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ORIGINAL SCIENTIFIC REPORT

Hepatectomy Offers Superior Survival Compared with Non-surgical Treatment for ≤3 Metastatic Tumors with Diameters <3 cm from Gastric Cancer: A Retrospective Study

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Abstract

Background A consensus has almost been reached in favor of hepatic resection for colorectal cancer metastases. It remains unclear whether resection of gastric cancer metastases in the liver is justified. The purpose of this study was to assess the survival benefit of surgical resection for gastric cancer metastases confined to the liver.

Methods We reviewed the clinicopathological features and outcome of 107 patients with liver metastases without other non-curative factors from the case records of 5437 gastric cancer patients. These subjects included 34 synchronous cases with tumors present at the time of gastrectomy and 73 metachronous cases with new lesions that appeared after radical gastrectomy.

Results Hepatectomies were performed in nine synchronous and four metachronous cases that had ≤3 tumors with diameters <3 cm. The overall survival rates after hepatectomy were significantly higher than those in eligible candidates who did not receive hepatectomy despite having comparable metastatic status (synchronous, $n = 8$, $p = 0.009$; metachronous, $n = 24$, $p = 0.016$). The survival rate of patients who underwent hepatectomy for synchronous metastases was not inferior to that of patients who underwent hepatectomy for metachronous metastases. The median disease-free interval in metachronous cases was significantly shorter in patients who did not undergo resection than those who underwent resection. However, multivariate analyses revealed that hepatectomy was the only significant ($p = 0.001$) prognostic factor whereas DFI was not.

Conclusions Hepatectomy for ≤3 metastatic tumors with diameters <3 cm offered superior survival compared with non-surgical treatment even for metastases detected synchronously or within a short period after radical gastrectomy.

Introduction

The liver is one of the most common sites for distant metastases from gastric cancer [1, 2]. Although non-surgical approaches including systemic or hepatic artery infusion chemotherapy are regarded as standard treatment [2–5], they do not achieve satisfactory results [6]. Reported median survival time in patients with gastric cancer liver metastases (LM) treated by chemotherapy were limited to

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2.9–11.8 months [3–5]; these are far lower than those in colorectal LM [7–10]. The clinical benefit of surgical treatment is unknown. Multiple or scattered, bilobar metastases in the liver and coexisting peritoneal and lymph node (LN) metastases were associated with low resection rates [2, 11–13].

Several studies have made an effort to examine the indications for liver resection for metastatic tumors from gastric cancer by analyzing prognostic factors including serosal invasion of primary gastric cancer [2, 11, 12, 14], extent of LN metastases [15], number of intrahepatic lesions [6, 15–17], hepatic tumor size [2, 12, 18], timing of hepatic metastases [12, 17, 19], and disease-free interval (DFI) [13] in patients who underwent synchronous or metachronous hepatectomies. However, unlike in LM from colorectal cancer, a consensus has not yet been reached in favor of hepatic resection for LM from gastric cancer. In the present study, we retrospectively assessed the survival benefit for patients who received surgical resection for gastric cancer metastases confined to the liver with no other non-curative factors, compared with eligible candidates who did not undergo hepatectomy despite having similar metastatic status.

Materials and methods

The case records of 5437 patients with gastric carcinoma treated at Toranomon Hospital, Tokyo, Japan, between January 1985 and August 2014 were reviewed. In this study, the presence of liver lesions at the time of gastrectomy for patients with primary gastric cancer without any other non-curative factors such as peritoneal dissemination, positive peritoneal lavage cytology, para-aortic LN metastases, or extrahepatic metastases was defined as synchronous metastases. New lesions appearing after radical gastrectomy were defined as metachronous metastases. The group of 107 subjects, which comprised 34 patients with synchronous metastases and 73 with metachronous metastases, were analyzed. None of the patients died during the initial hospital stay or within 1 month after surgery. All patients were followed up every 1–3 months in the first 2 years after gastrectomy and every 3–6 months thereafter. The follow-up protocol included physical examination, serum tumor marker (CEA, CA19-9) levels, X-ray, abdominal ultrasonography, and computed tomography. Incorporation of magnetic resonance imaging to detect liver metastasis was started from 1990.

