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ORIGINAL ARTICLE

Oncological outcomes after hepatic resection and/or surgical microwave ablation for liver metastasis from gastric cancer

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Summary *Background:* Indications and efficacy of surgical treatment for liver metastases from gastric cancer (LMGCs) remain controversial. This retrospective study was designed to clarify the benefits of surgical treatment and identify prognostic factors.
Methods: Between December 1997 and December 2015, 34 consecutive patients underwent hepatic resection and surgical microwave ablation for synchronous or metachronous LMGCs at our institution. We analyzed their cumulative overall survival (OS) and recurrence-free survival (RFS) rates and clinical parameters to identify predictors of prognosis.
Results: Of the 34 patients, 14 underwent hepatic resection, 13 underwent surgical microwave ablation, and 7 underwent hepatic resection combined with surgical microwave ablation. Their OS rates were 1-year: 84.4%, 3-year: 38.6%, and 5-year: 34.7%; and their RFS rates were 1-year: 38.5%, 3-year: 28.0%, and 5-year: 28.0%. OS did not significantly vary among the surgical procedures. In multivariable analysis, positive of both CEA and CA19-9 were independent predictors of poor survival (hazard ratio [HR] 4.51; $P = 0.049$) and early recurrence (HR 5.70; $P = 0.047$).
Conclusions: Both hepatic resection and surgical microwave ablation for LMGCs are effective and can improve survival in selected patients.

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1. Introduction

Gastric cancer is the third most common cause of cancer-related death worldwide,[1] and the second leading cause of cancer death in Japan.[2] Owing to early detection through screening and appropriate R0 surgery with D2 lymph node dissection and perioperative chemotherapy, the reported 5-year overall survival (OS) for early-stage gastric cancer is now over 90%.[3] However, the prognosis of patients with distant metastases, such as liver metastases, extensive lymph node metastases and peritoneal seeding, show poor prognosis, with a 3-year OS rate below 10%.[4–7] The liver is a common site of distant metastasis from gastric cancer, and liver metastases from gastric cancer (LMGCs) develop in 5–14% of all patients with gastric cancer.[8–10] LMGCs are often detected as multiple intrahepatic nodules; they can coexist with extrahepatic disease including extensive lymph node metastases and peritoneal seeding, which are generally considered to be a systemic disease, for which systemic chemotherapy is the standard treatment.[11,12] However, its prognosis is unfortunately poor.

However, several previous studies have reported 5-year OS rates 0–42% after curative hepatic resection for resectable LMGCs.[13–17] The Guidelines Committee of the Japan Gastric Cancer Association recently reconsidered the treatment of potentially resectable distant metastasis disease.[18] Furthermore, some papers have reported that local thermal ablation, such as microwave ablation and radiofrequency ablation, was safe and effective for selected LMGCs.[19,20] This study evaluated outcomes of surgical procedures, including hepatic resection and surgical microwave ablation, and analyzed factors that influence survival in patients who undergo surgery for LMGCs.

2. Methods

2.1. Patients and diagnosis

From December 1997 to December 2015, 34 consecutive patients underwent hepatic resection and surgical microwave ablation for synchronous or metachronous LMGCs in the Department of Hepato-Biliary-Pancreatic Surgery at Kyushu Medical Center. All 34 patients had curative resection (R0 resection) for primary gastric cancer. Of the 34 patients, 14 underwent hepatic resection, 13 underwent surgical microwave ablation (microwave coagulo-necrotic therapy [MCN]), and 7 underwent hepatic resection combined with MCN. The surgical indications for LMGCs as follows: (1) histologically confirmed primary gastric cancer, (2) no unresectable sites other than liver metastases, (3) eligible for radical surgical treatment, and (4) good general health condition. LMGCs in each patient were preoperatively diagnosed by several imaging modalities, including ultrasonography, dynamic computed tomography and/or enhanced magnetic resonance imaging, with the final diagnosis of LMGC confirmed by pathologic examination of tumor biopsy and/or resected specimens. Preoperative Fluorodeoxyglucose Positron.

