Indication for Hepatic Resection in the Treatment of Liver Metastasis from Gastric Cancer

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Abstract. *Background: The significance of hepatic resection for liver metastasis after gastric cancer is not well established. This study aimed to evaluate the effect of hepatic resection in such patients. Patients and Methods: A retrospective analysis was performed on the outcome of 63 patients with liver metastases without other non-curative factors of gastric cancer who underwent gastrectomy with or without hepatic resection. Results: Overall 1-, 3-, and 5-year survival rates were 61.9%, 17.2%, and 10.3%, respectively, with a median survival time of 16 months. This increased to 82.3%, 46.4%, and 37.1%, respectively, with a median survival time of 31.2 months in patients who underwent hepatic resection. Multivariate analysis showed that hepatic resection was an independent prognostic factor. Moreover, unilobar liver metastases significantly influenced favorable prognosis in patients receiving hepatic resection by univariate analysis. Conclusion: In patients with liver metastases, hepatic resection may be a therapeutic option in the presence of unilobar liver metastases.*

Liver metastasis occurs in 3.5-14% of patients who undergo surgery for gastric cancer (1-9). Unfortunately, most liver metastases from gastric cancer are multiple, bilobar, and frequently combined with peritoneal or extensive lymph node metastases and tumors in adjacent organs (10, 11). Therefore, many patients with liver metastasis are not suitable candidates for hepatic resection, even if only a solitary hepatic metastasis is involved. However, complete surgical resection of the primary gastric tumor and liver metastases is a promising treatment for this disease (6, 8).

Many studies have reported on the benefit of hepatic resection for metastatic tumors deriving from colorectal cancer, and the indications for hepatic resection have been extended to technically resectable metastases numbering four or more (12-18). By contrast, the significance and indications of hepatic resection for liver metastasis from gastric cancer remains controversial, although some studies indicate that hepatic resection is associated with long-term survival (2-9, 13, 19-26). Most previous reports evaluated the benefits of hepatic resection on survival in patients who underwent hepatic resection. Few have compared surgical outcomes between patients with and without hepatic resection, and without non-curative factors except liver metastasis (5, 9, 25, 26). In this study, we retrospectively evaluated prognostic factors using univariate and multivariate analyses in gastric cancer patients with liver metastasis to evaluate the need and effect of hepatic resection for liver metastasis.

Patients and Methods

Between June 1992 and May 2007, 1,608 patients with gastric cancer underwent surgery at the Department of Surgery, Gastroenterological Center, Yokohama City University, Japan, and the Department of Gastroenterological Surgery, Yokohama City University School of Medicine, Japan. All patients were preoperatively confirmed to have gastric adenocarcinoma by endoscopic biopsy analysis.

Of these, 63 patients (3.9%) had liver metastasis without other non-curative factors. Fifty-one males and 12 females participated in this study, with a mean age of 65.8±7.6 years (±standard deviation). Thirty-one patients (1.9%) had synchronous liver metastases and 32 (2.0%) developed metachronous liver metastases after curative resection of the primary gastric cancer.

Our criteria for hepatic resection of liver metastases from gastric cancer were the absence of extrahepatic non-curative factors and feasible complete macroscopic removal of liver deposits. Surgery was performed after all of the possible alternative treatments had

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Key Words: Gastric cancer, hepatic resection, liver metastasis, prognostic factor.

Table I. *Characteristics of patients with liver metastasis.*

	With hepatectomy (n=16)	Without hepatectomy (n=47)	*p*-Value
Age (years)			
<70	11	31	0.9999
≥70	5	16	
Gender			
Male	13	38	0.9999
Female	3	9	
Macroscopic type[a]			
Well-defined	8	24	0.9999
Ill-defined	8	23	
Size of primary gastric tumor (mm)			
<50	5	16	0.9999
≥50	11	31	
Histological type[a]			
Differentiated	10	35	0.3598
Undifferentiated	6	12	
Serosal invasion			
Absent	8	21	0.7766
Present	8	26	
Lymph node metastasis			
Absent	3	6	0.6811
Present	13	41	
Lymphatic invasion			
Absent	4	6	0.2586
Present	12	41	
Venous invasion			
Absent	2	4	0.6388
Present	14	43	
Pathological stage[a]			
I, II, III	6	16	0.9999
IV	10	31	
Curability of primary gastric tumor[a]			
A, B	15	26	-[b]
C	1	21	
Timing of metastasis			
Synchronous	9	22	0.5722
Metachronous	7	25	
Distribution of liver metastasis			
Unilobar	11	19	0.0810
Bilobar	5	28	
Number of liver metastases			
Solitary	9	15	0.1349
Multiple	7	32	
Systemic chemotherapy before gastrectomy			
Absent	13	28	0.1405
Present	3	19	
Systemic chemotherapy after gastrectomy			
Absent	6	23	0.5639
Present	10	24	
Hepatic arterial infusion			
Absent	12	30	0.5443
Present	4	17	

