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A Study of Gastric Cancer Cases with Liver Metastasis

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Abstract

The prognosis of gastric cancer patients with liver metastasis is very poor because many cases of gastric cancer with liver metastasis have multiple metastatic nodules in the liver and other non-curative factors, such as severe lymph node metastasis and/or peritoneal metastasis. The prognosis for gastric cancer patients with synchronous liver metastasis and the significance of hepatectomy including metachronous liver metastasis from gastric cancer in Kurume University Hospital are reported.

Methods: A total of 77 gastric cancer patients with synchronous liver metastasis were admitted between 1995 and 2010 to Kurume University Hospital. There were 17 hepatectomy cases (synchronous metastasis 12 cases, metachronous metastasis 5 cases) from 1984 to 2010.

Results: With respect to prognostic factors for gastric cancer cases with liver metastasis, significant differences were observed for peritoneal metastasis, histology, lymph node metastasis, gastrectomy, systemic chemotherapy, the number of stage IV factors, the number of metastatic nodules (within 3), and intra-hepatic arterial infusion (HAI). Multivariate analysis showed that histology, chemotherapy, and HAI were independent prognostic factors. The number of metastatic nodules in all 17 hepatectomy cases was within 3. Three of five cases with hepatectomy for metachronous metastasis were alive more than 5 years after hepatectomy. On the prognosis of hepatectomy cases, there were significant differences for synchronous or metachronous metastasis, lymph node metastasis, the number of stage IV factors, and the stromal volume of the primary site.

Conclusions: Multimodal treatment including HAI is considered effective for gastric cancer cases with liver metastasis. If patients have no stage IV factors except for H factor, and the number of metastatic nodules is within 3, hepatectomy is recommended, especially for patients with metachronous liver metastasis, medullary stromal volume type, and low-grade lymph node metastasis.

Keywords: Gastric cancer; Hepatectomy; Intrahepatic arterial infusion (HAI); Liver metastasis

Introduction

Gastric cancer is the fourth most common cancer worldwide and accounts for 1.5% of all diagnoses made by physicians and 5.2% of all cancer deaths [1,2]. At the time of diagnosis, 35% of patients have evidence of distant metastases, and 4% to 14% have metastatic disease to the liver [3,4]. The prognosis of gastric cancer patients with liver metastasis is very poor. The six-month survival rate of such cases has been only 20-50% [5]. Because the biological malignant potential and proliferative activity of gastric cancer are higher than of colorectal cancer, many gastric cancer patients with liver metastasis have multiple metastatic tumors in the liver, and surgical resection is rarely indicated. Moreover, the non-curative factors of many cases are not only liver metastasis but also lymph node metastasis and peritoneal dissemination. Therefore, the number of reports about liver metastasis from gastric cancer has been few. So far, various systemic chemotherapies or intra-hepatic arterial infusion (HAI) has been performed, but prolonged survival has generally not been achieved. However, new anticancer drugs (S-1, CPT-11, and taxanes) have recently been widely used for advanced gastric cancer in many institutes in Japan, and some gastric cancer patients with liver metastasis are effectively treated by chemotherapy and remain alive for a long time after the therapy. In this study, a retrospective clinicopathologic evaluation of gastric cancer cases with synchronous liver metastasis and hepatectomy cases including metachronous liver metastasis was performed.

Materials and Methods

Patients

Between 1995 and 2010, 319 patients with stage IV gastric cancer according to the 14th Edition Japanese Classification of Gastric Carcinoma were treated at Kurume University Hospital. Among these cases, there were 77 with synchronous liver metastasis. The mean age was 68.6 years (range: 50-91 years) and the male:female ratio was 66:11.

The number of patients with no stage IV factors except H factor was 44; their mean age was 69.2 years (range: 51-91 years), with a male:female ratio of 40:4.

There were 17 cases that underwent hepatectomy for liver metastasis, including 5 cases with metachronous liver metastasis, from 1984 to 2010. Their mean age was 64.0 years (range: 43-79 years), with a male:female ratio of 11:6.

For this study, clinicopathological examinations were undertaken according to the 14th Japanese Classification of Gastric Carcinoma [6].

Clinical variables

A total of 29 clinicopathological variables, consisting of sex (male or female), age (≥ 60 or <60 years), macroscopic type (type 0, (1, 2), (3, 4) or 5), site (L, M, or U), tumor size (≥ 100 or <100 mm), number of sites (1, 2, or ≥ 3), peritoneal metastasis (P0 or P1), lymph node metastasis (N0, N1,2, or N3), distant lymph node metastasis (M0 (LYM) or M1 (LYM)), distant organ metastasis (M0 or M1), depth of invasion (*T1,2,3), T4a, or T4b), histology (differentiated type or undifferentiated type), stromal pattern (medullary type (med), intermediate type (int), or scirrhous type (sci)), tumor infiltration pattern (INFa, INFb, or INFc), lymphatic invasion (ly0, ly1,2, or ly3), venous invasion (v0,1, or v2,3), gastrectomy

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(- or +), the number of stage IV factors (1, ≥ 2), lymph node dissection (D0,1, or ≥ D2), residual tumor (R0, R1, or R2), new anticancer drugs such as S-1, irinotecan, and taxanes (-or +), the number of metastatic nodules (solitary or multiple), the number of metastatic nodules (≤ 3 or ≥ 4), hepatectomy (- or +), hepatic arterial infusion (HAI), and systemic chemotherapy (- or +), were investigated. Moreover, in hepatectomy cases, two clinical variables, such as partial resection or anatomic hepatic resection (segmentectomy or lobectomy) and synchronous or metachronous metastasis, were added.