Emission Tomography scans were obtained at the discretion of the treating physicians in a few patients. Tumor markers higher than the upper limits of normal range (5 ng/ml for CEA and 40 U/ml for CA19-9 at our institution) were defined as positive markers. Clinicopathological characteristics were classified according to the Japanese Classification of Gastric Carcinoma (3rd English Edition).[11] Synchronous liver metastases were defined as those detected before or during surgery or within 3 months of primary tumor resection. This retrospective study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies of the Ministry of Health, Labor and Welfare in Japan, and its protocol was approved by the Ethics Committee on Clinical Investigations of Kyushu Medical Center. Written informed consent was obtained from all patients.

2.2. Treatments

Treatment decisions were made on an individual basis, considering the patient's performance status, tumor location, tumor size, and timing of metastasis. If curative resection of LMGCs was feasible, allowing adequate hepatic reserve, hepatic resection was preferred. When metastases were smaller than 3 cm and ineligible for hepatic resection because of comorbidities and metastasis-specific features, or when patients refused hepatic resection, MCN was considered for the treatment of LMGCs. As some patients tended to prefer the less invasive treatment to the more aggressive resection, they were treated by MCN even when the hepatic lesion was resectable. Decisions were also influenced by the preference of the doctors in charge. Both hepatic resection and MCN were performed by the same surgical team of dedicated liver surgeons led by at least 1 consultant specialist. All MCN procedures were performed as reported.[21–23] Microwaves at a frequency of 2450 MHz were generated by a Microtaze generator (Alfresa Pharma, Osaka, Japan). The types of hepatic resection were classified according to the Brisbane 2000 classification.[24]

2.3. Statistical analysis

Continuous variables were compared using unpaired t tests and categorical variables using Fisher's exact test or the χ^2 test. OS was defined as the interval from hepatic surgery to death or the date of the last or most recent follow-up visit. Recurrence-free survival (RFS) was defined as the interval between the hepatic surgery and the date when recurrence was detected by radiological examination. Survival curves were calculated by the Kaplan–Meier method and compared by the log-rank test. A Cox proportional hazards model was used for multivariate analyses of factors related to survival and recurrence. $P < 0.05$ was considered significant (two-tailed tests). All statistical analyses were performed using the JMP 12 software package (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Clinicopathological characteristics of the 34 patients are presented in Table 1. They included 24 men and 10 women,

Table 1 Demographic and clinical characteristics of patients.

Variable	No. of patients (n = 34)
Age (years)[a]	66 (42–84)
Sex	
Male	24
Female	10
Type of gastrectomy	
Total gastrectomy	9
Distal gastrectomy	24
Other	1
Pathological T classification of primary tumor (pT)	
pT1, pT2	19
pT3, pT4	12
Pathological N classification of primary tumor (pN)	
pN0	6
pN1, pN2, pN3	26
Histological differentiation of primary tumor	
Differentiated	18
Undifferentiated	10
Lymphatic invasion of primary tumor	
ly0/ly1	11
ly2/ly3	19
Venous invasion of primary tumor	
v0/v1	14
v2/v3	16
Timing of hepatic metastasis	
Synchronous	15
Metachronous	19
Maximum size of hepatic tumors (mm)[a]	36 (5–80)
Number of hepatic tumors[a]	2 (1–9)
1	18
2	8
3	2
>4	6
Operative method	
Hepatectomy	14
MCN	13
Hepatectomy + MCN	7
Adjuvant chemotherapy after liver surgery	
Yes	10
No	24

MCN, microwave coagulo-necrotic therapy; hepatectomy + MCN, simultaneous hepatectomy and MCN.
[a] values are shown as median (range).

with a median age of 66 years, of whom 15 patients (44.1%) were diagnosed with synchronous metastasis and underwent simultaneous liver surgery and gastrectomy, and 19 patients (55.9%) with metachronous metastasis. The median tumor size was 3.6 cm (range: 0.5–8.0 cm). The number of hepatic lesions was one in 18 patients (52.9%), two in 8 (23.6%), three in 2 (5.9%) and four or more in 6 patients (17.6%). Of the 34 patients, 14 (41.2%) underwent hepatic resections, 13 (38.2%) underwent MCN, and 7 (20.6%) underwent hepatic resection with MCN. Table 2 shows the median tumor sizes and numbers of tumors for each surgical procedure, which

Table 2 Status of metastatic hepatic tumors by surgical procedure.