For statistical analyses, pairwise differences of proportions and means were analyzed by χ^2 test and two-sample t test. Cumulative overall survival (OS) was analyzed by the Kaplan–Meier method. The prognostic factors involved in OS were evaluated by log-rank test. Results were regarded as statistically significant when $p < 0.05$. All statistical analyses were performed using SPSS ver.19 (SPSS Inc., Chicago, IL). This study was approved by our hospital's Institutional Review Board and informed consent was obtained.

Results

Synchronous liver metastases

The clinicopathological features of the 34 patients with synchronous LM are shown in Table 1. The median follow-up period after diagnosis was 22.4 months (range 1.0–69.0). Combined hepatic resection was performed in 9 patients (anatomic resection in 3 and limited resection in 6) at the time of gastrectomy, whereas the remaining 25 patients received chemotherapy alone (systemic in 14 and hepatic artery infusion in 11). There were no significant differences between patients who underwent resection and those who did not, in terms of age, sex, tumor markers, serosal involvement of gastric cancer, and LN metastases from the primary tumor. Postoperative chemotherapy was performed in 8 (88.9 %) resected cases and 25 (100 %) unresected cases. Fluorouracil-based regimens (5-FU plus cisplatin, S-1 alone or combined with cisplatin) were most commonly used. Chemotherapy was performed as long as possible, and tumor recurrence and adverse events that prevent the continuation of chemotherapy were addressed through dose reduction or regimen modification. As the 2nd or 3rd line chemotherapy, PTX and CPT-11 were generally used. The actuarial survival rates of patients who underwent hepatectomy (1-year survival, 88.9 %; 3-year survival, 29.6 %) were significantly ($p = 0.024$) higher than those of patients who did not (1-year survival, 52.0 %; 3-year survival, 9.0 %), as shown in Fig. 1a.

We further examined the number and maximum size of tumors in patients with synchronous LM. All nine hepatic resections were performed for metastases numbering ≤ 3 (3 lesions in 1, 2 lesions in 2, and 1 lesion in 6) and their maximum diameters were <3 cm. Among patients who did not undergo hepatic resection, 8 cases with such metastatic conditions (3 lesions in 1, 2 lesions in 2, and 1 lesion in 5) were deemed to be surgical candidates retrospectively. Survival curves of these 17 patients are shown in Fig. 1b. Under these comparable conditions, the survival rate of patients who underwent resection was significantly ($p = 0.009$) higher than that of patients who did not undergo resection (1-year survival, 37.5 %; 3-year survival, 0 %).

Metachronous liver metastases

The clinicopathological features of the 73 patients with metachronous LM are shown in Table 2. The median

Table 1 Clinicopathological features of patients with synchronous liver metastases

	Total ($n = 34$)	Hepatectomy ($n = 9$)	Non-hepatectomy ($n = 25$)	p value
Age: average (range)	67.2 (46–87)	66.0 (51–77)	67.6 (46–87)	0.394
Sex				0.105
Male	25 (73.5 %)	9	19	
Female	9 (26.5 %)	0	6	
Tumor marker				
CEA				0.112
<10.0 ng/ml	23 (67.6 %)	8	15	
≥10.0 ng/ml	11 (32.4 %)	1	10	
CA19-9				0.339
<50 U/ml	22 (64.7 %)	7	15	
≥50 U/ml	12 (35.3 %)	2	10	
Depth of invasion				0.581
T1-3	10 (29.4 %)	2	8	
T4	24 (70.6 %)	7	17	
Lymph node metastases				0.458
Positive	29 (85.3 %)	7	22	
Negative	5 (14.7 %)	2	3	
Liver metastasis				<0.001
Number ≤3 and diameter <3 cm				
Yes	17 (50.0 %)	9	8	
No	17 (50.0 %)	0	17	

