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Intestinal-type histology is associated with better prognosis in patients undergoing liver resection for gastric/esophagogastric-junction liver metastasis

Daisuke Ito[1], Yoshikuni Kawaguchi[1,*], Hiroharu Yamashita[2], Junichi Arita[1], Nobuhisa Akamatsu[1], Junichi Kaneko[1], Yoshihiro Sakamoto[1], Norihiro Kokudo[3], Yasuyuki Seto[2], Kiyoshi Hasegawa[2,*]

[1] Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan;
[2] Gastrointestinal Surgery Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan;
[3] Department of Surgery, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The indication for resection of gastric/esophagogastric-junction liver metastasis (GELM) has yet to be established. This study aimed to investigate prognostic factors in patients undergoing GELM resection. From 2001 to 2015, 31 consecutive patients underwent resection for GELM; and factors for poor prognosis were evaluated. Of the 31 patients, 23 (74.2%) developed multiple liver metastases. The histology of gastric cancer was intestinal-type adenocarcinoma in 21 patients (67.7%). Median overall survival (OS) was 3.2 years. The 1-, 3-, and 5-year OS rates were 92.8%, 56.2%, and 42.2%, respectively. The 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 58.5%, 31.3%, and 31.3%, respectively. Multivariate analysis indicated that intestinal-type adenocarcinoma was associated with a significantly lower risk of OS (hazard ratio [HR], 0.26; p =0.022) and RFS (HR, 0.25; p = 0.008). In multiple logistic regression analysis, intestinal-type adenocarcinoma (odds ratio, 0.14; p = 0.012) reduced incidence of extra-hepatic recurrence after GELM resection. In conclusion, GELM resection in patients with intestinal-type histology is preferable because intestinal-type adenocarcinoma is associated with better prognosis and a lower incidence of extra-hepatic recurrence than diffuse/other-type adenocarcinoma.

Keywords: Gastric liver metastasis, gastric/esophagogastric-junction liver metastasis, the intestinal-type adenocarcinoma, liver resection

Introduction

The prognosis of gastric cancer has improved over the last two decades, but it remains the third highest cause of cancer-related death worldwide (1-3). Surgical resection of the stomach is the mainstay of management for resectable gastric cancer, but cumulative recurrence rates still remain high; 79% within 2 years of operation (*1*). Liver is one of the major organs that develop gastric cancer metastases, with an incidence of 4-34% (*2*).

Although chemotherapy is regarded as the standard treatment for gastric/esophagogastric-junction liver metastases (GELMs), several retrospective studies have reported favorable prognosis for liver resection concerning GELM (*3-7*). These studies demonstrated the following risk factors for poor prognosis: number and maximum size of liver metastases; R1/R2 resection; synchronous metastases; primary tumor stage pT4; and the presence of other distal metastases. However, the study periods were mainly limited before the year 2000. The appropriate indication criteria for GELM resection are still debatable because effective chemotherapies for gastric cancer were introduced in the early 2000s. Additionally, factors for poor prognosis regarding liver resection for GELM are not well established, as compared with those for colorectal liver metastases.

The aim of this study was to investigate prognostic factors for GELM by evaluating patients who underwent liver resection for GELM.

Materials and Methods

Indication for liver resection for GELMs

Liver resection was indicated for three or fewer GELMs without metastases at other sites, based on previous reports (*6*). In patients with four or more GELMs, preoperative chemotherapy was performed. In cases where no extra-hepatic gastric metastases occurred after chemotherapy, liver resection was indicated. Simultaneous resection of the stomach and GELM was performed for synchronous GELMs, when they

were easily removed using limited non-anatomic liver resection. The final surgical procedures were planned to resect all GELMs to secure negative histologic margins.

Definition of histology

Histopathological classification of gastric cancer was classified into three groups, intestinal type, diffuse type, and other type, based on the criteria of Japanese Classification of Gastric Cancer third edition. Intestinal-type adenocarcinoma was defined as a tumor with glandular architecture, resembling colonic carcinoma, whereas diffuse-type adenocarcinoma was defined as a tumor composed of solitary or small clusters of cells, and lacking glandular structures. Gastric cancer with uncommon variant was classified as other type (*8*).