Statistical analysis

Associations between clinical variables of patients with only H factor and patients with multiple stage IV factors were compared by univariate analysis using the χ^2 test. The disease-specific survival rate was calculated with the Kaplan-Meier method. The significance of any difference between the survival curves was determined using the log-rank test. The Cox proportional hazards model was used in the multivariate analysis of the factors determined to be significant for disease-specific survival on univariate analysis. The statistical analyses were performed using statistical analysis software (SPSS II; IBM Co., Armonk, NY, USA). For all analyses, significance was defined as P <0.05.

Results

The number of stage IV factors

The number of patients who had no Stage IV factors except H1 was 44 (57.1%), and the number of patients with multiple Stage IV factors was 33 (42.9%). The most frequent stage IV factor other than H1 was P1 (n=11), the second was M1 (LYM) (distant lymph node metastasis) (n=9), the third was synchronous P1 and M 1(LYM) factors (n=5), and the fourth was M1 (distant organ metastasis) (n=4). The number of synchronous M1 (LYM) and M1 was 2. The number of synchronous P 1 and M1 factors, and CY 1 was 1 each.

Seven clinicopathological factors (INF, ly, N factor, gastrectomy, grade of lymph node dissection, the number of metastatic nodules in the liver (within 3 or not), and HAI) were significantly different between the patients with only H factor and the patients with multiple Stage IV factors (Table 1).

Factor	No.	Only H (n=44) (n=65)	Multiple (n=33) (n=239)	*P* value
Sex				0.143
Male	66	40 (90.9%)	26 (78.9%)	
Female	11	4 (9.1%)	7 (21.2%)	
Age /years old				0.350
≧60	63	38 (86.4%)	25 (78.1%)	
< 60	13	6 (13.6%)	7 (21.8%)	
Macroscopic type				0.066
Type 0	1	1 (2.3%)	0	
1, 2	31	22 (50.0%)	9 (29.0%)	
3, 4	37	18 (40.9%)	19 (61.3%)	
5	6	3 (6.8%)	3 (9.7%)	
Site				0.863
L (lower)	32	19 (43.2%)	13 (40.6%)	
M (middle)	20	10 (22.7%)	10 (31.3%)	
U (upper)	24	15 (34.1%)	9 (28.1%)	
The number of sites				0.357
1	23	14 (31.8%)	9 (28.1%)	
2	28	18 (40.9%)	10 (31.3%)	
≥3	25	12 (27.3%)	13 (40.6%)	
Depth				0.692
T1, T2, T3	4	4 (10.0%)	0	
T4a	51	27 (67.5%)	24 (82.8%)	
T4b	14	9 (22.5%)	5 (17.2%)	
Histology				0.239
differentiated	33	24 (66.7%)	9 (50.0%)	
undifferentiated	21	12 (33.3%)	9 (50.0%)	
Stromal pattern				0.111
medullary	31	23 (63.9%)	8 (44.4%)	
intermediate	22	13 (36.1%)	9 (50.0%)	
scirrhous	1	0	1 (5.6%)	
INF				0.006*
a	20	17 (47.2%)	3 (16.7%)	
b	26	17 (47.2%)	9 (50.0%)	
c	8	2 (5.6%)	6 (33.3%)	
ly				0.015*
0	1	1 (2.8%)	0	
1,2	19	17 (47.2%)	2 (11.8%)	
3	33	18 (50.0%)	15 (88.2%)	
v				0.153
0,1	13	11 (30.6%)	2 (11.8%)	
2,3	40	25 (69.4%)	15 (88.2%)	
Lymph node metastasis				0.011*
0	6	6 (17.1%)	0	
1,2	15	14 (40.0%)	1 (6.3%)	
3	30	15 (42.9%)	15 (93.8%)	
Gastrectomy				0.012*
(-)	23	8 (18.2%)	15 (45.5%)	
(+)	54	36 (81.8%)	18 (54.5%)	
Chemotherapy				0.144
(-)	29	13 (31.7%)	16 (48.5%)	
(+)	45	28 (68.3%)	17 (51.5%)	
New anti-cancer drug				0.900
(-)	18	11 (39.3%)	7 (41.2%)	
(+)	27	17 (60.7%)	10 (58.8%)	
Lymph node dissection				0.016*
D0,D1	32	17 (47.2%)	15 (83.3%)	
≥ D2	22	19 (52.8%)	3 (16.7%)	
Tumor size				0.146
< 100mm	39	28 (80.0%)	11 (61.1%)	
≥ 100mm	14	7 (20.0%)	7 (38.9%)	
Residual tumor				0.800
R0	2	2 (5.6%)	0	
R2	52	34 (94.4%)	18 (100%)	
The number of metastatic nodule				0.268
solitary	11	8 (18.2%)	3 (9.1%)	
multiple	66	36 (81.8%)	30 (90.9%)	
The number of metastatic nodule				0.007*
≤ 3	25	20 (45.5%)	5 (15.2%)	
≥ 4	52	24 (54.5%)	28 (84.8%)	
Hepatectomy				0.744
(-)	71	38 (86.4%)	33 (100%)	
(+)	6	6 (13.6%)	0	
HAI				0.025*
(-)	60	30 (68.2%)	30 (90.9%)	
(+)	17	14 (31.8%)	3 (9.1%)	
Systemic chemotherapy				0.304
(-)	31	15 (36.6%)	16 (48.5%)	
(+)	43	26 (63.4%)	17 (51.5%)	

*P<0.05 indicates statistical significance.