[a]: According to Japanese Classification of Gastric Cance, 2nd English Edition (27); [b]: The two-tailed Fisher exact test was not indicated in comparing the incidence of curability of primary gastric tumor because the sample size of curability C was one in patients with hepatic resection.

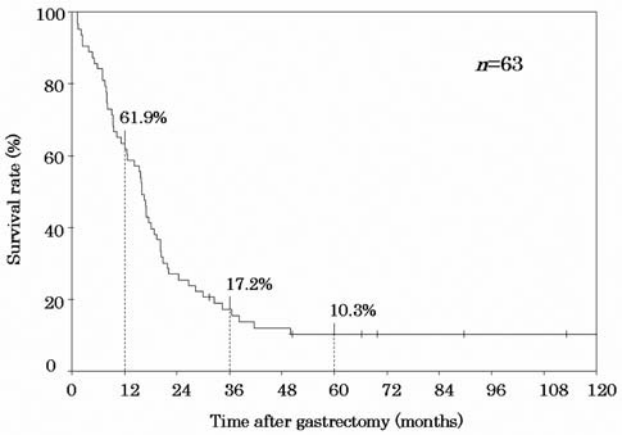

Figure 1. *Disease-specific survival in all registered patients (n=63). Disease-specific survival rates in all registered patients were 61.9% (1-year), 17.2% (3-year), and 10.3% (5-year), with a median survival time of 16 months.*

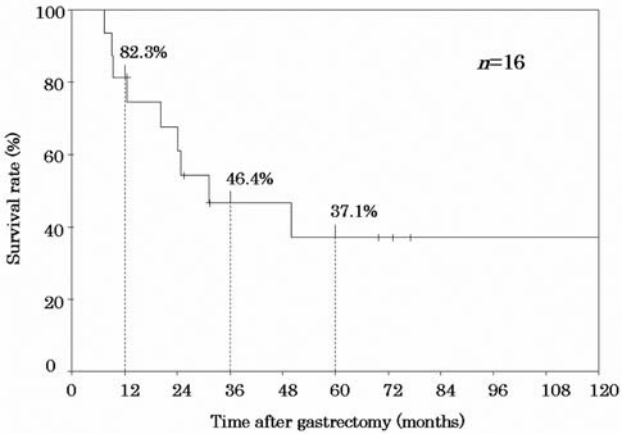

Figure 2. *Survival in patients following hepatic resection (n=16). In patients receiving hepatic resection, the 1-, 3-, and 5-year survival rates were 82.3%, 46.4%, and 37.1%, respectively, with a median survival time of 31.2 months.*

been explained to each patient, and informed consent was obtained. Treatment with or without hepatic resection was selected by intention for patients who met the criteria for hepatic resection of liver metastases from gastric cancer. A total of 16 patients underwent hepatic resection. Nine out of 31 patients with synchronous liver metastases concurrently underwent gastrectomy and hepatic resection. Seven out of 32 patients with metachrous liver metastases underwent hepatic resection. Nonanatomically limited hepatic resection was the standard surgical procedure in this study. Hepatic resection was not performed in 22 patients with synchronous liver metastases. Fourteen of them had bilobar multiple liver metastases and macroscopic complete removal of liver deposits could not be performed. Eight patients did not select hepatic resection for their liver metastases. Hepatic resection was also not performed in 25 patients with metachronous liver metastasis. Six of them had bilobar multiple liver metasasis and macroscopic complete removal of liver deposits could not be performed. Nineteen patients did not select hepatic resection for their liver metastases. The incidence of liver

Table II. *Univariate analysis of survival of all registered patients*.

