

ORIGINAL

Results of Hepatic Resection for Liver Metastasis of Gastric Cancer -A Single Center Experience-

Masaaki Nishi, Mistuo Shimada, Kozo Yoshikawa, Jun Higashijima, Takuya Tokunaga, Hideya Kashiwara, Chie Takasu, Daichi Ishikawa, Yuma Wada, and Shohei Eto

Department of Surgery, Tokushima University, Tokushima, Japan

Abstract : Background : Surgical indication for hepatic resection is controversial in gastric cancer liver metastasis (GLM). The aim of this study is to clarify the effect of hepatic resection for GLM. **Methodology :** Ten patients who underwent hepatic resection for GLM between 2001 and 2013 were enrolled in this study. Six patients underwent synchronous hepatic resection and gastrectomy, and the remaining four patients underwent metachronous hepatic resection. Six patients had solitary liver metastasis, and 4 patients had multiple liver metastasis. The median follow-up period was 12.4 months (the range being 0.5 months to 50 months). **Result :** The actual 1-year and 3-year overall survival rates for the patients who underwent hepatic resection are 88.9% and 17.8%, respectively. The median survival time was 21.5 months. And the 1-year recurrence free survival time was 20.0%. The median recurrence free survival rate was 4.7 months. Regarding post-operative recurrence, synchronous hepatic resection tended to be a recurrence factor ($p=0.08$). **Conclusion :** Hepatic resection for GLM has an acceptable outcome. Metachronous hepatic resection tends to have a better outcome than synchronous hepatic resection for the treatment of GLM. *J. Med. Invest.* 65 : 27-31, February, 2018

Keywords : gastric cancer, liver metastasis, hepatic resection

INTRODUCTION

Gastric cancer is the fourth most common cancer in the world, and the second most common cause of cancer deaths in Japan (1, 2). The treatment strategy for curable gastric cancer is adequate local control. The standard treatment for curable gastric cancer is gastrectomy with D2 lymphadenectomy (3). However, 4% to 14% of patients with primary gastric cancer have liver metastasis. Gastric cancer liver metastasis (GLM) is a fatal disease and the prognosis is dismal. In Japan, the first line treatment for GLM is systemic chemotherapy (4-6). However, the effect of chemotherapy is unsatisfactory and limited.

In contrast to GLM, the feasibility and oncologic outcome of hepatic resection for colorectal cancer liver metastasis has been established. The 5-year survival rate of patients after hepatic resection of colo-rectal cancer liver metastasis is 40% to 58% (7, 8). Complete surgical resection of the primary lesion and the liver metastasis appears to be the only chance for cure. However, in gastric cancer, surgical indication for GLM remains controversial. Patients with GLM often have locally advanced disease, peritoneal dissemination, lymph node metastasis, and distant metastasis. Although in some reports a feasible outcome of hepatic resection for GLM has been presented, hepatic resection for GLM is rarely indicated. There have been few reports about hepatic resection for GLM and a reported 5-year survival rate after hepatic resection for GLM is 18% to 42% (9-15).

The aim of this study is to clarify the long-term effect of hepatic resection for GLM.

METHODOLOGY

Ten patients in this study underwent hepatic resection for gastric cancer liver metastasis at Tokushima University Hospital between 2001 and 2013. These 10 patients comprised 9 men and 1 woman with a median age of 71.7 years (a range of 50 to 81 years). Six patients underwent synchronous hepatic resection and gastrectomy, and the remaining 4 patients underwent metachronous hepatic resection. Six patients had solitary liver metastasis, and 4 patients had multiple liver metastasis. The median maximum tumor size was 23.5 mm. Pre-operative chemotherapy was administered in 2 cases (20%). That is, S-1 in 1 case and Docetaxel plus Cisplatin plus S-1 in 1 case. Five patients underwent hepatic lobectomy; 2 patients underwent hepatic segmentectomy, and 5 patients underwent partial resection of the liver. Postoperative adjuvant chemotherapy was administered in six (6) cases (60%). That is, S-1 in 1 case; S-1 plus Cisplatin in 1 case; S-1 plus CPT-11 in 2 cases; and UFT in 2 cases. The median follow-up period was 12.4 months (the range being between 0.5 months and 50 months). The patients' characteristics are shown in Table 1. No patient underwent repeat hepatic resection.