	No. of patients	Maximum size of hepatic tumors (mm)[a]	Number of hepatic tumors[a]
Hepatectomy	14	42 (5–80)*	1 (1–2)*
MCN	13	22 (9–51)*	2 (1–7)*
Hepatectomy + MCN	7	32 (9–51)	3 (2–9)*

MCN, microwave coagulonecrotic therapy; hepatectomy + MCN, simultaneous hepatectomy and MCN.
*$P < 0.05$ (unpaired t tests).
[a] Values are shown as median (range).

both varied significantly between hepatic resection and MCN. Among patients who received hepatic resections, 7 patients (33.3%) had hemihepatectomies, 6 patients (28.6%) had sectionectomies, 2 patients (9.5%) had segmentectomies, and 6 patients (28.6%) had wedge resections. The major morbidity rate (Clavien–Dindo classification grade III or higher) was 2.9% (1/34) and the mortality rate was 0%. Only one patient, who received a simultaneous hepatic resection and MCN, suffered a liver abscess that required drainage after a segmentectomy (segment 6). Perioperative systemic chemotherapy was administered in 13 patients (38.2%), 3 patients (8.8%) received neoadjuvant and 10 patients (29.4%) received adjuvant therapy.

3.2. Patient prognosis

The median follow-up time was 29.4 months (range: 2.2–170.4 months). The OS rates after surgery were 1-year: 84.4%, 3-year: 38.6%, and 5-year: 34.7% (Fig. 1); and the RFS rates were 1-year: 38.5%, 3-year: 28.0%, and 5-year: 28.0% (Fig. 2). The OS rates for patients treated with hepatic resection were 1-year: 84.6%, 3-year: 51.3%, and 5-year: 51.3%; for patients treated with MCN were 1-year: 91.7%, 3-year: 37.5%, and 5-year: 25.0%; and for patients treated with hepatic resections + MCN were 1-year: 71.4%,

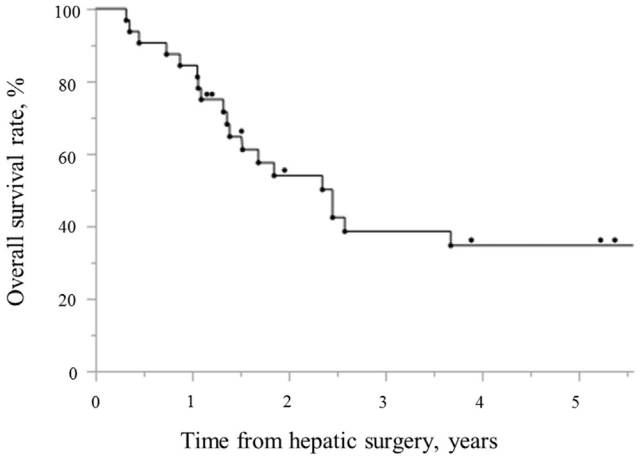

Figure 1 Kaplan–Meier analysis of overall survival among 34 patients who underwent hepatic surgery for liver metastases of gastric cancer. Their 5-year survival rate was 34.7%.

