Significance of Surgical Treatment of Liver Metastases from Gastric Cancer

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Abstract. *Background/Aim: The optimal treatment of liver metastases from gastric cancer (LMGC) remains uncertain. We retrospectively compared surgical treatment with chemotherapy alone and identified prognostic determinants. Patients and Methods: We reviewed the records of 50 consecutive patients with LMGC: 25 patients with gastrectomy plus hepatic resection (group A), 13 patients with palliative gastrectomy (group B), and 12 patients with chemotherapy alone (group C). We compared the overall survival among these three groups, and assessed prognostic factors. Results: Median survival time in groups A, B, and C was 33.4, 10.5, and 8.7 months, respectively. Univariate analysis found T stage, number of liver metastases, and treatment group to be significant prognostic factors. In the multivariate analysis, T stage was shown to be an independent prognostic determinant, while gastrectomy plus hepatic resection was of marginal significance compared with chemotherapy alone. Conclusion: T Stage was a significant prognostic determinant, and gastrectomy plus hepatic resection could be a promising treatment for patients with LMGC.*

Liver metastases from gastric cancer (LMGC) occur in approximately 3.5 to 14% of patients with primary gastric cancer (1-16). Chemotherapy is the most common treatment option for LMGC, since surgical treatment is rarely indicated due to the presence of numerous liver metastases and/or extrahepatic disease, such as peritoneal dissemination and extensive lymph node metastasis. Although chemotherapy for metastatic gastric cancer has recently evolved, the prognosis of patients with LMGC is still disappointing, with a median survival time (MST) of approximately 12 months and a 3-year survival rate of around 5% (17) when treated with chemotherapy alone.

Although palliative gastrectomy was reported to be prognostically beneficial for selected patients with a single non-curative factor including LMGC (18), the efficacy of palliative gastrectomy in patients with liver-only metastases remains uncertain. However, this might be clarified by the results of an ongoing prospective randomized controlled trial investigating the role of palliative gastrectomy for patients with advanced gastric cancer (AGC) with a single non-curative factor (19).

On the other hand, complete resection of the primary gastric tumor and LMGC has resulted in MST of approximately 23 months and a 5-year survival rate of 11-42% (1-16). Hepatic resection provides a potential opportunity for cure, although the complete resection rate for LMGC has been reported to be approximately 20% due to frequently associated peritoneal dissemination or advanced lymph node metastasis.

No standard treatment has yet been established for patients with LMGC, partly because there has only been one report (1) concurrently comparing the three treatment options, and partly because of the variability in patients' background non-curative factors in the literature (1–16). Therefore, in this study, we retrospectively compared these three treatment options and identified prognostic determinants through univariate and multivariate analyses for patients with LMGC as the sole non-curative factor that is considered crucial for better survival (18, 19).

Patients and Methods

Patient inclusion criteria. We retrospectively reviewed the records of 50 consecutive patients with LMGC treated at Osaka National Hospital between January 1, 1995 and December 31, 2009. In this study, patients diagnosed with synchronous or metachronous liver metastasis as a single non-curative factor were included. Those who met any of the following criteria were excluded: (i) any other non-curative factor except for liver metastasis, such as T4 tumor (tumor infiltrating to adjacent organs), para-aortic lymph node metastasis,

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

Table I. *Patient characteristics*.

	Group A (n=25)	Group B (n=13)	Group C (n=12)	*P*-value
Male/female	23/2	11/2	11/1	0.77
Age (years), median (range)	72 (47-80)	70 (49-78)	67 (54-80)	0.71
Primary tumor				
Intestinal/diffuse	17/8	9/4	7/5	0.81
T Stage: 1/2/3	1/7/17	0/0/13	0/2/10	0.08
N Stage: 0/1/2	7/7/11	2/6/5	4/5/3	0.62
Liver metastasis				
Synchrounous/metachronous	16/9	13/0	12/0	<0.01
Unilobar/bilobar	20/5	4/9	1/11	<0.01
Solitary/multiple	18/7	1/12	1/11	<0.01
Diameter (mm), median (range)	20 (5-98)	20 (10-57)	40 (20-100)	0.02

peritoneal dissemination, positive abdominal lavage cytology, or distant metastasis; (ii) *linitis plastica*; (iii) other concurrently active malignancy; (iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or more at initial diagnosis; and (v) any prior chemotherapy or radiation therapy.