STATISTICAL ANALYSIS

All statistical analysis has been calculated through Stat View statistical software (Stat View 5.0, SAS Institute, Cary, NC). The clinico-pathological variables have been analyzed with the chi-square test and Mann-Whitney *U* test. Survival curves have been

Abbreviations

gastric cancer liver metastasis (GLM); radio-frequency ablation (RFA); trans-arterial chemo-embolization (TACE).

Received for publication July 10, 2017; accepted August 20, 2017.

Address correspondence and reprint requests to Masaaki Nishi, MD, Department of Surgery, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-631-9698.

Table 1 Patients' characteristic

Characteristic	
Age	71.7 (50-81)
Sex (male/ female)	9/1
Serosal Invasion primary gastric cancer (Yes/ No)	2/8
Timing of hepatectomy (Synchronous/ Metachronous)	6/4
Type of hepatic resection (lobectomy/segmentectomy/partial resection)	3/2/5
Preoperative Chemotherapy (Yes/ No)	3/7
Postoperative chemotherapy (Yes/ No)	8/2
Maximum tumor size (mm)	23.5 (10-74)
Number of liver metastasis (solitary/ multiple)	6/4
Follow up period (m)	12.4 (0.5-50)

calculated using the Kaplan-Meier method and compared using the Wilcoxon test. Statistical significance has been defined as $p < 0.05$.

RESULTS

The actual 1-year and 3-year overall survival rates for the patients who underwent synchronous hepatic resection and gastrectomy and those who underwent metachronous hepatic resection are 88.9% and 17.8%, respectively. The median survival time is 21.5 months (Figure 1) and the 1-year recurrence free survival rate is 20.0%. The median recurrence free survival rate is 4.7 months (Figure. 2). There has been no postoperative mortality, and 1 patient has had postoperative bile leakage. Six patients have had recurrence in the liver, and 1 patient has had recurrence in the brain after hepatic resection.

Uni-variate analysis has presented no significant risk factor in overall survival in age ; serosal invasion of primary gastric cancer ; timing of hepatic resection ; type of hepatic resection ; pre-operative chemotherapy ; post-operative chemotherapy ; maximum tumor size of GLM ; and the number of GLM. Regarding post-operative recurrence after hepatic resection, synchronous hepatic resection tended to be a recurrence factor ($p=0.08$). The 1-year recurrence free survival rate is 41.7% in metachronous hepatic resection, and 27.8% in synchronous hepatic resection, respectively.

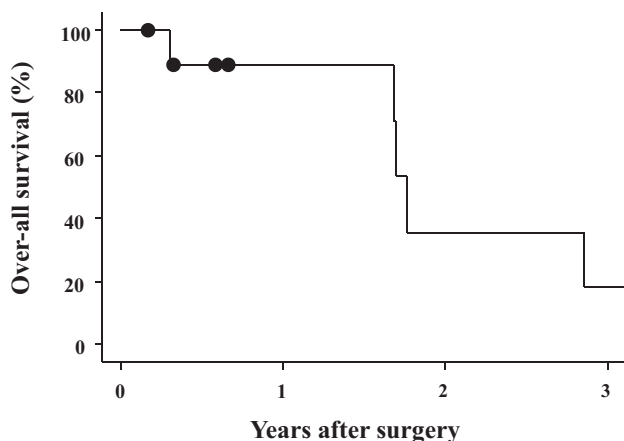


Figure 1.
Overall survival after hepatic resection for gastric liver metastasis

No significant difference in recurrence free survival has been found in age ; serosal invasion of primary gastric cancer ; type of hepatic resection ; preoperative chemotherapy ; postoperative chemotherapy ; maximum tumor size of GLM ; and the number of GLM.