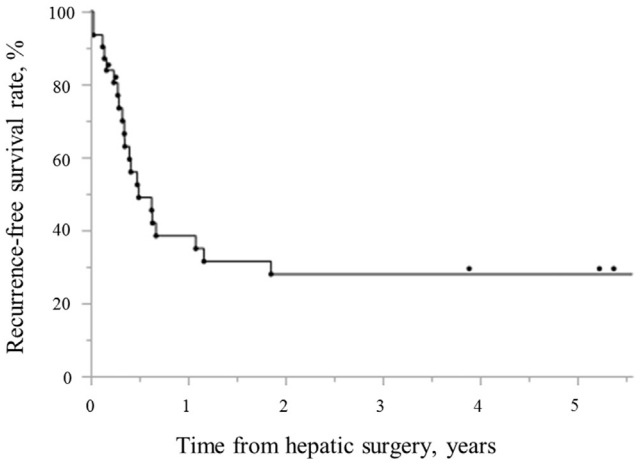

Figure 2 Kaplan–Meier analysis of recurrence-free survival among 34 patients who underwent hepatic surgery for liver metastases of gastric cancer. Their 5-year recurrence-free survival rate was 28.0%.

and 3-year: 19.5%; with no significant survival differences among the surgical procedures (P = 0.213; Fig. 3). Of the 34 patients, 7 patients survived without recurrence for more than 5 years after surgery, including 6 patients who underwent hepatic resections for single hepatic lesions, and 1 patient who received MCN for 7 bilobar tumors.

3.3. Recurrence patterns

Recurrences were detected in 24 patients (70.6%) during follow-up, of whom 21 patients died from their recurrent disease. The predominant recurrence site was the liver, in 17 patients (70.8%), followed by lymph nodes in 2 (8.3%), lung in 2 (8.3%) and peritoneum in 1 (4.2%). The recurrence site was unknown in 2 patients. Among the 24 patients with recurrences, 18 patients (75.0%) underwent treatment for recurrent lesions, including chemotherapy in 11 patients (systemic chemotherapy in 7, and hepatic arterial infusion in 4), and surgery in 7 patients (MCN in 5, and partial hepatectomy in 2).

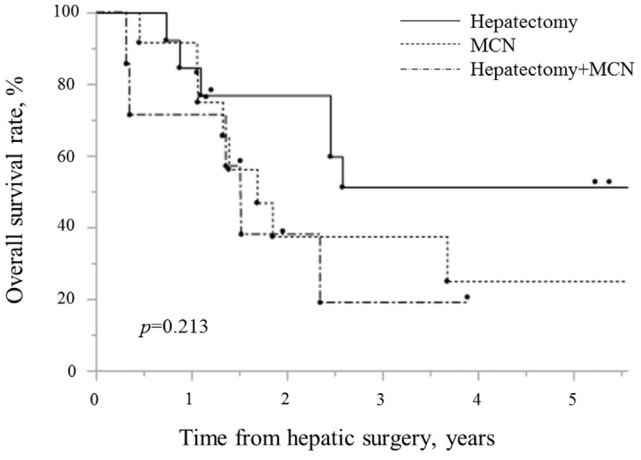

Figure 3 Kaplan–Meier analysis of overall survival by the surgical procedures. There was no significant difference among the surgical procedures ($P = 0.213$).

3.4. Prognostic factors

Factors associated with OS and RFS were evaluated by univariate and multivariate analyses. Univariate analysis for OS revealed that lymphatic invasion, multiple hepatic tumors, and positive of both CEA and CA19-9 were significantly associated with poor survival. Univariate analysis for RFS revealed that lymphatic invasion, positive of both CEA and CA19-9 and surgery procedures were significantly associated with earlier recurrence (Table 3). In multivariate analysis identified positive of both CEA and CA19-9 was the only independent predictor of poor survival (hazard ratio [HR]: 4.51; 95% confidence interval [95% CI]: 1.01–20.0; P = 0.049) and early recurrence (HR: 5.70; 95% CI: 1.01–30.8; P = 0.047; Table 4).