Table 1: Correlations between H factor only and multiple stage IV factors

The therapy of synchronous liver metastasis from gastric cancer

The numbers of gastrectomy only, gastrectomy plus postoperative systemic chemotherapy, and preoperative chemotherapy cases were 17, 12, and 5 cases, respectively. HAI was given to 14 cases, systemic chemotherapy only was given to 8 cases, hepatectomy was performed in 3 cases, hepatectomy plus HAI was performed for 3 cases, and best supportive care (BSC) was given to 12 cases. Chemotherapy status was unknown in 3 cases (1 case underwent gastrectomy, 2 cases did not undergo gastrectomy). All 6 hepatectomy cases underwent gastrectomy and systemic chemotherapy. Of the 17 HAI cases including 3 hepatectomy cases, 15 cases underwent systemic chemotherapy, but 2 cases did not undergo systemic chemotherapy.

Prognosis

With respect to the prognostic factors for gastric cancer cases with liver metastasis, there were significant differences for peritoneal metastasis, histology, lymph node metastasis, gastrectomy, the number of stage IV factors, the number of metastatic nodules in the liver (within 3 or not), HAI, and systemic chemotherapy ($P = 0.0001$, $P = 0.0234$. $P = 0.0086$, $P = 0.0104$, $P = 0.0026$, $P = 0.0368$, $P = 0.0012$, and $P < 0.0001$, respectively). Multivariate analysis showed that histology [HR 2.873 (95%CI 1.342 – 6.151 P= 0.007)], HAI [HR 0.226 (95%CI 0.104 – 0.494 $P < 0.001$)], and systemic chemotherapy [HR 0.233 (95%CI 0.099-0.546 $P = 0.001$)] were independent prognostic factors (Table 2).

With respect to the prognostic factors for gastric patients with only H factor, significant differences were apparent in histology, HAI, and systemic chemotherapy ($P = 0.0260$, $P = 0.0034$, and $P = 0.0001$ respectively). Multivariate analysis showed that histology [HR 3.602 (95%CI 1.072 – 12.106 P= 0.038)], HAI [HR 0.255 (95%CI 0.112 – 0.580 $P = 0.001$)], and systemic chemotherapy [HR 0.239 (95%CI 0.093-0.612 $P = 0.003$)] were independent prognostic factors (Table 3).

On histology, the survival curve of the differentiated type cases was significantly higher than that of the undifferentiated type cases. For HAI, the survival curve of cases who underwent HAI was significantly higher than that of cases who did not undergo HAI. For systemic chemotherapy, the survival curve of cases that underwent systemic chemotherapy was significantly higher than that of cases that did not undergo systemic chemotherapy.

Cases that underwent hepatic arterial infusion (HAI)

Seventeen cases underwent HAI. Of these cases, three underwent

	Univariate analysis (log-rank test)			Multivariate analysis (Cox proportional hazards model)		
Variables	Statistic	df	*P*	Hazard ratio	95%CI	*P*
Sex	2.37	1	0.1236			
Age	0.56	1	0.4534			
Macro type	2.05	3	0.5627			
Site	3.24	2	0.1977			
The number of site	0.51	2	0.7743			
P	15.87	1	0.0001*	0.826	0.192-3.556	0.797
Depth	3.57	2	0.1676			
Histology	5.14	1	0.0234*	2.873	1.342-6.151	0.007*
Stroma	2.74	2	0.2542			
INF	0.39	2	0.8209			
ly	5.12	2	0.0773			
v	0.11	1	0.7444			
LN metastasis	9.50	2	0.0086*	1.340	0.728-2.465	0.347
M1	0.00	1	0.9725			
Gastrectomy	6.56	1	0.0104*	-	-	-
St. IV factor	9.09	1	0.0026*	2.412	0.831-7.004	0.105
New drugs	0.27	1	0.6011			
LN dissection	1.08	1	0.2991			
Tumor size	0.03	1	0.8578			
R	0.12	1	0.7309			
M1(LYM)	0.99	1	0.3196			
Liver meta (1)	0.12	1	0.7280			
Liver meta (2)	4.36	1	0.0368*	1.520	0.707-3.267	0.284
Hepatectomy	3.25	1	0.0716			
HAI	10.46	1	0.0012*	0.226	0.104-0.494	< 0.001*
Systemic chem.	30.79	1	< 0.0001*	0.233	0.099-0.546	0.001*

df degree of freedom, *CI* confidential interval, *P* peritoneal metastasis, *INF* tumor infiltrative pattern, *ly* lymphatic invasion, *v* venous invasion, *M1* distant organ metastasis, *LN* lymph node, *R* residual tumor, *M1(LYM)* distant lymph node metastasis, *Liver meta (1)* the number of metastatic nodule (solitary or multiple), *Liver meta (2)* the number of metastatic nodule (≤ 3 or 4 ≤), *HAI* hepatic arterial infusion, *chem.* Chemotherapy *$P<0.05$ indicates statistical significance

Table 2: Disease-specific survival in all cases with liver metastasis.