Data collection. Data collected retrospectively include patient characteristics, such as age and gender, pathological characteristic of the primary gastric cancer, clinicopathological characteristics of metastasis, and treatment modality used. The histology of the primary gastric cancer was based on the Lauren classification. T and N stage were classified according to the Japanese Classification of Gastric Carcinoma (20). Clinicopathological characteristics of liver metastasis included timing of emergence, intrahepatic distribution, number of nodules, and maximum diameter of each nodule.

Survival analysis. The therapeutic course of each patient was censored at death or on February 11, 2010. Twelve patients in the gastrectomy plus hepatic resection (group A, n=25), two patients in the palliative gastrectomy (group B, n=13), and three patients in chemotherapy alone (group C, n=12) were alive on February 11, 2010, and treated as censored cases for survival analyses. Overall survival (OS) was defined as the time from the date of diagnosis of liver metastasis to the date of death from any cause or the last follow-up, and was compared among the three treatment options. Univariate analysis was used to assess the association between each clinicopathological factor and OS. A multivariate analysis was performed to identify variables independently associated with OS.

Statistical analysis. With regard to the associations between treatment options and clinicopathological characteristics, the chi-square test was used for categorical variables, and Student's *t*-test or the Wilcoxon test was used for continuous variables as appropriate. OS curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox's regression analyses were performed to identify prognostic factors for survival by adjusting potential confounding factors. Variables achieving a *p*-value less than 0.05 in the univariate analysis were subsequently introduced into the multivariate analysis. All statistical analyses were performed with JMP software, version 8.0 (SAS Institute, Cary, NC, USA). *P*-values less than 0.05 were considered statistically significant, and all tests were two-sided.

Results

Patient characteristics. The clinicopathological characteristics of the 50 patients are presented in Table I. There were 45 males and 5 females with a median age of 70 (range 47-80) years. These 50 patients were categorized into three groups according to the treatment modality performed. Twenty-five patients in group A underwent complete resection of both the primary gastric cancer and liver metastasis with D2 lymphadenectomy, and 13 patients in group B received D1 gastrectomy with liver metastasis untouched, while 12 patients in group C underwent chemotherapy alone without any surgical intervention. Histologically, approximately two-thirds of the patients had intestinal-type adenocarcinoma and one-third had diffuse-type adenocarcinoma. Most patients had an advanced primary cancer of T3 or deeper, with positive lymph node metastases. There were clear imbalances among the groups with respect to clinicopathological features of liver metastasis. Metachronous metastasis was observed only in group A. The median disease-free interval from primary surgery to the detection of metachronous liver metastasis was 645 (range 240-1682) days. Both unilobar metastasis and solitary metastasis were also more frequent in group A than in groups B and C ($p<0.01$). The maximum tumor diameter was significantly higher in group C than in groups A and B ($p=0.02$). In group A, 10 out of 25 patients received adjuvant chemotherapy, however, this treatment had no impact on OS (data not shown). After hepatectomy, relapse of disease was found in 18 patients, with a median recurrence-free interval of 154 days, involving the remnant liver in 15 patients, lymph nodes in 2 patients, and pleura in 1 patient.

Prognostic factors. The MST ranged from 33.4 months in group A to 8.7 months in group C. The 1-, 3-, and 5-year survival rates were 73.9%, 42.8%, and 36.7% in group A; 46.2%, 23.1%, and 15.4% in group B; and 36.7%, 12.2%, and 0% in group C, respectively. OS in group A was