4. Discussion

In the present study, we investigated the significance of surgical treatment, such as hepatic resection and MCN, for LMGCs. Our results demonstrated that hepatic resection and MCN for LMGCs showed acceptable morbidity and favorable long-term outcomes. The 5-year OS and RFS were 34.7% and 28.0%, respectively, although patients were highly selected. Systemic chemotherapy is the standard treatment for most patients with LMGCs.[11,12] However, Glimelius et al reported patients with LMGCs had a median OS of less than 1 year with chemotherapy alone and Yoshida et al reported a 5-year survival rate of only 1.7% in patients with LMGCs treated by systemic chemotherapy alone; although these studies included not only resectable diseases, but all patients with LMGCs.[25,26] Our results suggest that surgical treatment should be strongly considered for surgery-eligible patients with LMGCs.

In this study, not only hepatic resection but MCN led to favorable perioperative and long-term outcomes. Those findings indicate the feasibility of applying these modalities in selected patients. Local thermal ablation procedures, such as microwave ablation and radiofrequency ablation, are reportedly safe and effective for selected LMGCs.[19,20] Operative microwave ablation, termed microwave coagulonecrotic therapy (MCN), has been used in Japan since 1988. Saitsu et al[27] started MCN from 1988 and first reported its efficacy for HCC in 1991. We have reported on the feasibility and safety of MCN not only for HCC, but also for metastatic liver tumors from colorectal cancer and breast cancer.[21–23,28] In this study, hepatic resection was preferred for larger metastases or metastases located in regions suitable for hepatectomy, such as liver surface or edges, whereas MCN was performed in patients with multiple tumors, in regions where hepatic resection would have been difficult, patients whose high operative risk was associated with poor general condition, and as well as for patients who refused hepatic resections. Because of the lack of consensus on patient selection criteria, practical indications for properly selecting patients for individual treatment modalities are yet to be established. However, we believe that these two modalities are complementary to each other, and one should

Table 3 Univariate analyses of overall and recurrence-free survival by clinicopathological factors.

Variable	Overall survival		Recurrence-free survival	
	Hazard ratio	*P*	Hazard ratio	*P*
Serosal invasion of primary tumor	2.56 (0.97–6.87)	0.057	2.12 (0.79–5.57)	0.129
Lymph node involvement	1.71 (0.56–7.40)	0.370	1.16 (0.37–5.05)	0.812
Histological grade (poorly differentiated)	1.40 (0.47–3.80)	0.522	1.27 (0.42–3.52)	0.656
Lymphatic invasion grade 2/3	2.81 (1.02–7.80)	0.046	3.17 (1.12–9.10)	0.029
Venous invasion grade 2/3	0.92 (0.34–2.61)	0.876	0.76 (0.27–2.19)	0.604
Synchronous metastasis	0.84 (0.31–2.11)	0.720	0.70 (0.28–1.68)	0.433
Size of largest hepatic tumor ≥3 cm	1.72 (0.67–4.69)	0.256	1.44 (0.59–3.58)	0.416
Multiple hepatic tumor	2.74 (1.08–7.86)	0.034	2.31 (0.97–5.58)	0.059
CEA ≥5 ng/ml and CA19-9 ≥40 U/ml	3.65 (1.14–10.1)	0.031	2.75 (0.89–7.18)	0.050
Hepatic surgery (MCN or Hepatectomy + MCN)	2.26 (0.87–6.55)	0.093	3.01 (1.24–8.81)	0.015
Adjuvant chemotherapy after liver surgery	1.74 (0.70–4.52)	0.232	1.45 (0.61–3.49)	0.396

CEA, carcinoembryonic antigen; CA, carbohydrate antigen.
MCN, microwave coagulo-necrotic therapy; hepatectomy + MCN, simultaneous hepatectomy and MCN.

be selected over the other after considering their technical limitations and patient factors.