Variables	No. of patients	Survival rate(%)			Median survival time (months)	*p*-Value[b]
		1-year	3-year	5-year		
Age (years)						
<70	42	69.1	18.5	10.6	16.9	0.2322
≥70	21	47.6	14.3	9.5	12.0	
Gender						
Male	51	62.8	15.7	9.8	16.4	0.8496
Female	12	58.3	25	12.5	15.7	
Macroscopic type[a]						
Well-defined	32	62.5	15.6	9.4	16.0	0.9684
Ill-defined	31	61.3	19.4	11.6	16.0	
Tumor size of primary gastric tumor (mm)						
<50	21	57.1	9.5	4.8	16.0	0.6581
≥50	42	64.3	21.4	13.4	16.0	
Histological type[a]						
Differentiated	45	66.7	17.8	11.1	16.9	0.4233
Undifferentiated	18	50.0	14.8	7.4	11.4	
Serosal invasion						
Absent	34	73.5	20.6	14.7	16.9	0.1175
Present	29	48.3	13.8	4.6	12.0	
Lymph node metastasis[a]						
Absent	9	55.6	44.4	26.7	15.8	0.2341
Present	54	63.0	13.0	7.4	16.0	
Lymphatic invasion						
Absent	10	70.0	26.7	26.7	20.2	0.1874
Present	53	60.4	15.1	7.6	16.0	
Venous invasion						
Absent	6	50.0	16.7	16.7	11.4	0.7270
Present	57	63.2	17.2	9.6	16.0	
Pathological stage[a]						
I, II, III	22	81.8	27.3	13.6	20.4	0.0398
IV	41	51.2	12.2	9.2	12.6	
Curability of primary gastric tumor[a]						
A, B	41	78.1	24.0	13.3	19.4	0.0003
C	22	31.8	4.6	4.6	7.8	
Timing of metastasis						
Synchronous	31	41.9	16.1	12.1	9.5	0.0987
Metachronous	32	81.3	18.8	9.4	18.8	
Distribution of liver metastasis						
Unilobar	30	80.0	33.3	22.2	20.2	0.0002
Bilobar	33	45.5	0	0	9.4	
Number of liver metastases						
Solitary	24	79.2	33.3	23.8	20.2	0.0036
Multiple	39	51.3	7.8	2.6	12.6	
Hepatic resection						
Absent	47	53.2	4.2	0	15.2	<0.0001
Present	16	87.5	56.3	42.2	38.3	
Systemic chemotherapy before gastrectomy						
Absent	41	65.9	26.6	16.0	17.5	0.0050
Present	22	54.5	0	0	12.6	
Systemic chemotherapy after gastrectomy						
Absent	29	44.8	13.8	13.8	8.2	0.0323
Present	34	76.5	20.6	8.8	20.2	
Hepatic arterial infusion						
Absent	42	57.1	23.8	15.9	15.2	0.5378
Present	21	71.4	4.8	0	16.9	

[a]: According to Japanese Classification of Gastric Cancer, 2nd English Edition (27); [b]: Survival time was determined using the Kaplan-Meier method and compared using the log-rank test.

Table III. *Cox proportional hazard regression model in all registered patients.*

Clinical variable		Hazard ratio	95% Confidence interval	*p*-Value
Hepatic resection	Present *vs.* Absent	0.160	0.048-0.527	0.003
Stage[a]	IV *vs.* I,II,III	2.756	0.774-9.816	0.118
Curability of the primary gastric tumor[a]	C *vs.* A, B	1.044	0.369-2.948	0.936
Distribution of liver metastasis	Bilobar *vs.* Unilobar	1.755	0.427-7.220	0.436
Number of liver metastases	Solitary *vs.* Multiple	1.170	0.282-4.858	0.828
Systemic chemotherapy before gastrectomy	Present *vs.* Absent	1.077	0.421-2.754	0.877
Systemic chemotherapy after gastrectomy	Present *vs.* Absent	0.490	0.193-1.245	0.134

[a]: According to Japanese Classification of Gastric Cancer. 2nd English Edition (27).

resection was 25.4% (16/63) for all 63 patients, 29.0% (9/31) for those with synchronous liver metastasis and 21.9% (7/32) for those with metachronous liver metastasis.