	Univariate analysis (log-rank test)			Multivariate analysis (Cox proportional hazards model)		
Variables	Statistic	df	*P*	Hazard ratio	95%CI	*P*
Sex	0.06	1	0.8004			
Age	0.20	1	0.6531			
Macro type	2.16	3	0.5404			
Site	1.65	2	0.4384			
The number of site	1.14	2	0.5641			
Depth	3.24	2	0.1978			
Histology	4.96	1	0.0260*	3.602	1.072-12.106	0.038*
Stroma	1.20	1	0.2730			
INF	0.66	2	0.7180			
ly	2.52	2	0.2836			
v	0.23	1	0.6370			
LN metastasis	4.74	2	0.0933			
Gastrectomy	2.18	1	0.1396			
New drugs	0.58	1	0.4464			
LN dissection	0.41	1	0.5202			
Tumor size	0.86	1	0.3534			
R	0.00	1	0.9537			
Liver meta (1)	0.02	1	0.8862			
Liver meta (2)	0.94	1	0.3328			
Hepatectomy	1.94	1	0.1642			
HAI	8.57	1	0.0034*	0.255	0.112-0.580	0.001*
Systemic chem.	14.82	1	0.0001*	0.239	0.093-0.612	0.003*

df degree of freedom, *CI* confidential interval, *INF* tumor infiltrative pattern, *ly* lymphatic invasion, *v* venous invasion, *LN* lymph node, *R* residual tumor , *Liver meta (1)* the number of metastatic nodule (solitary or multiple), *Liver meta (2)* the number of metastatic nodule (≤ 3 or 4 ≤), *HAI* hepatic arterial infusion, *chem* chemotherapy **P*<0.05 indicates statistical significance

Table 3: Disease-specific survival in cases with only liver metastasis.

hepatectomy. The mean age was 65.6 years (range: 54-77 years). The male:female ratio was 16:1. For the macroscopic type of primary site, there were 2 type 1 cases, 6 type 2 cases, 8 type 3 cases, and 1 type 5 case. There were no type 4 cases. For the T factor, there were 1 T3 case, 13 T4a cases, and 3 T4b cases. For the N factor, there were 2 N0 cases, 2 N1 cases, 5 N2 cases, 3 N3a cases, and 5 N3b cases. For the P factor, there was only 1 P1 case. Three cases had distant lymph node metastasis, and no cases had distant organ metastasis. On histology, there were 7 tub1 cases, 3 tub2 cases, 1 pap case, 5 por1 cases, and 1 por2 case. For the number of metastatic nodules, 9 had within 3, and 8 had 4 or more. All HAI cases underwent gastrectomy. For the gastrectomy, 9 patients underwent distal gastrectomy, and 8 patients underwent total gastrectomy. For the lymph node dissection, 8 patients underwent D0 or D1, 8 patients underwent D2, and 1 patient underwent D3. Fifteen patients underwent systemic chemotherapy, and 2 patients underwent only HAI. Two patients underwent pre-operative chemotherapy, using S-1+CDDP and S-1+taxol (TXL), respectively. For the HAI regimen, 12 cases were given CDDP, 2 cases were given CDDP+5-FU, 1 case was given CDDP +MMC, 1 case was given CDDP+5-FU+MMC, and 1 case was given 5-FU. For systemic chemotherapy, 12 cases were administered S-1, 1 case was administered 5'-DFUR+PSK, 1 case was administered UFT, and 1 case was administered 5-FU as first-line therapy. Two cases were administered 5'-DFUR, 1 case was administered S-1+TXL, 1 case was administered CPT-11, and 1 case was administered S-1 as second-line therapy. One case was administered S-1+CDDP+TXL as third-line therapy. The range of the duration of HAI was 3-15 months, with a mean of 7.1 months. With respect to the clinical effect of these chemotherapies, the numbers of CR, PR, SD, and PD were 1, 6, 5 and 3, respectively. In 2 cases, the effect could not be determined, because these cases underwent hepatectomy synchronously (Table 4). The response rate was 46.7%. Eleven cases were administered S-1 along with HAI using CDDP [CDDP 20 mg/week (days 1, 8, 15), S-1 80 mg/m^2 (3 weeks daily oral administration, followed by 2 weeks of rest)], and the numbers of CR, PR, SD, and PD were 0, 5, 5, and 1, respectively. The response rate to this regimen was 45.5%.

With respect to prognosis, the 1-year survival rate was 76.4%, the 2-year survival rate was 47.1%, the 3-year survival rate was 23.5%, the 5-year survival rate was 5.9%, and the median survival time was 19 months. In H1-only cases, the 1-year survival rate was 78.6%, the 2-year survival rate was 57.1%, the 3-year survival rate was 28.6%, and the 5-year survival rate was 7.1%. For the prognosis of HAI + systemic chemotherapy in H1-only cases, the 1-year survival rate was 75.0%, the 2-year survival rate was 66.7%, the 3-year survival rate was 33.3%, the 5-year survival rate was 8.3%, and the median survival time was 32 months. On the other hand, for the prognosis of systemic chemotherapy-only cases, the 1-year survival rate was 46.2%, the 2-year survival rate was 23.1%, the 3-year survival rate was 7.7%, the 5-year survival rate was 0%, and the median survival time was 13 months. The survival curve of HAI + systemic chemotherapy cases was significantly higher than that of systemic chemotherapy-only cases ($P = 0.0275$).