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9

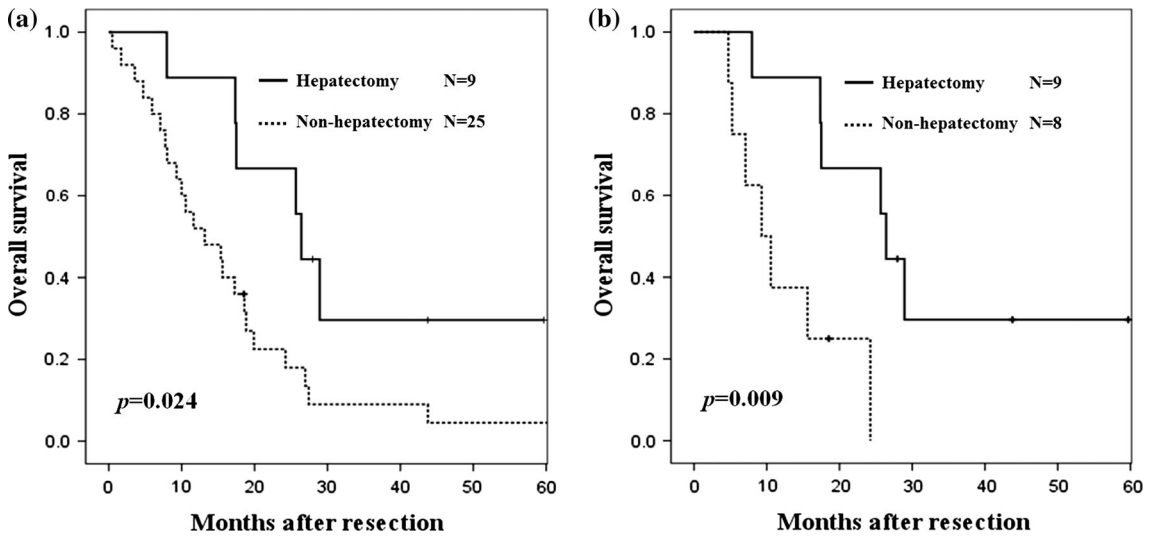

Fig. 1 **a** Survival curves of patients with synchronous liver metastases. Actuarial survival rates of patients who underwent hepatectomy (1-year survival, 88.9 %; 3-year survival, 29.6 %) were 88.9 and 29.6 %, respectively, were significantly ($p = 0.024$) higher than those of patients who did not (1-year survival, 52.0 %; 3-year survival, 9.0 %). **b** Survival curves of patients with synchronous liver metastases numbering ≤3 with maximum diameters <3 cm. Actuarial survival rates of patients who underwent hepatectomy were significantly ($p = 0.009$) higher than that of patients who did not undergo resection (1-year survival, 37.5 %; 3-year survival, 0 %)

follow-up period after diagnosis was 9.7 months (range 1.1–205.7). Five hepatic resections (anatomic resection in 1 and limited resection in 4) were performed in 4 patients, whereas the remaining 69 patients received chemotherapy (systemic in 30 and hepatic artery infusion in 27) or the best supportive care. Again, there were no significant

Table 2 Clinicopathological features of patients with metachronous liver metastases

	Total ($n = 73$)	Hepatectomy ($n = 4$)	Non-hepatectomy ($n = 69$)	p value
Age: average(range)	67.2 (44–89)	59.8 (47–71)	68.3 (44–89)	0.797
Sex				0.479
Male	61 (83.6 %)	4	57	
Female	12 (16.4 %)	0	12	
Tumor marker				
CEA				
<10.0 ng/ml	62 (84.9 %)	4	58	0.603
≥ 10.0 ng/ml	11 (15.1 %)	0	11	
CA19-9				
<50 U/ml	55(76.4 %)	3	53	0.185
≥ 50 U/ml	17 (23.6 %)	1	16	
Depth of invasion				0.413
T1-3	50 (68.5 %)	2	48	
T4	23 (31.5 %)	2	21	
Lymph node metastases				0.107
Positive	59 (80.8 %)	2	57	
Negative	14 (19.2 %)	2	12	
DFI after gastrectomy (months)	16.7(1.0–88.3)	34.5	15.7	0.016
Liver metastasis				0.020
Number ≤3 and diameter <3 cm				
Yes	28 (38.4 %)	4	24	
No	45 (61.6 %)	0	45	

CEA carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *DFI* disease-free interval

differences between patients who underwent hepatectomy and those who did not, in terms of age, sex, tumor markers measured at the time of diagnosis, serosal involvement of gastric cancer and LN metastases from the primary tumor evaluated at gastrectomy. The median DFI from gastrectomy to the first detection of liver lesions of 34.5 months in patients who underwent resection was significantly ($p = 0.016$) longer than that of 15.7 months in patients who did not undergo resection. After hepatectomy, all 4 patients were treated with fluorouracil-based chemotherapy (S-1 alone in 1 and S-1 plus cisplatin in three cases). As shown in Fig. 2a, the actuarial survival rate of patients who underwent hepatectomy was significantly ($p = 0.003$) higher than that of patients who did not. There was no significant difference in survival rate after hepatectomy between those with synchronous LM and those with metachronous LM ($p = 0.135$).