DISCUSSION

The discussion focuses on the outcome of hepatic resection for GLM. The actual 1 to 3-year overall survival rates for patients who underwent synchronous hepatic resection and gastrectomy and those who underwent metachronous hepatic resection are 88.9% and 17.8%, respectively and the median survival time is 21.5 months. Synchronous hepatic resection tends to be a recurrence factor.

There have been several retrospective reports from Japan of small numbers of patients undergoing hepatic resection for GLM. The 5-year survival rate is 18% to 42% and the median survival time after surgery is reported as 12 months to 34 months (9-15). Overall survival time and median survival time of our study is comparable to other trial. According to previous reports, the prognostic factors after hepatic resection for GLM are serosal invasion of the primary gastric cancer ; lymph node metastasis ; the number of hepatic metastasis ; the surgical margin ; the maximum diameter of hepatic metastasis ; and the timing of hepatic resection. Recently, Takemura *et al.* demonstrated that the overall 1-year, 3-year and 5-year

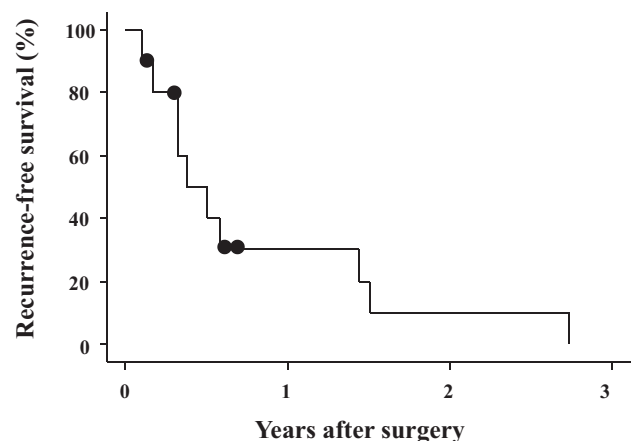


Figure 2.
Recurrence free survival after hepatic resection for gastric liver metastasis

Table 2 Univariate analysis for overall survival

Characteristic	No of patients	1-yr OS(%)	3-yr OS(%)	P value
All patients	10	71.1	17.8	
Age				0.87
<70	5	66.7	0	
≥70	5	75.0	37.5	
Serosal Invasion				0.99
Positive	2	100	0	
Negative	8	85.7	21.4	
Timing of hepatic resection				0.79
Synchronous	6	80	40	
Metachronous	4	100	0	
Type of hepatic resection				0.58
Major	5	100	0	
Minor	5	80	20	
Preoperative Chemotherapy				0.69
Yes	3	100	0	
No	7	85.7	21.4	
Postoperative chemotherapy				NA
Yes	8	87.5	17.5	
No	2	NA	NA	
Maximum tumor size				0.74
<25mm	5	80.0	26.7	
≥25mm	5	100	0	
Number of liver metastasis				0.27
Solitary	6	80	26.7	
Multiple	4	100	0	

Table 3 Univariate analysis for recurrent free survival

Characteristic	No of patients	1-yr RFS(%)	P value
All patients	10	71.1	
Age			0.28
<70	5	60.0	
≥70	5	40.0	
Serosal Invasion			0.59
Positive	2	100	
Negative	8	43.8	
Timing of hepatic resection			0.08
Synchronous	6	27.8	
Metachronous	4	41.7	
Type of hepatic resection			0.58
Major	5	33.3	
Minor	5	60	
Preoperative Chemotherapy			0.46
Yes	3	50.0	
No	7	51.4	
Postoperative chemotherapy			NA
Yes	8	50.0	
No	2	NA	
Maximum tumor size			0.89
<25mm	5	40.0	
≥25mm	5	66.7	
Number of liver metastasis			0.96
Solitary	6	41.7	
Multiple	4	66.7	