Age/Sex	Site	type	TNM	Hist.	Nod.	Ope	Hepa.	Chemtherapy	Prog.(M)
60/M	LD	3	T4bN2	pap	2	D. D2 Colon	+	CDDP+5-FU*, PR	19D. H.,bone
66/M	M	2	T3N2	por1	3	D. D2	+	CDDP+5-FU/5-FU	43D. H.
63/M	UE	3	T4aN1	por2	1	T+SD2	-	5-FU, PD	13D. H.
54/M	UE	2	T4bN0	tub1	1	T. D3	+	MMC,5-FU+CDDP/UFT, S-1	32D. H.,L.
61/M	L	2	T4aN1	tub1	2	D. D2	-	CDDP/S-1,5'-DFUR, SD	32D.H.N.
75/M	LMU	3	T4bN2	tub1	≥ 4	D. D1	-	CDDP/5'-DFUR,PSK,CR	67A.
72/M	LMU	5	T4aN3b	tub1	≥ 4	T. D1	-	CDDP/S-1**, PR	44D. H.
67/M	UE	2	T4aN2	tub1	3	T, D1	-	CDDP/S-1, PR	33DN,bone
66/M	ML	2	T4aN3a	tub1	≥ 4	D.D1	-	CDDP/S-1, SD	26D. H.
64/M	U	1	T4aN3a M1LYM	por1	≥ 4	T+S,D1	-	CDDP/S-1, SD	12D. H.
56/M	LD	3	T4aN3b M1LYM	tub1	≥ 4	D. D1	-	CDDP/S-1, SD	8D. H.
77/F	LMU	3	T4aN3b P1M1LY	tub2	≥ 4	D. D0	-	CDDP/S-1, PR CDDP/CPT-11	19D.
71/M	U	3	T4aN3b	por1	2	T+S,D2	-	CDDP/S-1, SD	10D. H.
65/M	U	2	T4aN2	tub2	≥ 4	T, D2	-	CDDP/S-1,PR, S-1+TXL, S-1+CDDP+TXL	19D. L.
65/M	UM	3	T4aN3a	por1	2	T, D1	-	pre.S-1+CDDP(4 c. PD) CDDP/S-1 PD	6D. N.,H.
65/M	LM	3	T4aN3b	por1	≥ 4	D,D2	-	pre.S-1+TXL(5c. PR) CDDP+MMC/S-1 PD	3D. N.,H.
68/M	LD	1	T4aN0	tub2	2	D, D2	-	CDDP/S-1,5'-DFUR, PR	38D.

M male, *F* female, *L* lower third portion, *M* middle third portion, *U* upper third portion, *T* depth of tumor invasion, *N* lymph node metastasis, *M* distant metastasis, *M1LYM* distant lymph node metastasis, *P* peritoneal metastasis, *Hist* histology, *pap* papillary adenocarcinoma, *por1* poorly differentiated adenocarcinoma solid type, *por2* poorly differentiated adenocarcinoma non-solid type, *tub1* tubular adeno carcinoma well-differentiated, *tub2* tubular adenocarcinoma moderately differentiated, *Nod* the number of metastatic nodule, *Ope* operation, *D* distal gastrectomy, *T* total gastrectomy, *S* splenectomy, *Hepa* hepatectomy, *pre* preoperative chemotherapy, *c* cycle, *Prog* prognosis, *M* month, *D* dead, *A* alive, *H* recurrence in the liver, *L* recurrence in the lung, *N* recurrence in the lymph node, *patient underwent hepatectomy after HAI, **patient underwent coagulation after surgery

Table 4: Cases who underwent hepatic arterial infusion (HAI).

Sex : Male/Female = 11/6,
Age : < 60/60 ≦ = 6/11
Stage IV factor : H1 only/multiple = 14/3
Macroscopic findings : 0/1,2/3,4/5 = 0/11/5/1
Tumor size : < 100/100 ≤ = 16/1
Residual tumor : R0/R2 = 7/10
Site of primary tumor : U/M/L = 5/5/7
The number of primary tumor site : 1/2/3 = 7/7/3
Depth of invasion : T1,T2,T3/T4a/T4b = 5/9/3
Histology : differentiated type/undifferentiated type = 12/5
Stromal volume of primary tumor : med/int/sci = 111/5/1
Tumor infiltrative (INF) pattern : INFa/INFb/INFc = 6/10/1
Lymphatic invasion : ly0/ly1,ly2/ly3 = 0/10/7
Venous invasion : v0,v1/v2,v3 = 4/13
Lymph node metastasis : N0/N1,N2/N3 = 4/8/5
Gastrectomy : diastal gastrectomy/total gastrectomy = 10/7
Lymph node dissection : D0,D1/D2 ≤ = 4/13
The number of liver metastasis : 1/2,3 = 12/5
HAI : -/+ = 13/5
Systemic chemotherapy : -/+ = 4/13
Radiofrequency ablation (RFA) : -/+ = 14/3
Phase : synchronous/metachronous = 12/5
The method of hepatectomy : partial resection/segmental resection or lobectomy = 13/5

Table 5: The clinicopathological characteristics of cases who underwent hepatectomy.

Hepatectomy cases including metachronous liver metastasis (1984-2010)

The clinicopathological characteristics of cases who underwent hepatectomy are summarized in Table 5. All 12 gastric cancer cases with synchronous liver metastasis underwent gastrectomy plus hepatectomy. Five cases underwent hepatectomy for metachronous liver metastasis. One patient underwent hepatectomy twice for synchronous metastasis and metachronous metastasis after 24 months. For the macroscopic type of primary site, there were 11 type 2 cases, 4 type 3 cases, 1 type 4 case, and 1 type 5 case. For the T factor, there were 10 T4a cases, 4 T3 cases, 2 T4b cases, and 1 T1 case. For the N factor, there were 4 N0 cases, 2 N1 cases, 6 N2 cases, 3 N3a cases, and 2 N3b cases. For the P factor, there was only 1 P1 case. Two cases had distant lymph node metastasis. All 17 hepatectomy cases had within 3 metastatic nodules. There were no cases with distant organ metastasis. On histology, 4 were tub1, 6 were tub2, 2 were pap, 3 were por, and 2 were por1. The primary tumor size of all hepatectomy cases except 1, which was type 4 cancer, was less than 100 mm.