Data were retrieved from operative and pathologic reports. Follow-up data were obtained from the outpatient clinical database. The following demographic variables were evaluated: age (<70 years or ≥70 years) and gender (male or female). The following clinicopathologic variables were evaluated by experienced pathologists from each institution: macroscopic type (defined or ill defined), tumor size of primary gastric tumor (<50 mm or ≥50 mm), histological type (differentiated: well-differentiated, moderately differentiated, or papillary) or undifferentiated: (poorly differentiated, signet-ring cell, or mucinous), serosal invasion of tumor (absent or present), lymph node metastasis (absent or present) (27), lymphatic invasion (absent or present), venous invasion (absent or present), pathologic stage (I, II, III, or IV) (27), curability (A, B, or C) of primary gastric tumor (27), detection timing of liver metastasis (synchronous or metachronous), distribution of liver metastases (unilobar or bilobar), number of liver metastases (solitary or multiple), hepatic resection (absent or present), systemic chemotherapy before gastrectomy (absent or present), systemic chemotherapy after gastrectomy (absent or present), type of hepatic resection (<hemihepatectomy or ≥hemihepatectomy), liver tumor size (<30 mm or ≥30 mm), systemic chemotherapy before hepatic resection (absent or present), systemic chemotherapy after hepatic resection (absent or present), and hepatic arterial infusion chemotherapy (HAI) (absent or present).

Preoperative imaging studies were used to determine the tumor site, macroscopic type, tumor size, depth of invasion, lymph node metastasis and distant metastasis of the primary gastric cancer. Imaging studies were routinely performed using an upper gastrointestinal barium enema, endoscopic examination and computed tomography (CT). Tumor size and depth of tumor invasion were measured by both endoscopic examination and a barium-enema study. The clinocopathologic terminology used in this study was based on the Japanese Classification of Gastric Carcinoma (JGC) (27).

The Japanese Gastric Cancer Association has standardized lymph node dissections for gastric cancer. In this study, D1 gastrectomy (complete dissection of the first-tier lymph nodes) plus lymph node dissection along the left gastric artery or common hepatic artery was performed in 25 patients, while standard D2 gastrectomy (complete dissection of the first-tier and second-tier lymph nodes) was performed in 19 patients. D3 gastrectomy (complete dissection of the first-, second- and third-tier lymph nodes) was performed in 19 patients. These procedures were performed in accordance with the JGC.

Systemic chemotherapies before gastrectomy were administrated in 22 patients. A combination of 5-fluorouracil (5-FU) 300 mg/m^2 and cisplatin (CDDP) 3 mg/m^2 was intravenously administered for 2 weeks at 2-days intervals.

Systemic chemotherapies after gastrectomy were administered in 34 patients. Before April 2000, a combination of 5-FU 300 mg/m^2 and CDDP 3 mg/m^2 was intravenously administered for 2 weeks at 2-day intervals. The regimen was repeated as many times as possible until treatment failure due to progressive disease was observed in 19 patients. After April 2000, S-1 80 mg/m^2/day was administered for four weeks followed by two-week intervals as the first-line regimen to 15 patients at the outpatient department. A combination of docetaxel 60 mg/m^2 and CDDP 60 mg/m^2 was administered tri-weekly as the second-line regimen after the failure of S-1 in 13 patients. A combination of irrinotecan (CPT-11) 60 mg/m^2 and CDDP 30 mg/m^2 was administered tri-weekly as the third-line regimen in 6 patients.

Systemic chemotherapies before hepatic resecrion were administered in 5 patients. A combination of 5-FU 300 mg/m^2 and CDDP 3 mg/m^2 was intravenously administered for 2 weeks at 2-day intervals to 2 patients. S-1 80 mg/m^2/day was administered for four weeks followed by two-week intervals as the first-line regimen to 3 patients at the Outpatient Department.

Systemic chemotherapies after hepatic resection were administered in 9 patients. A combination of 5-FU 300 mg/m^2 and CDDP 3 mg/m^2 was intravenously administered for 2 weeks at 2-day intervals to 5 patients. S-1 80 mg/m^2/day was administered for four weeks followed by two-week intervals as the first-line regimen to 4 patients at the Outpatient Department. A combination of docetaxel 60 mg/m^2 and CDDP 60 mg/m^2 was administered tri-weekly as the second-line regimen after the failure of S-1 in 4 patients. A combination of CPT-11 60 mg/m^2 and CDDP 30 mg/m^2 was administered tri-weekly as the third-line regimen in 2 patients.