Table 4 Hepatic resection for gastric cancer liver metastasis

Authors	No of patients	1-yr OS(%)	3-yr OS(%)	MST (m)
Ambiru et al. ⁹⁾	40	71.1	NA	12
Okano et al. ¹⁰⁾	19	77	34	21
Shirabe et al. ¹¹⁾	36	64	26	NA
Sakamoto et al. ¹²⁾	37	NA	NA	31
Koga et al. ¹³⁾	42	76	48	34
Takemura et al. ¹⁴⁾	64	84	50	31.5
Cheon et al. ¹⁵⁾	64	71.5	31.7	17
Our trial	10	88.9	17.8	21.5

NA : not available

survival rates after hepatic resection for GLM are 84%, 50% and 37% in the selected patients, respectively. They also found that GLM patients with a maximum diameter of hepatic metastasis of 5 cm and negative serosal invasion of primary gastric cancer were good candidates for hepatic resection (14). Sakamoto *et al.* recommends hepatic resection for GLM with unilobar liver metastasis of 4 cm or less tumor size (15).

In the last two decades, chemotherapy has improved in its use in gastric cancer. We can now use several chemo-therapeutic agents in the treatment of gastric cancer. In Japan, the combination of S-1 and Cisplatin is standard treatment for advanced gastric cancer. As second line or third line treatment regimens, patients have received Ramucirumab, Nab-paclitaxel, Paclitaxel, Docetaxel, Irinotecan, Trastuzumab, Capecitabine and others. However, chemotherapy is not a curative treatment, and the effect is limited. Trials undertaken by Spirits show that the median survival time using S-1 and Cisplatin chemotherapy is 13.0 months (16). If hepatic resection contributes to local control of metastatic gastric cancer, treatment option would be widened.

Radio-frequency ablation (RFA) and trans-arterial chemo-embolization (TACE) are standard treatment options in hepato-cellular carcinoma as non-surgical treatments. In GLM, only small-sized retrospective studies or case reports have been presented to date. Yamakado *et al.* demonstrated the results of RFA following hepatic arterial infusion therapy for 7 patients with GLM. RFA was performed on sixteen (16) liver tumors, resulting in complete tumor necrosis, and a median survival time of 16.5 months (17). Hirasawa *et al.* reported 8 cases of TACE using degradable starch microspheres for the treatment of GLM (18). The actual 1 year and 2-year survival rates are 87.5% and 52.5%, respectively and the median survival time is 36.1 months. These results show that RFA and TACE may be treatment options for GLM. As this is a retrospective study and includes only a small number of patients, a larger series of prospective randomized control trials are needed to clarify surgical indications for GLM. We hope that aggressive surgical resection, combined with systemic chemotherapy, and/or RFA and TACE, will contribute to patients' outcomes in future cases of GLM.

In conclusion, hepatic resection for GLM has an acceptable outcome and, of the two types of resection considered in this study, metachronous hepatic resection tends to have a better outcome than synchronous hepatic resection for the treatment of GLM. Thus, surgeons should consider hepatic resection for GLM as a treatment option.

CONFLICT OF INTEREST STATEMENT

Masaaki Nishi and other co-authors have no conflict of interest.