All hepatectomy cases underwent gastrectomy. For gastrectomy, 10 patients underwent distal gastrectomy, and 7 patients underwent total gastrectomy. For the lymph node dissection, 3 patients

Age/Sex	Site	type	TNM	Hist.	Nod.	Ope	Hep.	RFA	HAI.	Phase	Prog.(M)
67/M	L	3	T4aN0	tub2	1	D.R2	P	-	-	sync.	13D.
70/F	L	2	T2N3a	tub1	1	D.D2,R2	P	-	-	sync.	5D.
43/M	UE	3	T3N3aP1	por	2:S2,3	T+S,D1 R2	S	-	+	sync.	6D.
58/M	ULE	4	T4bN3b M1LYM	por	1	T+S.D1 R2	P	-	-	sync	15D.H.,N
67/F	U	2	T3N1	tub2	1:S5	T.D2,R2	P	-	+	sync.	11D. H.
58/F	L	2	T4aN3b M1LYM	tub2	1:S6	D.D1,R2	P	-	-	sync.	8D. N.
56/M	MU	2	T4aN1	tub1	1:S6	T.D3,R0	P	-	-	meta.15M	173A.
79/F	MLU	2	T4aN3a	pap	1:S6	D,D2,R0	P	-	-	sync.	29D.N.,H
60/M	LD	3	T4bN2	pap	2:S3,4	D,D2,R2 Colon	L	-	+	sync*	19D H, bone
55/M	UE	2	T4aN2	tub2	2:S4,7	T+S.D2 R2	P:S7	S4	- TAE	sync.	42D.H.,L.
66/M	M	2	T3N2	por1	3:S3,6,7	D,D2,R2	P:S3	S6,7	+	sync.	43D, H.
54/M	UE	2	T4bN0	tub1	1:S7 1:S6	T.D3,R2	P P	- -	+ -	sync. meta.24M	34D.H.,L.
61/F	L	5	T3N2	por	2:S3,4	D.D2,R0	S:S3	S4	-	meta.9M	72D.Ac.
70/M	L	3	T4aN0	tub1	1:S2	D,D2,R0	S	-	-	meta.12M	86A.
71/M	MU	2	T4aN0	tub2	1	T,D2,R0	S	-	-	meta.4M	42A.
74/M	MLU	2	T4aN2	tub2	1:S8	D,D2,R0	P	-	-	sync.	13D. bone
78/F	LM	2	T4aN2	por1	1:S6	D,D2,R0	P	-	-	meta.10M	24D. L

M male, *F* female, *L* lower third portion, *M* middle third portion, *U* upper third portion, *T* depth of tumor invasion, *N* lymph node metastasis, *M* distant metastasis, *M1LYM* distant lymph node metastasis, *P* peritoneal metastasis, *Hist* histology, *pap* papillary adenocarcinoma, *por1* poorly differentiated adenocarcinoma solid type, *por2* poorly differentiated adenocarcinoma non-solid type, *tub1* tubular adeno carcinoma well-differentiated, *tub2* tubular adenocarcinoma moderately differentiated, *Nod* the number of metastatic nodule, *Ope* operation, *D* distal gastrectomy, *T* total gastrectomy, *S* splenectomy, *Hepa* hepatectomy, *P* partial resection of the liver, *S* segmental resection of the liver, *L lobectomy of the liver, RFA* radiofrequency ablation, *HAI* hepatic arterial infusion, *TAE* transcatheter arterial embolization, *sync* synchronous, *meta* metachronous, *Prog* prognosis, *M* month, *D* dead, *A* alive, *H* recurrence in the liver, *L* recurrence in the lung, *N* recurrence in the lymph node, *Ac* accidental death, * patient underwent hepatectomy after gastrectomy and HAI

Table 6: Cases who underwent hepatectomy for liver metastasis from gastric cancer.

underwent D1, 12 patients underwent D2, and 2 patients underwent D3. For the hepatectomy, 12 patients underwent partial resection, 3 patients underwent left lateral segmentectomy, 1 patient underwent extended right posterior segmentectomy, and 1 patient underwent left lobectomy after HAI. Three patients underwent partial resection and radiofrequency ablation (RFA). Four patients did not receive systemic chemotherapy. Five patients underwent hepatectomy combined with HAI. One patient underwent partial resection, RFA, and transcatheter arterial embolization (TAE). For residual tumor, there were 7 R0 cases and 10 R2 cases. All 5 metachronous metastasis cases underwent R0 surgery. All 3 cases with multiple Stage IV factors underwent R2 surgery. The duration after first surgery was from 4 to 24 months, and the average duration was 12.3 months in metachronous metastasis cases (Tables 5 and 6).

On the prognosis of hepatectomy cases, the 1-year survival rate was 76.5%, the 2-year survival rate was 52.9%, the 3-year survival rate was 35.3%, the 5-year survival rate was 17.6%, and the median survival time was 29 months. There were significant differences in the stromal volume of the primary site, lymph node metastasis, Stage IV factors, residual tumor, and synchronous or metachronous metastasis ($P = 0.0097$, $P = 0.0076$, $P = 0.0101$, $P = 0.0208$, and $P = 0.0030$, respectively). There was no significant difference between partial resection and systemic resection (Table 7). For stromal volume, the survival curve of medullary type cases was significantly higher than those of intermediate and scirrhous types. For lymph node metastasis, the survival curves of N0, N1, and N2 cases were significantly higher than of N3 cases. With respect to the number of Stage IV factors, the survival curve of H1-only cases was significantly higher than that of multiple Stage IV factor cases. For residual tumor, the survival curve of R0 cases was significantly higher than that of R2 cases. The survival curve of metachronous metastasis was significantly higher than that of synchronous metastasis. All three cases that underwent RFA were alive more than three years after surgery.