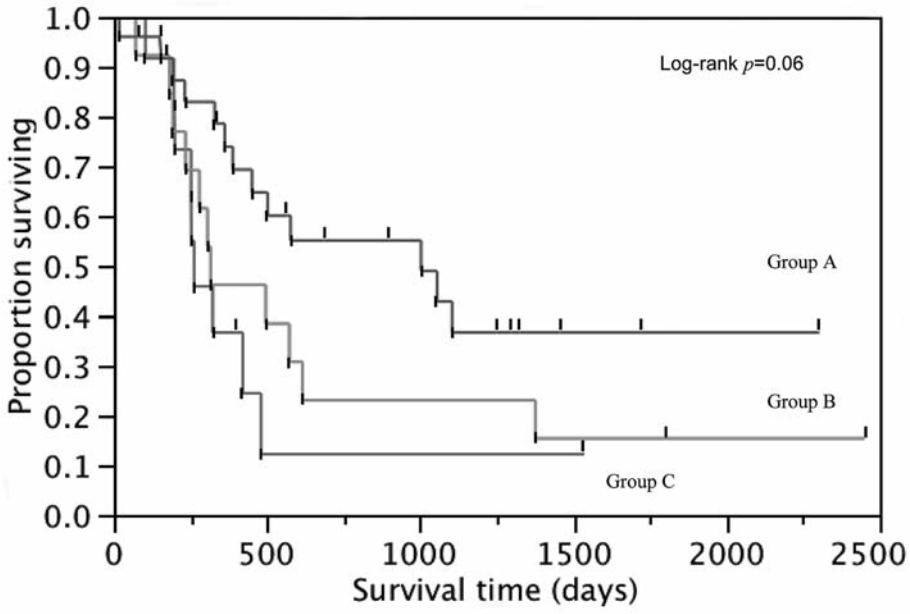

Figure 1. *Overall survival by treatment modality.*

significantly longer than in group C (p=0.04), whereas there was no significant difference in OS between groups A and B (p=0.12), nor B and C (p=0.50), as shown in Figure 1. Hazard ratios (HRs) for death, compared with group A, were 1.93 (95% confidence interval (CI): 0.84-4.33) in group B, and 2.65 (95% CI: 1.07-6.29) in group C. Univariate analysis revealed that T stage, number of liver metastases, and treatment group (group A *versus* group C) were significant prognostic factors, as shown in Table II. T Stage of the primary gastric cancer was the only independent prognostic determinant after adjustment for other factors in the multivariate analysis (HR=13.9; 95% CI=2.8-251.7), as shown in Table III. Treatment modality was not a significant prognostic factor, although gastrectomy plus hepatic resection was of a marginal significance (HR=2.8; 95% CI=0.93-9.26) when compared with chemotherapy alone (group A *versus* group C).

Discussion

The incidence of LMGC has been reported to be approximately 3.5-14% (1-16). Systemic chemotherapy is the most common treatment for LMGC, but it fails to achieve satisfactory outcomes (17, 21). Although the efficacy of surgical treatment for LMGC remains uncertain, palliative gastrectomy might be prognostically beneficial for patients with liver-only metastasis (18, 22). Furthermore, complete resection of both the primary gastric tumor and the LMGC results in MST of approximately 23 months, and a 5-year survival rate of approximately 25% (1-16), although surgical resection of hepatic nodules is rarely indicated due to the presence of extrahepatic non-curative factors, such as peritoneal dissemination and extensive lymph node metastasis. However, these three treatment options have rarely been compared in patients with LMGC as a single non-curative factor.

As summarized in Table IV, there are only retrospective studies in the literature on the efficacy of hepatic resection for LMGC (1-16). In those reports, the number of patients receiving hepatic resection was limited, ranging from 10 to 40, consistent with the rare situation when complete resection of LMGC is indicated. In this study, 25 patients underwent hepatic resection, and our study ranks sixth in terms of sample size as shown in Table IV. Most of the previous studies evaluated the efficacy of hepatic resection alone, while different treatment options were simultaneously compared with hepatic resection in only three studies (1, 15, 16). Okuyama *et al*. (1) compared three different treatment options, hepatic resection plus curative gastrectomy *versus* palliative gastrectomy *versus* chemotherapy alone, as we have done here. However, in contrast to our study, they included patients with non-curative factors other than liver metastasis, which could affect the outcomes of hepatic resection. The remaining two studies (15, 16) compared hepatic resection with palliative gastrectomy. To the best of our knowledge, ours is the first study in which three different treatment options were compared in a head-to-head manner for patients with liver-only metastasis from gastric cancer.