Similar to the cases of synchronous metastases, all 5 hepatic resections for metachronous LM were performed for tumors numbering ≤3 (3 lesions in 1, and 1 lesion in 4) with diameters <3 cm. Among patients who did not undergo hepatic resection, 24 cases with such metastatic conditions (3 lesions in 4, 2 lesions in 11, and 1 lesion in 9) were deemed to be surgical candidates retrospectively. Survival curves of these 28 patients are shown in Fig. 2b. Under these comparable conditions, the survival rate of patients who underwent resection was significantly ($p = 0.016$) higher than that of patients who did not undergo resection.

In addition, we examined the prognostic factors of 73 patients using stepwise Cox proportional hazard model. Hepatectomy was the only determinant that had a significant ($p = 0.001$) effect on survival, and DFI did not significantly affect the survival rate after diagnosis of metachronous LM ($p = 0.170$).

Outcome after hepatectomy

Cancer recurred in 9 (69.2 %, 7 synchronous and 2 metachronous) of 13 patients between 2 and 30 months after hepatic resection, most commonly in the remnant liver with multiple bilobar distribution ($n = 7$). Only 1 patient with solitary recurrence underwent re-hepatectomy 7 months after the initial resection of metachronous LM. One patient failed to be treated due to rapid growth of the recurrent tumors. Eight patients, including a patient who underwent transarterial chemoembolization, received further chemotherapy mainly using cisplatin, paclitaxel, docetaxel, and CPT-11. A patient who received re-hepatectomy and

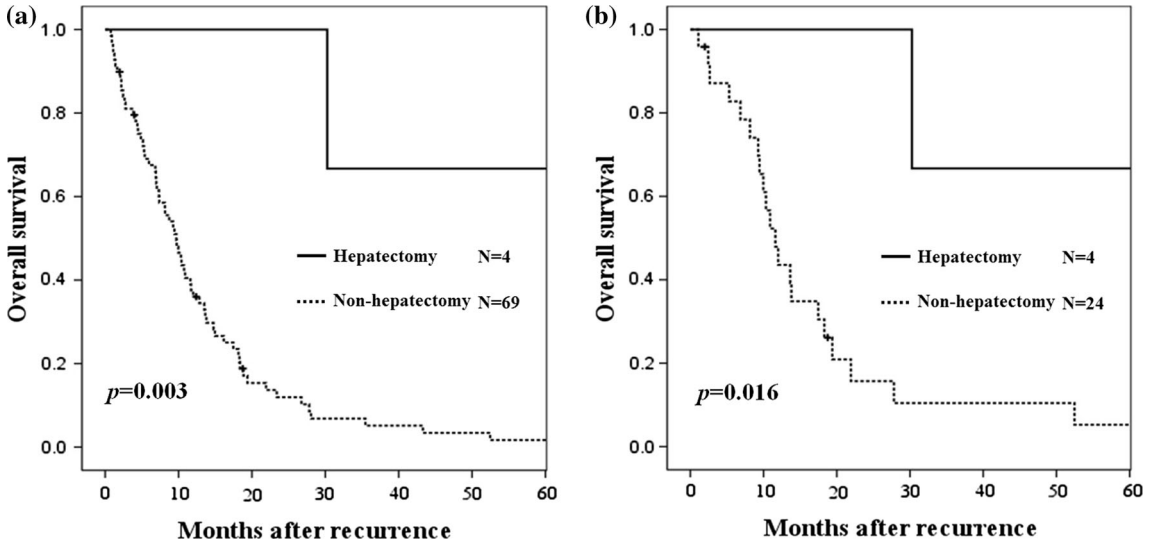

Fig. 2 **a** Survival curves of patients with metachronous liver metastases. Actuarial survival rates of patients who underwent hepatectomy were significantly ($p = 0.003$) higher than those of patients who did not. **b** Survival curves of patients with metachronous liver metastases numbering ≤3 with maximum diameters <3 cm. Actuarial survival rates of patients who underwent hepatectomy were significantly ($p = 0.016$) higher than those of patients who did not undergo resection

all the remaining 4 patients with no hepatic recurrence have survived, with a median DFI of 77.5 months (range 28–105.2 months).