Discussion

The prognosis of gastric cancer cases with liver metastasis is extremely poor because most patients with gastric cancer with concomitant liver metastases are excluded as candidates for curative surgery accompanied by hepatic resection due to incurable simultaneous factors, such as peritoneal dissemination, widespread lymph node metastases, and direct invasion to adjacent structure. Moreover, many cases have multiple metastatic lesions in both lobes of the liver. In the present study, H1-only cases accounted for only 44 cases (57.1%), and the number of cases with 4 or more liver metastases with multiple Stage IV factors was significantly more frequent than in H1-only cases.

Histology, systemic chemotherapy, and HAI were independent prognostic factors. Differentiated histological type, systemic chemotherapy, and HAI were associated with a good prognosis in gastric cancer patients with liver metastasis. Moreover, all HAI cases underwent gastrectomy, and 14 of 17 cases were H1-only cases. Therefore, gastrectomy and H1-only were thought to be absolutely necessary for a good prognosis. The response rate of HAI was 46.7%, and the SMT was 19 months. In H1-only cases, the SMT of HAI cases was 25 months, and in patients who underwent systemic chemotherapy associated with HAI, the SMT was 32 months. The prognosis was significantly better for patients who underwent chemotherapy associated with HAI than for patients who underwent systemic chemotherapy only. Aoki et al. [7] reported that intra-hepatic arterial infusion of anti-cancer drugs was better than systemic administration for treating liver metastasis. A

	Univariate analysis (log-rank test)		
Variables	Statistic	df	*P*
Sex	0.83	1	0.3622
Age	0.41	1	0.4201
Macro type	1.56	2	0.4580
Site	1.83	2	0.4011
The number of site	2.90	2	0.2351
Depth	0.52	2	0.7716
Histology	0.10	1	0.7520
Stroma	9.26	2	0.0097*
INF	1.07	2	0.5860
ly	0.01	1	0.9214
v	2.18	1	0.1394
LN metastasis	9.75	2	0.0076*
St. IV factor	6.61	1	0.0101*
New drugs	1.13	1	0.2876
LN dissection	3.21	1	0.0734
Tumor size	0.48	1	0.4900
R	5.34	1	0.0208*
M1(LYM)	2.65	1	0.1035
Liver meta	0.64	1	0.4231
Phase	8.83	1	0.0030*
Hepatectomy	3.16	1	0.0754
HAI	0.44	1	0.5071
Systemic chem.	0.10	1	0.7477

df degree of freedom, *CI* confidential interval, *P* peritoneal metastasis, *INF* tumor infiltrative pattern, *ly* lymphatic invasion, *v* venous invasion, *LN* lymph node, *R* residual tumor , *M1(LYM)* distant lymph node metastasis, *Liver meta* the number of metastatic nodule (solitary or multiple), *Phase* synchronous or metachronous metastasis, *Hepatectomy* partial resection or segmental resection, *HAI* hepatic arterial infusion, *chem.* Chemotherapy *P<0.05 indicates statistical significance.

Table 7: Disease-specific survival in cases who underwent hepatectomy.

good result was obtained in the present study from administration of CDDP as HAI and of S-1, but one CR case was administered CDDP as HAI and 5'-DFUR. Nakagawa et al. [8] reported three cases of gastric cancer with multiple liver metastases who were treated with intra-hepatic arterial infusion of low-dosage CDDP and oral administration of high dosage 5'-DFUR after surgery, and all patients lived more than one year, but there has been no case responsive to intra-hepatic arterial infusion of 5-FU alone. However, the number of patients alive for more than 5 years after surgery was only one, who had CR. Several authors reported that non-surgical treatments, including systemic or hepatic arterial infusion chemotherapy, do not achieve satisfactory results, and in patients treated by gastrectomy and chemotherapy, median survival times are reported to range from 2.9 to 11.8 months [9,10]. However, the prognosis of cases that were administered CDDP as HAI and S-1 was better than that of reported cases. Thus, we would like to aggressively perform HAI using CDDP along with administration of S-1 for H1-only cases from now on.

In the review of the literature, the hepatectomy rate was low, and it was indicated in only 0.4% to 1% of gastric cancer patients with liver metastases [11]. The resectability rate of the liver of gastric cancer patients with liver metastases is low, approximately 10% of cases, and it seems to be the same for cases of metachronous and synchronous metastases [12]. In the present cases, 6 (7.8%) of 77 gastric cancer patients had synchronous liver metastases.

The effectiveness of hepatic resection has not been well defined. The cumulative survival rate reported in early studies was generally poor, reflecting a generalized disease. Elias et al. [13] showed that the 3-year survival rate after hepatic resection was less than 20%. In recent reports, the 1-year survival rate ranged from 42% to 90%, and the 5-year survival rate ranged from 0% to 38% [14-16]. The long-term results after liver resection for metastases from gastric cancer show a wide range. In the present hepatectomy cases, the 1-year survival rate was 76.5%, the 2-year survival rate was 52.9%, the 3-year survival rate was 35.3%, the 5-year survival rate was 17.6%, and the median survival time was 29 months. Thus, we believe that there was a clinical benefit from resection of hepatic metastases from gastric carcinoma. Therefore, it is crucial to clarify the condition of 5-year survivors and to determine the indications for liver surgery.