HAI consisted of a combination of 5-FU, methotrexate (MTX), and CDDP infused into the hepatic artery through an implanted arterial access port (Vital-Port; Cook Vascular, Leechburg, PA). 5-FU (500-600 mg/m^2/day), MTX (10 mg/m^2/day), and CDDP (10 mg/m^2/day) were delivered over 24 h once a week for eight weeks whenever possible. After hepatic resection, 4 patients received HAIs and 17 patients without hepatic resection received HAIs.

The participants underwent hematological examinations, and ultrasonography or CT every three months. Follow-up ranged from 1 to 127 months (median 16 months) after gastric resection for gastric cancer.

Statistical analysis. Data were analyzed using the SPSS statistical software program version 10.0 for Windows (SPSS Inc., Chicago,

Table IV. *Univariate analysis of survival of patients who underwent hepatic resection*

Variable	No. of patients	Survival rate (%)			Median survival time (months)	*p*-Value[b]
		1-year	3-year	5-year		
Age (years)						
<70	11	90.9	53.0	39.8	49.9	0.2160
≥70	5	60.0	30.0	30.0	12.6	
Gender						
Male	13	76.9	42.7	32.1	24.8	0.2882
Female	3	100	66.7	66.7	61.8*	
Macroscopic type[a]						
Well-defined	8	75.0	50.0	33.3	24.8	0.8009
Ill-defined	8	87.5	43.8	43.8	31.2	
Tumor size of primary gastric tumor (mm)						
<50	5	80	20	20	24.1	0.2562
≥50	11	81.8	59.7	44.7	49.9	
Histological type[a]						
Differentiated	10	90.0	42.2	42.2	31.2	0.5756
Undifferentiated	6	66.7	50.0	25	12.6	
Serosal invasion						
Absent	8	87.5	72.9	43.8	24.8	0.7452
Present	8	75.0	46.8	23.4	31.2	
Lymph node metastasis[a]						
Absent	12	87.5	72.9	72.9	49.9	0.4198
Present	4	75.0	50.0	25.0	12.6	
Lymphatic invasion						
Absent	4	75.0	75.0	75.0	62.9*	0.2325
Present	12	75.0	37.5	28.1	24.8	
Venous invasion						
Absent	2	100	50.0	50.0	20.2	0.7728
Present	14	78.6	45.8	34.4	31.2	
Pathological stage[a]						
I, II, III	6	83.3	41.7	41.7	31.2	0.8224
IV	10	80.0	50.0	33.3	24.8	
Curability of primary gastric tumor[a]						
A,B	15	80.0	43.6	34.9	31.2	0.4231
C	1	100	0	0	25.4*	
Timing of metastasis						
Synchronous	9	77.8	55.6	37.0	49.9	0.9518
Metachronous	7	85.7	34.3	34.3	31.2	
Distribution of liver metastasis						
Unilobar	11	81.8	71.6	57.3	82.1*	0.0271
Bilobar	5	80.0	0	0	24.1	
Number of liver metastases						
Solitary	9	77.8	66.7	66.7	87.2*	0.0647
Multiple	7	85.7	17.1	0	24.8	
Type of hepatic resection						
<hemihepatectomy	14	78.6	45.8	34.4	31.2	0.7728
≥hemihepatectomy	2	100	50	50	20.2	
Liver tumor size (mm)						
<30	8	87.5	37.5	25	24.1	0.4123
≥30	8	75	60	60	81.2*	
Systemic chemotherapy before gastrectomy						
Absent	13	76.9	58.6	46.9	49.9	0.0801
Present	3	100	0	0	20.2	
Systemic chemotherapy after gastrectomy						
Absent	6	66.7	66.7	66.7	54.2*	0.2210
Present	10	90.0	30.0	15.0	24.8	
Systemic chemotherapy before hepatic resection						
Absent	11	72.7	54.6	43.6	49.9	0.7455
Present	5	75.0	0	0	24.8	
Systemic chemotherapy after hepatic resection						
Absent	7	71.4	71.4	71.4	57.5*	0.1778
Present	9	88.9	29.6	14.8	24.8	
Hepatic arterial infusion						
Absent	12	83.3	54	54	76.1*	0.0853
Present	4	75	25	0	20.2	

[a]: According to Japanese Classification of Gastric Cancer, 2nd English Edition (27); [b]: Survival rates were determined using the Kaplan-Meier method and compared using the log-rank test. *: Mean survival time was used instead of median survival time.