Discussion

We reported a retrospective analysis of 107 patients with gastric cancer metastases confined to the liver without other non-curative factors. The survival rate of patients who underwent hepatectomy was significantly higher than that of patients who also had ≤3 tumors with diameters <3 cm but did not undergo resection. These results emphasize that LM from gastric cancer that are detected under such conditions should be treated by surgical resection.

Hepatic resection is widely accepted as a potentially curative treatment for colorectal LM, with resection rates of 17–46 % [20–22] and reported 5-year survival rates of 40–58 % [23–27]. In contrast, relatively few patients with gastric cancer LM are ideal candidates for hepatectomy, and therefore, the role of surgery is still unclear. Ochiai et al. reported that hepatic resection should be attempted in patients with no primary gastric cancer serosal invasion [11]. In terms of the number of tumors, some authors reported that solitary metastasis was a significant determinant of a favorable prognosis after hepatic resection [12, 14]. Thus, no absolute surgical indications exist to date. In our hospital, only 13 (12.1 %) out of 107 patients with synchronous or metachronous LM, and no other synchronous distant metastases or recurrent lesions in metachronous disease, underwent 14 hepatic resections. All hepatectomies had been performed for cases with ≤3 metastatic tumors individually measuring <3 cm, and they resulted in significantly better outcomes than the 32 cases that underwent non-surgical treatment with comparable tumor numbers and sizes. These results suggest that surgery for gastric cancer LM confers a better prognosis, and more patients should receive hepatectomy. Our indication of tumor size (<3 cm) for hepatic resection is, however, not obligatory since several studies reported favorable prognosis for the patients with tumors <4–5 cm in maximum diameter [2, 12]. These previous findings suggest that hepatectomy performed in patients with tumors ≥3 cm might have helped prolong their OS.

Regarding the timing of hepatectomy, our study showed no significant difference in survival between synchronous and metachronous LM. Okano et al. reported significantly longer survival in patients with metachronous LM (3-year survival, 60 %) than those with synchronous disease (3-year survival, 18 %)[6]. Similar results showing favorable outcomes in patients with metachronous LM were reported by other authors [9, 28]. In contrast, Sakamoto et al. reported that the survival rates of patients with synchronous and metachronous metastases were comparable [12]. In our series, 2 out of 4 patients who survived for more than 3 years had synchronous LM. Thus, synchronous gastric cancer LM is not necessarily a contraindication for hepatic resection at the time of gastrectomy. In metachronous LM, short DFI has been

proposed as a poor survival factor [22]. Indeed, in our series, the median DFI of 4 patients who underwent resection was significantly longer than that of 69 unresected patients, including 24 possible candidates for hepatectomy. However, this low resection rate in metachronous LM maybe influenced by the preconceptions of surgeons. Multivariate analysis using stepwise Cox proportional hazard model revealed that hepatectomy was the only determinant that had a significant effect on survival after diagnosis of metachronous LM, whereas DFI was not. These results demonstrate that short DFI after radical gastrectomy should not be regarded as an unfavorable prognostic factor, and surgeons should not hesitate to perform hepatectomy for metachronous LM.

We realize that the prognosis of patients who received surgical treatment for gastric cancer LM is still unsatisfactory compared with colorectal LM, which has reported 5-year survival rates of 40–58 % [23–27]. In our series, cancer recurred in approximately 70 % of patients after hepatic resection, particularly in the remnant liver. Recurrent tumors in both lobes were more frequent, suggesting that liver recurrence develop from multiple metastatic foci of primary disease and not from intrahepatic metastasis lesions. It should be recognized that the number and size of liver tumors as discussed here might vary with the differing accuracy of examinations and follow-up intervals after surgery. In addition, indications for liver resection will change with the development of other non-surgical treatments. In fact, the indications for hepatectomy in colorectal LM patients have expanded after the development of new chemotherapy drugs and regimens [29, 30]. Likewise, several perioperative protocols have been reported to decrease tumor size and stage and improve survival of patients with advanced gastric cancer [31, 32]. We hope more effective adjuvant or neoadjuvant treatments will increase the opportunity for hepatectomy for gastric cancer LM, resulting in long-term cure.

In conclusion, the present retrospective study strongly implied that hepatic resection for patients with ≤ 3 metastases with diameters <3 cm in the liver may offer superior survival compared with non-surgical treatment. Surgical resection for such candidates would be beneficial even when metastases are detected synchronously or within a short period after radical gastrectomy.

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