Table II. *Univariate analysis of prognostic factors for overall survival.*

	No. of patients	MST (months)	Survival rate			HR (95% CI)	*P*-value
			1-Year	3-Year	5-Year		
Gender							0.74
Male	45	15.0	56.8	30.7	23.7	1	
Female	5	19.1	66.7	33.3	NA	0.79 (0.13-2.62)	
Age, years							0.83
<70	25	16.0	58.4	30.3	19.0	1	
>70	25	14.0	57.1	31.7	31.7	1.04 (0.50-2.39)	
Histological type							0.92
Intestinal	33	16.5	62.5	28.1	NA	1	
Diffuse	17	12.0	47.8	39.8	39.8	1.04 (0.50-2.39)	
T Stage							<0.01
1, 2	10	NA	100.0	83.3	83.3	1	
3, 4	40	12.0	47.6	20.6	13.2	12.7 (2.73-226.42)	
N Stage							0.34
0, 1	31	16.0	56.8	36.4	30.3	1	
2, 3	19	14.0	59.4	20.8	NA	1.41 (0.69-2.81)	
Timing							0.15
Synchrounous	9	35.1	100	42.9	28.6	1	
Metachronous	41	12.0	48.9	29.5	23.6	1.92 (0.80-5.68)	
Distribution							0.05
Unilobar	25	35.1	72.6	39.3	26.2	1	
Bilobar	25	10.2	44.0	22.0	17.6	2.00 (1.00-4.14)	
Number							0.03
Solitary	20	36.8	70.8	50.1	41.7	1	
Multiple	30	10.8	50.0	19.2	15.4	2.27 (1.09-5.19)	
Size							0.35
<50	38	16.7	59.5	35.6	25.6	1	
>50	12	12.9	50.5	13.4	NA	1.49 (0.62-3.19)	
Treatment group							
A	25	33.4	73.9	42.8	36.7	1	
B	13	10.5	46.2	23.1	15.4	1.93 (0.84-4.33)	0.12
C	12	8.7	36.7	12.2	NA	2.65 (1.07-6.29)	0.04

MST: Median survival time; HR: hazard ratio; CI: confidence interval.

Previous studies demonstrated an MST of 8.8–34 months and a 5-year survival rate of 0-42% after hepatic resection, as shown in Table IV. In the present study, a relatively favorable MST of 33.4 months and a 5-year survival rate of 36.7% were obtained after hepatic resection. The wide difference in OS among studies is partly due to patient selection bias with small sample sizes, although most of the studies adopted liver-only metastasis as a common indication for hepatic resection.

To date, various prognostic factors have been proposed. As shown in Table IV, the number of liver metastases was found to be a significant prognostic factor in five reports, timing of liver metastasis (synchronous or metachronous), lymphatic and venous invasion and T stage of primary gastric cancer in two reports; and intrahepatic distribution of liver metastases, size of hepatic nodules, tumor differentiation, and negative surgical margins in the liver specimen, each in one report with univariate or multivariate analyses. In accordance with these findings, the number of liver metastases and T stage of the primary gastric tumor were significant prognostic factors found in the univariate analysis of this study. In addition, when incorporating treatment modality into the multivariate analysis, hepatic resection was shown to be independently associated with

Table III. *Multivariate analysis of prognostic factors for overall survival.*

Variable	HR	95% CI	*P*-value
T Stage (3, 4 vs. 1, 2)	13.90	2.82-251.70	<0.01
Multiple vs. solitary	1.09	0.37-3.09	0.88
Treatment, B vs. A	1.18	0.43-3.44	0.75
Treatment, C *vs.* A	2.83	0.93-9.26	0.07

HR: Hazard ratio, CI: confidence interval.