Table V. *Recurrent sites in patients with liver metastasis.*

Site	Synchronous liver metastasis (n=8)	Metachronous liver metastasis (n=7)
Liver	1	3
Lung	2	1
Lymph node	3	1
Peritoneum	2	2

IL, USA). Patient characteristics were compared using the two-tailed Fisher exact test or the Chi-square test with the Yates correction. Survival curves were constructed using the Kaplan-Meier method and compared between subgroups according to univariate analysis in the resulting distributions using the log-rank test. Significant factors selected by univariate analysis were inserted into the Cox proportional hazard regression analysis. Probability (*p*) values were considered to be statistically significant below 0.05.

Results

Comparison of characteristics of 63 gastric cancer patients with liver metastasis. There was no significant difference between patients with and without hepatic resection (Table I). Figure 1 shows disease-specific survival time in all registered patients. Disease-specific survival in patients receiving hepatic resection is shown in Figure 2.

Univariate and multivariate analyses in all registered patients. Univariate analysis revealed that pathologic stage (pStage) I-III, curability of the primary gastric tumor of A or B, unilobar liver metastases, solitary liver metastases, hepatic resection, and systemic chemotherapy positively influenced prognosis (Table II).

Multivariate analysis using the Cox proportional hazard regression model of five clinicopathologic factors (pStage, curability of the primary gastric tumor, hepatic resection, distribution of liver metastases, number of liver metastases, systemic chemotherapy before gastrectomy, and systemic chemotherapy after gastrectomy) revealed that hepatic resection was the only variable which independently affected prognosis in all patients (Table III).

Liver metastases with hepatic resection. Univariate analysis revealed that distribution of liver metastases influenced prognosis in 16 patients who underwent hepatic resection (Table IV). Recurrences in the liver and the other sites after hepatic resection for liver metastasis were observed in 8 patients (50%). Of these, liver recurrence occurred in four patients (25.0%) (Table V).

Details of patients with hepatic resection. Four patients with solitary liver metastases survived for more than five years after hepatic resection. One patient had serosal invasion after the primary gastric tumor, while another had distant lymph node metastasis at the third tier. Three patients had

Table VI. *Details of patients who survived more than five years after hepatic resection*

				Primary tumor										
No.	Age (years)	Gender	Operation	Lymph node dissection[1]	Location[1]	Type[1]	Size (mm)	Histological differentiation[1]	Depth of tumor	Lymph node metastasis	Lymphatic invasion	Venous invasion	Curability[1]	Stage[1]
1	75	Male	TG	D2	UM	2	65	Moderately	T2(SS)	N1	+	+	B	II
2	68	Female	DG	D3	ML	2	30	Well	T2(MP)	N0	-	-	A	IB
3	68	Male	DG	D2	ML	5	55	Poorly	T3(SE)	N1	+	+	B	IV
4	67	Male	TG	D3	UE	3	120	Moderately	T2(SS)	N3	+	+	B	IV

	Liver metastases					Systemic chemotherapy						
No.	No. of liver metastases	Size (mm)	Timing of appearance	Type of hepatic resection	Curability of hepatic resection	Before gastrectomy	After gastrectomy	Before hepatic resection	After hepatic resection	Hepatic arterial infusion	Recurrence	Survival after hepatic resection (years)
1	1	45	Metachronous	Lateral segmentectomy	Curative	-	-	-	-	-	-	6.1
2	1	20	Metachronous	Lateral segmentectomy	Curative	-	-	-	+	-	-	6.4
3	1	25	Synchronous	Partial resection	Curative	-	-	-	-	-	-	5.8
4	1	120	Synchronous	Left hemihepatectomy	Curative	-	+	-	+	-	-	10.5

TG: Total gastrectomy; DG: distal gastrectomy; [1]: according to Japanese Classification of Gastric Cancer, 2nd English Edition (27).