REFERENCES

- American Cancer Society. Global cancer facts and figures 2007. http://www.cancer.org/downloads/STT/Global_Facts_and_Figs_2007_rev2.pdf. Accessed 16 Jun 2009
- Ministry of Health, Labor and Welfare, Japan. Figures for vital statistics in 2007. <http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei07/hyo7.html>. Accessed 16 Jun 2009
- Sano T, Aiko T : New Japanese classifications and treatment guidelines for gastric cancer : revision concepts and major revised points. *Gastric Cancer* 14(2) : 97-100, 2011
- Koga S, Kishimoto H, Tanaka K, Miyano Y, Kawaguchi H, Takeda R, Nishidoi H, Kimura O : Results of total gastrectomy for gastric cancer. *Am J Surg* 140(5) : 636-8, 1980
- Okuyama K, Isono K, Juan IK, Onoda S, Ochiai T, Yamamoto Y, Koide Y, Satoh H : Evaluation of treatment for gastric cancer with liver metastasis. *Cancer* 15 ; 55(10) : 2498-505, 1985
- Okano K, Maeba T, Ishimura K, Karasawa Y, Goda F, Wakabayashi H, Usuki H, Maeta H : Hepatic resection for metastatic tumors from gastric cancer. *Ann Surg* 235(1) : 86-91, 2002
- Ueno H, Mochizuki H, Hashiguchi Y, Hatsuse K, Fujimoto H, Hase K : Predictors of extrahepatic recurrence after resection of colorectal liver metastases. *Br J Surg* 91(3) : 327-33, 2004
- Fortner JG, Silva JS, Cox EB, Golbey RB, Gallowitz H, Maclean BJ : Multivariate analysis of a personal series of 247 patients with liver metastases from colorectal cancer. II. Treatment by intrahepatic chemotherapy. *Ann Surg* 199(3) : 317-24, 1984
- Ambiru S, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, Shimizu Y, Nakajima N : Benefits and limits of hepatic resection for gastric metastases. *Am J Surg* 181(3) : 279-83, 2001
- Okano K, Maeba T, Ishimura K, Karasawa Y, Goda F, Wakabayashi H, Usuki H, Maeta H : Hepatic resection for metastatic tumors from gastric cancer. *Ann Surg* 235(1) : 86-91, 2002
- Shirabe K, Shimada M, Matsumata T, Higashi H, Yakeishi Y, Wakiyama S, Ikeda Y, Ezaki T, Fukuzawa S, Takenaka K, Kishikawa K, Ikeda T, Taguchi K, Maehara Y, Sugimachi K : Analysis of the prognostic factors for liver metastasis of gastric cancer after hepatic resection : a multi-institutional study of the indications for resection. *Hepatogastroenterology* 50(53) : 1560-3, 2003
- Sakamoto Y, Sano T, Shimada K, Esaki M, Saka M, Fukagawa T, Katai H, Kosuge T, Sasako M : *J Surg Oncol*. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. *J Surg Oncol* 1 ; 95(7) : 534-9, 2007
- Koga R, Yamamoto J, Ohyama S, Saiura A, Seki M, Seto Y, Yamaguchi T : Liver resection for metastatic gastric cancer :

- experience with 42 patients including eight long-term survivors. *Jpn J Clin Oncol* 37(11) : 836-42, 2007
14. Takemura N, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, Hiki N, Sano T, Yamamoto J, Kokudo N, Yamaguchi T : Long-term outcomes after surgical resection for gastric cancer liver metastasis : an analysis of 64 macroscopically complete resections. *Langenbecks Arch Surg* 397(6) : 951-7, 2012
 15. Cheon SH, Rha SY, Jeung HC, Im CK, Kim SH, Kim HR, Ahn JB, Roh JK, Noh SH, Chung HC : Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. *Ann Oncol* 19(6) : 1146-53, 2008
 16. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M : S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial) : a phase III trial. *Lancet Oncol* 9(3) : 215-21, 2008
 17. Yamakado K, Nakatsuka A, Takaki H, Mori Y, Tonouchi H, Kusunoki M, Kida H, Takeda K : Prospective study of arterial infusion chemotherapy followed by radio-frequency ablation for the treatment of liver metastasis of gastric cancer. *J Vasc Interv Radiol* 16(12) : 1747-51, 2005
 18. Hirasawa T, Asahara S, Fujisaki S, Kuraoka K, Takano K, Kamei A, Ikari T : Trans-catheter arterial chemo-embolization (TACE) using degradable starch microspheres (DSM) for metastatic liver tumors in patients with gastric cancer. *Nihon Shokakibyō Gakkai Zasshi* 105(3) : 367-72, 2008