

U upper third of the stomach, *M* middle third of the stomach, *L* lower third of the stomach, *HAI* hepatic arterial infusion

5-fluorouracil or fluoropyrimidine were orally administered to most patients following gastrectomy. The lymph node station number was classified according to the Japanese Gastric Cancer Association [11]. Perigastric lymph nodes were generally classified as first-tier lymph nodes (N1), and station 7, 8a, 9, 11p, 11d, 12a, and 14v lymph nodes along the left gastric artery, common hepatic artery, celiac axis, proximal half of the splenic artery, distal half of the splenic artery, proper hepatic artery, and superior mesenteric vein at the lower border of the pancreas, respectively, were classified as second-tier lymph nodes depending on the tumor location. D2 lymph node dissection was defined as the complete removal of all second-tier lymph nodes. D1 lymph node dissection was defined as the removal of perigastric and station 7 or additional station 8a and/or station 9 lymph nodes according to the depth, size, and location of tumor. Hepatic resection of gastric cancer metastasis was indicated only in patients with metastases in 1 lobe of the liver without peritoneal dissemination, or in patient with metastases who would have acceptable postoperative hepatic function assessed by preoperative indocyanine green test and Child–Pugh score following the resection. In addition, hepatectomy for metastasis from gastric cancer was performed only when the curative resection was intended. For patients with synchronous hepatic metastasis, hepatectomy was performed with gastrectomy at the same time. Resected specimens were examined histopathologically and described on the basis of a classification for gastric carcinomas [11]. The patients were evaluated from our computer database or medical and nursing charts for demographics, surgical procedure, pathological findings of the gastric cancer, number of the liver metastases, and overall survival. Overall survival time was measured from the date of hepatic resection to the date of death due to any cause. Patients who survived were censored in our survival analyses. All patients were observed at our hospital or the outpatient clinic at 3- to 4-month intervals during the first 2 years of the study and every 6 or 12 months thereafter for 3 years. Computed tomographic scan and serum carcinoembryonic antigen were tested every 6 month until 5 years

Fig. 1 Overall survival after hepatectomy in patients with hepatic metastasis from gastric cancer. *MST* median survival time

after gastrectomy and/or hepatectomy. After 5 years, annual follow-up was conducted through telephone conversations with patients, patients' family, or their practitioner.

Statistical analysis

The data are expressed as mean $\pm$ SEM. Statistical analyses were performed using either the Mann–Whitney *U* test or the chi-square test. Survival rates were obtained by the Kaplan–Meier method and the statistical significance was determined by the log-rank test. Multivariate analysis was performed with the Cox proportional hazards model. The prognostic variables were entered into the model when the univariate analysis revealed a significance level of $p < 0.1$. All values with $p < 0.05$ were considered statistically

Table 2 Clinical and pathologic factors examined in univariate analysis to determine prognostic factors for survival after hepatectomy

Characteristics	No. of patients (%)	Median survival time (months)	Survival rate (%)			<i>p</i> value
			1-year	3-years	5-years	
Overall	17 (100)	34.0	75.0 (12/16)	37.5 (6/16)	25.0 (4/16)	
Gastric cancer						
Age at gastrectomy						
≥ 65	9 (52.9)	22.5	75.0	25.0	25.0	0.48
< 65	8 (47.1)	32.2	87.5	62.5	37.5	
Depth of invasion						
T1, T2	12 (70.6)	32.3	91.7	50.0	33.3	0.37
T3, T4	5 (29.4)	9.9	50.0	25.0	25.0	
Maximal tumor size (mm)						
≥ 6.0	9 (52.9)	17.6	66.7	11.1	0	< 0.01
< 6.0	8 (47.1)	40.0	100	85.7	71.4	
Tumor location						
U	7 (37.5)	24.0	85.7	42.9	28.6	0.68
M, L	10 (62.5)	31.7	77.8	44.4	33.3	
Lymph node metastasis						
n0	7 (37.5)	30.6	85.7	57.1	42.9	0.42
n1, n2	10 (62.5)	26.4	77.8	33.3	22.2	
Histology						
Intestinal	12 (70.6)	31.0	81.8	45.5	27.3	0.96
Diffuse	5 (29.4)	10.8	80.0	40.0	40.0	
Venous invasion						
v0, v1	8 (47.1)	27.5	87.5	50.0	37.5	0.97
v2, v3	9 (52.9)	28.6	75.0	37.5	25.0	
Lymphatic invasion						
ly0, ly1	9 (52.9)	26.1	77.8	55.6	55.6	0.06
ly2, ly3	8 (47.1)	23.3	87.5	28.6	0	
Lymphadenectomy						
D1	7 (37.5)	20.1	85.7	14.3	0	< 0.01
D2	10 (62.5)	37.1	77.8	66.7	55.6	