Table VII. *Comparison of reports of hepatic resection for liver metastasis from gastric cancer.*

No.	Reference	Nation	Enrolment period	Rate of liver metastasis (%)	Resectability (%)	Sample size	Timing of liver metastasis		MST	Survival rate after hepatic resection (years)				Recurrence rate	
							Synchronous	Metachronous		1	2	3	5	Overall (%)	Liver (%)
1	Bines *et al*. (19)	U.S.A	1971-1989	-	-	10	7	3	15	60	30	30	30	-	-
2	Ochiai *et al*. (2)	Japan	1962-1991	4.3	7.4	21	13	9	-	-	-	-	-	-	-
3	Miyazaki *et al*. (20)	Japan	1980-1994	-	-	21	11	10	11	41.5	26	20.8	20.8	81	76.2
4	Roh *et al*. (21)	Korea	1988-1996	-	-	11	8	3	19	72.7	-	-	27.3	91	72.7
5	Imamura *et al*. (13)	Japan	1990-1997	-	-	17	7	10	-	47	22	22	0	-	-
6	Saiura *et al*. (3)	Japan	1981-1998	3.5	15.6	10	6	4	25	50	-	30	20	80	-
7	Ambiru *et al*. (22)	Japan	1975-1999	-	-	40	18	22	12	-	27	-	18	77.5	72.5
8	Fujii K*et al*. (23)	Japan	1979-1999	-	-	10	7	3	16.3	60	20	10	10	80	50
9	Zacherl *et al*. (4)	Austria	1980-1999	14	-	15	10	5	8.8	35.7	28.6	14.3	0	-	-
10	Okano *et al*. (5)	Japan	1986-1999	11.2	21.1	19	13	6	-	77	-	34	34	73.7	63.2
11	Shirabe *et al*. (24)	Japan	1979-2001	-	-	36	16	20	-	64	43	26	26	83.3	61.1
12	Sakamoto *et al*. (6)	Japan	1985-2001	4.8	9.6	22	12	10	21.4	72.7		38.3	38.3	68.2	59.1
13	Koga *et al*. (7)	Japan	1985-2005	4.5	17	42	20	22	34	76		48	42	66.7	50
14	Sakamoto *et al*. (8)	Japan	1990-2005	3.5	20.2	37	16	21	31	-	-	-	11	86.5	62.2
15	Cheon *et al*. (9)	Korea	1995-2005	9.9	4	41	30	11	17.9	75.3	38.4	31.7	20.8	63.6	50
16	This study	Japan	1992-2007	3.9	25.4	16	9	7	31.2	81.3	-	46.4	37.1	56.3	25

MST, Median survival time in months.

Table VII. *continued*

lymphovascular invasion of the primary gastric cancer. Two patients only had synchronous hepatic metastasis (Table VI).

Discussion

This study revealed that an independent prognostic factor in patients with liver metastases from gastric cancer was hepatic resection. A prognostic factor in patients undergoing hepatic resection was shown to be the distribution of liver metastases. Previous studies of patients undergoing hepatic resection for gastric cancer reported a median survival time of 8.8-34 months, a 1-year survival rate of 47-77% and a 5-year survival rate of 0-42% (3-9, 13, 19-24) (Table VII). Some previous studies also showed that recurrence after hepatic resection for liver metastasis from gastric cancer was 63.6-91% and that rates of recurrence in the remaining liver were 50-76% (3, 5-9, 20-24) (Table VII). Therefore, the clinical benefit of resection for liver metastasis from gastric cancer has not been widely accepted and remains controversial. Non-surgical treatments such as systemic or hepatic arterial infusion chemotherapy also failed to achieve satisfactory results (5, 19). Therefore, our evaluation of the potential role of hepatic resection is an important one.

In a previous study, the actuarial 1- and 3-year survival rates for patients with liver metastasis without peritoneal dissemination or other distant metastasis who did not undergo hepatic resection were 43% and 0%, respectively (5). Median survival time for these patients was six months after gastrectomy. The 1-, 3-, and 5-year survival rates in patients without hepatic resection were significantly lower

Table VII. *continued*

	Favorable prognostic factor by univariate analysis		Favorable prognostic factor by multivariate analysis	
No.	Primary gastric cancer	Liver metastasis	Primary gastric cancer	Liver metastasis
1				
2	Shallower than subserosa			
3		Solitary, resection margin longer than 10 mm		
4				
5				
6	Absence of lymph node metastases (p=0.067)			
7		Metachronous, resection margin longer than 10 mm		Metachronous, resection margin longer than 10 mm
8		Disease-free interval longer than 1 year, tumor size less than 5 cm, presence of lymphocyte aggregation		
9	Distal tumor (p=0.064)	Unilobar (p=0.052), metachronous (p=0.051),		
10		solitary, metachronous, well differentiated type, presence of pseudocapsule		
11	Lower grade of lymphatic invasion, lower grade of venous invasion, lower grade of lymph node meta	Tumor number less than 2	Low grade of lymphatic invasion, low grade of venous invasion	Tumor number less than 2
12		Solitary, unilobar		Solitary, tumor size less than 5 cm
13		Solitary	Absence of serosal invasion	Solitary
14	Absence of venous invasion, tumor diameter less than 4 cm	Unilobar	Tumor diameter less than 4 cm	Unilobar
15		Solitary		
16		Unilobar		