Table IV. *Summary of survival outcomes and prognostic indicators for patients undergoing hepatic resection for liver metastasis from gastric cancer.*

First author (ref)	Year	No. of pts. with liver metastasis	No. of pts who underwent hepatic resection	Median survival time (months)	Survival after resection			Prognostic factors	
					1-Year	3-Year	5-Year	Univariate	Multivariate
Okuyama *et al*. (1)	1985	9	9	24	NA	NA	NA		NA
Ochiai *et al*. (2)	1994	21	21	19	NA	NA	NA	T stage, ly, v	NA
Miyazaki *et al*. (3)	1997	21	21	NA	NA	NA	NA	Number, surgical margin	NA
Elias *et al*. (4)	1998	11	11	NA	90	35	NA	NA	NA
Ambiru *et al*. (5)	2001	40	40	12	NA	NA	18	Timing, surgical margin	Timing
Imamura *et al*. (6)	2001	17	17	NA	47	22	0	NA	NA
Saiura *et al*. (7)	2002	10	10	25	50	30	20	NA	NA
Okano *et al*. (8)	2002	90	19	21	77	34	34	Number, differentiation, timing, fibrous pseudocapsule	NA
Zackerl *et al*. (9)	2002	NA	15	8.8	35.7	14.3	0	None	NA
Sakamoto *et al*. (10)	2002	228	22	21	73	38	38	Number, distribution	Number
Shirabe *et al*. (11)	2003	NA	36	NA	64	26	26	ly, v, N stage, number	Ly, v, number
Roh *et al*. (12)	2005	NA	11	19	72.7	NA	27.3	NA	
Sakamoto *et al*. (13)	2007	182	37	31	NA	NA	11	Distribution, v, tumor size	Distribution, tumor size
Koga *et al*. (14)	2007	247	42	34	76	48	42	Number	Number, serosal invasion
Cheon *et al*. (15)	2008	1013	41	17.9	75.3	31.7	20.8	NA	None
Makino *et al*. (16)	2010	63	16	16.0	82.3	46.4	37.1	Stage, distribution, number, hepatic resection, chemotherapy,	Hepatic resection

ly, Lymphatic invasion; v, venous invasion; number, number of liver metastasis; distribution, hepatic distribution; timing, timing of metastasis (synchronous or metachronous); NA, not applicable; pts, patients.

longer survival by Makino *et al*. (16), which is consistent with our findings that gastrectomy plus hepatic resection was of marginal significance as a prognostic factor. T3/4 primary gastric cancer was chosen as an independent prognostic factor in the current study. Although T3/4 disease portends a potential risk for peritoneal seeding, the most frequent cause of death of our patients with T3/4 stage disease was liver metastasis, even after complete resection of the hepatic nodules. It is uncertain to what degree peritoneal seeding affected OS of our patients since accurate diagnosis of peritoneal dissemination was not possible in every case.

As for treatment options, the current study demonstrates the possibility that complete resection of both the primary gastric tumor and liver metastasis might contribute to a better prognosis than chemotherapy alone; however, this finding was of marginal statistical significance in the multivariate analysis. In contrast, there was no prognostic difference between gastrectomy plus hepatic resection and palliative gastrectomy. At present, a prospective randomized controlled trial is underway in Korea and Japan (19) comparing palliative gastrectomy with chemotherapy alone for patients with AGC including those with liver-only metastasis. The treatment option with better outcomes from this trial should be prospectively compared with gastrectomy plus hepatic resection for patients with liver-only metastasis in order to clarify which treatment strategy is optimal.

In conclusion, we believe that this is the first report comparing three different treatment options (gastrectomy plus hepatic resection *versus* palliative gastrectomy *versus* chemotherapy alone) for patients with LMGC as a single non-curative factor. T Stage of the primary gastric tumor was shown to be an independent prognostic factor for patients with LMGC. Limitations of this study, such as its retrospective nature correlating with selection bias between the treatment groups and small sample size, should be taken into account. Although gastrectomy plus hepatic resection might be a promising treatment option, with longer survival for patients with LMGC, further study is needed in a prospective, multi-institutional fashion to establish its role and clarify what constitutes optimal indications for hepatic resection in patients with LMGC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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