Table 2 continued

Characteristics	No. of patients (%)	Median survival time (months)	Survival rate (%)			<i>p</i> value
			1-year	3-years	5-years	
Liver metastasis						
Temporal relationship						
Synchronous	9 (52.9)	18.7	66.7	22.2	22.2	0.16
Metachronous	8 (47.1)	38.0	100	71.4	42.9	
Tumor number						
Solitary	13 (76.5)	29.3	83.3	50.0	41.7	0.13
Multiple	4 (23.5)	22.8	75.0	25.0	0	
Tumor size (mm)						
≥6.0	8 (47.1)	28.9	85.7	57.1	42.9	0.47
<6.0	9 (52.9)	27.1	77.8	44.4	33.3	
Surgical procedure						
Anatomical	11 (64.7)	33.4	90.0	60.0	40.0	0.17
Nonanatomical	6 (35.3)	18.7	66.7	16.7	16.7	
Date of hepatectomy						
Before 1995	8 (47.1)	20.5	75.0	25.0	25.0	0.38
After 1996	9 (52.9)	34.2	87.5	62.5	37.5	
Adjuvant chemotherapy						
Yes	14 (82.4)	24.0	76.9	30.8	23.1	0.13
No	3 (17.6)	46.0	100	100	66.7	

U upper third of the stomach, *M* middle third of the stomach, *L* lower third of the stomach

significant. All analyses were performed using StatView, Version 5.0 (SAS Institute Inc., Cary, NC, USA).

Results

All patients underwent gastric and hepatic resection with curative intent (i.e.; no gross residual disease was evident at the time of the operation). The patient demographics are presented in Table 1. The median follow-up time was 29.3 months (range 9–130 months), and there were no mortalities within 30 days after surgery. Four patients did not have a recurrence of tumor, six patients had general metastases, four patients had liver recurrences, and three patients had lung metastases. In 17 patients, the accumulated 5-year survival rate after hepatic resection was 31.5% and the median survival time (MST) was 34 months (Fig. 1). Nine patients had synchronous hepatic metastases and eight had metachronous metastases. In the 8 patients with metachronous metastases, the average interval between gastric and hepatic resection was 26.8 months (range 14–58 months). There was a significant difference in the maximum size of hepatic tumors between patients with synchronous and metachronous hepatic metastasis from gastric cancer (2.9 ± 0.8 vs. 6.8 ± 1.3 cm, respectively). The 5-year survival rate after hepatectomy in

patients with synchronous hepatic metastases was 22.2%, whereas it was 42.9% for those with metachronous hepatic metastases ($p = 0.06$). The MST for patients with synchronous metastases was 19 months, and it was 38 months for those with metachronous hepatic metastases. There was no significant statistical difference in survival after hepatectomy between the two groups.

Univariate and multivariate analyses showed that gastric tumors less than 6.0 cm and D2 lymphadenectomy were the most important predictors of survival. However, factors associated with the number and size of the hepatic tumors and the date of hepatic resection were not significantly related to survival (Tables 2, 3).

We also examined the clinicopathologic features between survivors ($n = 7$) and nonsurvivors ($n = 9$) 3 years after hepatectomy; one patient was excluded because he was alive 2 years after hepatectomy (Table 4). The average age at gastrectomy for survivors was significantly younger than for nonsurvivors. Nonsurvivors had significantly larger primary gastric tumors than survivors. Survivors had significantly more frequent D2 lymphadenectomies at the primary gastrectomy and more frequent metachronous liver metastasis than nonsurvivors.

Three of the five patients who survived for more than 5 years had metachronous metastasis (Table 5). One male patient (case 3) had lung metastasis 3 years after

Table 3 Multivariate analysis to determine prognostic factors for survival after hepatectomy for metastasis from gastric cancer

Multivariate analysis			
Factor	Hazard ratio	95% CI	<i>p</i> value
Maximal diameter of the gastric cancer			
<6.0 cm	1		
≥6.0 cm	7.82	1.50–40.8	0.0146
Lymphatic invasion			
ly1	1		
ly2, ly3	2.25	0.59–8.62	0.2363
Lymphadenectomy			
D1	1		
D2	0.18	0.03–0.99	0.0498

hepatectomy and brain metastasis 4 years after hepatectomy, which were successfully treated with chemotherapy and radiation therapy. Another male patient (case 5) had liver metastasis 7 years after hepatectomy. The other three patients survived without recurrence. All patients had curative resection for gastric cancer with D2 lymphadenectomy, modest lymphatic invasion, primary gastric tumors less than 6 cm, and had a solitary liver metastasis.