(29.4%, 0%, and 0%, respectively) than in patients with hepatic resection (75.3%, 31.7%, and 20.8%, respectively) (5, 9). Another study showed that of 12 patients who underwent gastrectomy combined with hepatic resection, four (33%) survived for more than 12 months, while all seven patients who did not undergo hepatic resection died within six months. There was a significant difference in survival between the two groups (p=<0.01) (26).

For these reasons, hepatic resection may be considered an option for gastric cancer patients with liver metastasis. However, these previous reports did not establish the prognostic factors of patients who lacked non-curative factors except liver metastasis. The present study revealed the favorable prognostic factors to be: pathologic stage I-III of the primary gastric tumor; curability A or B of the primary gastric tumor; unibolar liver metastasis; solitary liver metastasis; hepatic resection; and systemic chemotherapy after gastrectomy in patients without non-curative factors except liver metastasis according to univariate analyses. There was a trend toward a higher frequency of stage IV gastric cancer among the patients receiving systemic chemotherapy before gastrectomy (18 out of 22 *vs*. 23 out of 41, p=0.0542). Therefore, systemic chemotherapy before gastrectomy reduced the median survival time. Multivariate analysis revealed the only favorable prognostic factor to be hepatic resection in the present study.

The present study also showed that hepatic resection was recommended in patients with unilobar liver metastasis. It is reported that venous invasion (8, 24), lymphatic invasion (24), tumor diameter (8), lymph node metastasis (24), depth of tumor invasion (2), and histological type (5) of the primary gastric tumor are significant prognostic factors according to univariate analyses in patients undergoing hepatic resection for liver metastasis. Moreover, it is reported that number (5-7, 9, 20, 24), distribution (6, 8), timing (5, 22), surgical margin (20, 22), and tumor diameter (23) of liver metastases are significant prognostic factors according to univariate analyses in patients undergoing hepatic resection for liver metastasis. Similarly,

multivariate analyses have revealed depth of tumor invasion (4), tumor diameter (8), venous invasion (24), and lymphatic invasion (24) of the *primary* gastric cancer to be prognostic factors in patients undergoing hepatic resection for liver metastasis (Table VII). Furthermore, multivariate analyses have revealed number (6, 8, 24), distribution (8), tumor diameter (8), timing (22), and surgical margin (22) of *liver metastases* to be prognostic factors in patients undergoing hepatic resection for liver metastasis (Table VII). Several studies have found the presence of a solitary liver metastasis to be a favorable prognostic factor according to univariate and multivariate analyses (5-7, 9, 20). By contrast, the number of liver metastases was not a significant prognostic factor for survival after hepatic resection in this study, although patients with bilobar tumors had a worse outcome than patients with unilobar tumors. Therefore, it is possible to extend the indication of hepatic resection based on the distribution of liver metastases. However, the number of patients was small in this analysis, a further study is necessary to identify prognostic factors in patients receiving hepatic resection in a high-volume study.

Some authors have reported favorable outcomes in patients with metachronous liver metastasis according to univariate and multivariate analyses (2, 5, 22). In this study, the survival time tended to be longer in patients with metachronous liver metastasis than in patients with synchronous liver metastasis, but the differences were not significant. By contrast, two patients who survived more than five years after hepatic resection had synchronous liver metastasis. Thus, it is necessary to evaluate the therapeutic outcomes of patients receiving multidisciplinary therapy including hepatic resection in high-volume patients in order to clarify its feasibility.

Conclusion

Hepatic resection for unilobar liver metastases from gastric cancer may be beneficial in patients without extrahepatic non-curative factors. However, the number of patients in this retrospective study is small; a randomized study comparing therapeutic outcomes between patients receiving hepatic resection and chemotherapy alone should be conducted.

Conflicts of Interest

The Authors declare that they have no competing interests.

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