The actual accepted selection criteria are: synchronous metastases without peritoneal dissemination or other distant metastases; metachronous metastases without other recurrent lesions; and complete resection of metastases with acceptable postoperative liver function [11]. Contraindications to hepatic resection are: previous extrahepatic disease; advanced lymph node involvement; and the inability to obtain liver R0 resection [17,18]. In the present study, the survival curves of N0, N1, and N2 cases were significantly higher than of N3 cases. On the number of Stage IV factors, the survival curve of H1-only cases was significantly higher than that of multiple Stage IV cases. Finally, for residual tumor, the survival curve of R0 cases was significantly higher than that of R2 cases.

Regarding the primary gastric cancer, Ochiai et al. [19] reported that hepatic resection should only be attempted in patients with synchronous or metachronous metastases if there is non-serosal invasion by the primary gastric tumor, as did Morise et al. [20], and if the primary tumor has neither microscopic venous nor lymphatic invasion in metachronous cases. However, Miyazaki et al. [21] and Okano et al. [22] reported that there was a non-significant difference in terms of depth of invasion or lymph node metastases of the gastric cancer between surviving and non-surviving patients. In the present cases, non-significant differences were observed in survival rate in terms of depth of invasion, venous invasion, and lymphatic invasion, but significant differences were seen in survival rates in terms of stromal volume and lymph node metastasis. With respect to stromal volume, the survival rate of medullary type was significantly higher than that of intermediate and scirrhous types. The macroscopic type of most medullary types was localized, such as type 1 or type 2. There appear to have been no reports to date about the significance of the stromal volume of primary gastric cancer for hepatectomy for metastases from gastric cancer.

The number of metastatic nodules in the liver has been reported to be an important prognostic factor. Okano et al. [22] reported 3-year survival rates of 56% for single metastases and 0% for multiple metastases, and the number of liver metastases was a significant prognostic factor. Shirabe et al. [23] noted that the presence of three or more tumors was an independent poor prognostic factor on univariate and multivariate analyses. In the present cases, the presence of four or more tumors was a significant poor prognostic factor on univariate analysis, but it was not an independent poor prognostic factor on multivariate analysis. The favorable surgical outcome for patients with solitary metastases indicates that patients with a solitary metastasis of gastric cancer are good candidates for surgical resection. However, Saiura et al. [24] reported two long-term survivors with more than three metastases, concluding that if curative resection (R0) can be achieved, hepatic resection should not be abandoned in patients with multiple liver metastases. The number of metastatic nodules in the liver of the present hepatectomy cases was within three, and there was no

significant difference in the survival rate between solitary metastasis and multiple (2 or 3) metastases.

Three of five cases with multiple metastatic nodules in the liver underwent RFA. In three patients who were alive for more than 5 years after hepatectomy, 2 patients had a solitary metastatic nodule and 1 patient had two metastatic nodules, and they underwent RFA. If the patients have within 3 metastatic nodules in the liver, surgical resection ± RFA is indicated. All 3 cases who underwent RFA were alive for more than 3 years after surgery. Some authors reported that patients who underwent RFA compared favorably with patients who underwent radical surgery [9,25]. We think that RFA may be effective for patients in whom surgery is contraindicated because their general condition is poor.

The timing of hepatic resection has been reported to be a significant prognostic factor. In some papers, synchronous hepatectomy was a significant poor prognostic factor [23,26,27]. Ambiru et al. [26] reported significantly longer survival in patients with metachronous metastases than in those with synchronous disease. Some authors suggested that resection may be indicated only for patients with metachronous isolated metastases [23,28]. Other studies did not demonstrate any differences in terms of survival among the groups [19,29,30]. In the present study, the survival rate of metachronous hepatectomy cases was significantly higher than that of synchronous hepatectomy cases. This may depend on the concern about the use of aggressive liver surgery in conjunction with the treatment of gastric cancer under synchronous conditions.

All 3 patients who were alive for more than 5 years underwent hepatectomy metachronously at 9 months or more than 9 months (9M, 12M, 15M) after the first surgery for gastric cancer. The disease-free interval (DFI) between gastric and hepatic resections has been reported to be a prognostic factor. Fuji et al. [31] showed that a DFI > 1 year between gastric and hepatic resections has a significant survival advantage, due to the slow-growing nature of these tumors.

The survival rate of segmental or lobular resection cases tended to be higher than that of partial resection cases, but the difference was not significant. The relationship between the extent of hepatic resection and prognosis has not yet been established. Isono et al. [32] reported that micrometastases around the macroscopic tumor were found more frequently in hepatic metastases from gastric cancer than in those from colorectal ones, thus suggesting that wider surgical resection margins are required. Takahashi et al. [33] reported that partial resection was effective enough for metastasis from gastric cancer. In the present study, 3 of 5 patients who underwent segmentectomy or lobectomy had metachronous liver metastasis. One patient who underwent lobectomy had synchronous metastases, but this case underwent left lobectomy for nodules in S3 and S4 after HAI. The grade of the extent of the hepatic resection is still controversial. Anatomic hepatic resection (segmentectomy and lobectomy) may be recommended if the patient's systemic condition and residual function of the liver allow it.

In this study, adding HAI chemotherapy to liver surgery did not seem to offer patients a survival benefit. A report has suggested [34] that only liver surgery, but not HAI, could significantly prolong the survival period.

Conclusion

Multimodal treatment including gastrectomy, systemic chemotherapy, HAI, and hepatectomy for gastric cancer patients with liver metastasis is considered effective. If patients have no stage IV factors other than H factor, and the number of metastatic nodules is within 3, hepatectomy is recommended, especially in metachronous liver metastasis, medullary stromal volume type, and low-grade lymph node metastasis.

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