Discussion

Various factors may be associated with the outcomes following hepatectomy for patients with gastric cancer metastasis, such as histology, depth of invasion, and lymphatic or venous invasion, for a factor of primary gastric cancer, and number and size of metastases, timing of hepatectomy, and surgical margin for hepatic tumors. As several authors have emphasized a favorable outcome for patients with metachronous metastasis, survivors 3 years after hepatectomy for metastasis from gastric cancer had more frequently metachronous hepatic metastasis, although we did not find any survival advantage in univariate and multivariate analyses [12, 13]. Small sample size or different indications for hepatectomy may explain these conflicting results.

Surgical resection of liver metastasis from gastric cancer is rarely indicated. Multiple lobe metastases, peritoneal dissemination, and extensive lymph node metastases, or direct invasion of other organs, argue against surgical liver resection [1]. We reviewed recent studies of the clinical outcomes of patients following hepatectomy for gastric cancer metastasis (Table 6). Similar to our findings, the average 5-year survival rate and MST following hepatectomy were 24.9% (range 0–42%) and 23.5 months (range 12–34 months), respectively [9, 10, 12–19]. In addition,

Table 4 Demographic data of survivor and nonsurvivors 3 years after hepatectomy for metastasis from gastric cancer

	Survivors	Nonsurvivors	<i>p</i> value
Number	7	9	
Age at gastrectomy	59.4 ± 2.8	69.6 ± 2.8	0.01
Gender (M:F)	6:1	8:0	0.27
Gastric cancer			
Depth			
T1, T2	6	6	0.37
T3, T4	1	3	
Maximal size of gastric cancer (cm)	4.5 ± 0.5	6.7 ± 0.5	0.01
Location			
U	3	4	0.95
M, L	4	5	
Lymph node metastasis			
n0	4	3	0.57
n1	2	3	
n2	1	3	
Histology			
Intestinal	5	6	0.84
Diffuse	2	3	
Venous invasion			
v0, v1	4	4	0.61
v2, v3	3	5	
Lymphatic invasion			
ly0, ly1	5	4	0.28
ly2, ly3	2	5	
Lymphadenectomy			
D1	1	7	0.01
D2	6	2	
Liver metastasis			
Temporal relationship			
Synchronous	2	7	0.04
Metachronous	5	2	
Number of liver metastasis			
1	6	6	0.41
2	1	1	
3	0	2	
Maximal size of metastatic liver tumor (cm)	5.9 ± 1.1	3.8 ± 1.4	0.08
Surgical procedure			
Anatomical	6	4	0.08
Nonanatomical	1	5	

U upper third of the stomach, M middle third of the stomach, L lower third of the stomach

14.6% (range 0–26.7%) of patients who underwent hepatectomy survived for more than 5 years.

Nonsurgical intervention methods including hepatic arterial infusion (HAI) [20–22], systemic chemotherapy

Table 5 Five patients survived for more than 5 years after hepatectomy for metastasis from gastric cancer

	Case 1	Case 2	Case 3	Case 4	Case 5
Age at gastrectomy	52	53	71	66	53
Gender	Female	Male	Male	Male	Male
Temporal relationship	Synchronous	Metachronous	Metachronous	Metachronous	Synchronous
Location of tumor	M	M	U	U	M
Macroscopic type	2	1	1	2	3
Depth	T3	T2	T2	T2	T2
Maximal size of gastric cancer (cm)	2.5	4.5	4.5	5.0	4.8
Tumor differentiation	Diffuse	Diffuse	Intestinal	Intestinal	Intestinal
Lymphadenectomy	D2	D2	D2	D2	D2
Nodal involvement	n0	n1	n0	n0	n1
Venous invasion	v1	v0	v2	v2	v1
Lymphatic invasion	ly1	ly1	ly1	ly1	ly1
Stage	IV	II	I	I	IV
Number of liver metastasis	1	1	1	1	1
Period after primary gastrectomy (month)	–	15	15	42	–
Maximal size of metastatic liver tumor (cm)	3.0	2.0	7.3	10.7	7.0
Liver metastasis	S3	S4	S6	S7	S6
Liver resection	Segmental resection	Limited resection	Segmental resection	Right lobectomy	Right lobectomy
Adjuvant therapy after hepatectomy	No	HAI	Systemic	No	HAI
Survival periods (months)	130	99	61	65	85
Outcome	Alive	Alive	Alive	Alive	Alive
			Lung and brain metastases		Liver metastasis