Several previous studies have described many favorable prognostic factors after hepatic resection for LMGCs, including small tumor size, small number of liver metastases, unilobar lesions, negative margin (R0) resection, and absence of serosal invasion of the primary tumor, lymph node metastasis or extrahepatic disease.[13–18] The number of liver metastases is often described as an especially important prognostic factor, whereas solitary liver metastasis is a favorable prognostic factor. Our univariate analyses also identified solitary liver metastasis as a favorable prognostic factor. Similarly, univariate and multivariate analyses in the present study showed positive of both CEA and CA19-9 to be independent predictors of shorter survival and early recurrence. Patients with positive of both CEA and CA19-9 may be poor candidates for hepatic surgery.

Table 4 Multivariate Cox proportional hazards analysis of overall and recurrence-free survival.

	Hazard ratio	*P*
Overall Survival		
Serosal invasion of primary tumor	2.62 (0.82–8.64)	0.102
Lymphatic invasion grade 2/3	1.88 (0.48–6.97)	0.599
Multiple hepatic tumor	1.04 (0.12–8.87)	0.969
CEA >5, CA19-9 >40	4.51 (1.01–20.0)	0.049
Hepatic surgery (MCN or Hepatectomy + MCN)	1.06 (0.11–12.0)	0.962
Recurrence-free Survival		
Lymphatic invasion grade 2/3	2.55 (0.81–8.33)	0.109
Multiple hepatic tumor	2.77 (0.12–25.2)	0.440
CEA ≥5 ng/ml and CA19-9 ≥40 U/ml	5.7 (1.00–30.8)	0.047
Hepatic surgery (MCN or Hepatectomy + MCN)	4.76 (0.20–55.9)	0.277

CEA, carcinoembryonic antigen; CA, carbohydrate antigen.
MCN, microwave coagulo-necrotic therapy; hepatectomy + MCN, simultaneous hepatectomy and MCN.

Further analyses with a larger population are necessary to confirm the results.

It should be emphasized that about 60% of the recurrences developed within 1 year. The most frequent pattern of recurrence was intrahepatic; 17 (70.8%) of the 24 recurrent patients suffered liver recurrences. This might indicate a high incidence of occult micrometastases at the time of hepatic surgery, which highlights the importance of controlling the liver recurrence rate after hepatic surgery. However, no established treatment strategy is available for preventing recurrence in the liver remnant, and the efficacy of neoadjuvant or adjuvant chemotherapy in patients with LMGCs has not been fully evaluated.[8,9,29,30] We also did not find any effect of adjuvant chemotherapy after liver surgery in our analysis, possibly because this is a retrospective study and adjuvant chemotherapy is generally administered to patients with aggressive metastasis. Nonetheless, considering the potentially aggressive character of this disease and its high recurrence rate, it seems rational to administer neoadjuvant or adjuvant chemotherapy. As chemotherapy for gastric cancer has improved over the past decades, appropriate neoadjuvant or adjuvant chemotherapy may provide significant benefits to future patients.

The present study had some limitations. First, this study was a retrospective analysis that used a single-center prospective database. It also lacked statistical power because of its small sample size, although recruiting enough eligible patients for a prospective study would be difficult. Further studies, such as multicenter, well-designed, large-scale, case-matched studies, are needed to evaluate relative outcomes of hepatic surgery for LMGCs more precisely. Second, this study included two treatment modalities, hepatic resection and surgical microwave ablation. As treatment was assigned by the decision of each individual patient, some confounding factors, such as the feasibility of resection for multiple metastases and the lower efficacy of MCN for larger tumors, might influence survival. Third, as the study cohort included relatively few patients who met the eligibility criteria during more than 15 years of this study in a single institution, this study included some

patients with short follow up periods. Greater patient accumulation and follow up are needed to demonstrate the true benefits of hepatic surgery for LMGCs.

In conclusion, both hepatic resection and MCN are safe and effective for LMGCs, and can provide reasonable short- and long-term outcomes. Surgeons should consider patients' characteristics and tumor conditions in selecting candidates for these procedures. Although systemic chemotherapy is a standard treatment for LMGCs, we believe that hepatic resection and MCN could offer longer survival.

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None.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2017.09.005.

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