HAI hepatic arterial infusion

[9, 23], and radiofrequency ablation (RFA) have been reported to produce clinical benefits for patients with hepatic metastases from gastric cancer [24]. However, the MST of patients who received HAI was 19.2 months, and only 5.6% survived for more than 5 years [22]. There is no report demonstrating the efficacy of RFA for hepatic metastases from gastric cancer. Thus, nonsurgical treatment may not influence long-term survival for these patients, but a potentially curative surgical resection may bring some hope of long-term survival [19].

Our results showed that five patients who survived for more than 5 years after hepatic resection had D2 lymphadenectomy, modest lymphatic invasion in their primary gastric cancer, and a solitary liver metastasis. In Japan, D2 lymphadenectomy is recommended for advanced gastric cancer [25]; however, surgeons might not have performed this procedure because patients have extensive, locally advanced gastric cancer, or critical comorbidity.

In this study, we demonstrated that patients with smaller sized primary gastric tumors, especially less than 5 cm in size, had favorable outcomes following hepatic resection. The precise mechanism how smaller primary tumor may improve the survival of these patients who

developed hepatic metastasis remains unclear. We speculated that larger primary gastric tumor may have evolved to advanced stage of disease and already acquired metastatic potential.

We found 4 of 17 patients with remnant stomach cancer, 3 with synchronous metastasis and 1 with metachronous metastasis. Ikeguchi et al. [26] demonstrated a distinct difference in recurrence patterns between patients with curatively resected primary cancer in the upper third of the stomach and those with remnant gastric cancer. The main pattern of recurrence for patients with primary gastric cancer was peritoneal metastasis, whereas those with remnant gastric cancer developed hematogenic metastasis, such as metastasis to the liver. Nevertheless, further study will be necessary to prove the association of remnant gastric cancer with the incidence of hepatic metastasis.

Although recent progress in adjuvant therapy should be the key to a good prognosis, we believe that surgical resection may bring some hope of long-term survival for patients with hepatic metastases from gastric cancer. According to our data, patients with smaller sized primary gastric tumors and those who received a D2 lymphadenectomy at gastrectomy had the most favorable outcomes

Table 6 Recent literature regarding hepatectomy for metastasis from gastric cancer

Author	Year	Total No.	5-year survival rate (%)	MST (months)	No. of patient who survived over 5 years (%)	Factors associated with the outcome	References
Miyazaki	1996	21	NA	NA	2 (9.5)	Solitary hepatic metastasis	[9]
Ambiru	2001	40	18	12	6 (15.0)	Hepatic tumor margin (>10 mm) Metachronous hepatic metastasis	[12]
Imamura	2001	17	0	12	0 (0.0)	Hepatic tumor margin	[14]
Okano	2002	19	34	21	4 (21.1)	NA	[13]
Saiura	2002	10	20	25	2 (20.0)	Solitary hepatic metastasis, Metachronous hepatic metastasis	[15]
Shirabe	2003	36	26	NA	4 (11.1)	Lymph node metastasis in gastric cancer	[16]
						Lymphatic and venous invasion of gastric cancer	
						Solitary hepatic metastasis	
Roh	2005	11	27.3	19	2 (18.2)	Solitary hepatic metastasis	[10]
Hirai	2006	14	41.6	NA	NA	Solitary hepatic metastasis	[17]
Koga	2007	42	42	34	8 (19.0)	NA	[19]
Sakamoto	2007	37	11	31	2 (5.4)	Solitary hepatic metastasis	[18]
						Unilobar hepatic metastasis	
						Hepatic tumor size (<4 cm)	
Our series		17	31.5	34	5 (29.4)	Gastric tumor size (<6 cm)	–
						D2 lymphadenectomy	

MST median survival time, NA not available

following hepatic resection. These patients would make the best candidates for hepatic resection; however, this study included the small number of patients and was based on a retrospective analysis, which is the limitation of this study. Results from additional prospective studies or a detailed meta-analysis will be necessary to select patients who will have the greatest benefit from this resection.

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