Patients

Between January 2001 and December 2015, 31 consecutive patients underwent liver resection for GELM at the University of Tokyo Hospital. The clinical records of these patients were retrospectively reviewed from a prospectively maintained database. Patient characteristics are summarized in Table 1. All operations were performed after obtaining informed consent from each patient, and all aspects of the procedures were conducted according to the principles expressed in the Declaration of Helsinki. In the preparation of this study, all efforts have been made to protect patient privacy and anonymity. The study was approved by the institutional review board at the University of Tokyo (2158-5).

Preoperative evaluation

The surgical procedure was planned with reference to tumor location, size, and the results of the volumetric analysis. All patients underwent ultrasonography, plain and contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) for the staging of GELM; they underwent chest X-ray, chest CT, gastroscopy, and, if necessary, positron emission tomography-CT for the surveillance of extra-hepatic metastases. Intraoperative tumor surveillance was performed using visual inspection, manual palpation, and intraoperative ultrasonography, and the final surgical procedures were planned to resect all GELMs and secure negative histologic margins.

Surgical procedures

Liver resection was indicated under criteria based on preoperative liver function parameters, such as the presence/absence of uncontrolled ascites, serum bilirubin level, and indocyanine green retention rate at 15 min (*9,10*). Non-anatomical limited resection was principally performed to preserve as much liver parenchyma as possible. A major anatomical hepatectomy was performed when liver metastases were adherent to or invading major hepatic vessels and/or were identified in the hemi-liver. After retrieving surgical specimens,

Table 1. Patient characteristics

Variables	Value
Number of patients	31
Patient factor	
Age, years [range]	73 [47-84]
Sex, *n* (%)	
Male	27 (87.1)
Female	4 (12.9)
ASA score, *n* (%)	
1	13 (41.9)
2	18 (58.1)
3	0 (0.0)
BMI, kg/m^2 [range]	21.6 [14.6-30.7]
AFP, U/mL [range]	9.0 [1.0-32.5×10^5]
CEA, ng/mL [range]	9.0 [1.0-5370]
CA19-9, U/mL [range]	100 [69-100]
Primary lesion factors	
Location, *n* (%)	
Esophagogastric junction	4 (12.9)
Upper	5 (16.1)
Middle	11 (35.5)
Lower	11 (35.5)
Maximum size, cm [range]	4.0 [0.4-19]
Histology, *n* (%)	
Diffuse/other-type adenocarcinoma	10 (32.3)
Intestinal-type adenocarcinoma	21 (77.7)
T classification, *n* (%)	
T1	9 (29.0)
T2	3 (9.7)
T3	12 (38.7)
T4	7 (22.6)
N classification, *n* (%)	
N0	15 (48.4)
N1	3 (9.7)
N2	9 (29.0)
N3	4 (12.9)
Liver metastasis factor	
Timing of liver metastases, *n* (%)	
Synchronous	13 (41.9)
Metachronous	18 (58.1)
Tumor number, *n* (%)	
1	23 (74.2)
2-3	5 (16.1)
≥ 4	3 (9.7)
Maximum tumor size, cm [range]	3.1 [0.8-22]
Tumor distribution, *n* (%)	
Unilobular	23 (74.2)
Bilobular	8 (25.8)
Preoperative chemotherapy, *n* (%)	13 (41.9)
Regimen of preoperative chemotherapy, *n* (%)	
S-1 and CDDP	6 (19.4)
CPT-11 and CDDP	2 (6.5)
CPT-11 and MMC	1 (3.2)
S-1 and CDDP and Tmab	2 (6.5)
S-1 and Oxaliplatin	1 (3.2)
CDDP and 5-FU	1 (3.2)
wPTX and Tmab	1 (3.2)

Abbreviations: ASA, American society of anesthesiologists; BMI, body mass index; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; S-1, Tegafur gimestat otastat potassium; CDDP, Cisplatin; CPT-11, Irinotecan; MMC, Mitomycin C; Tmab, Trastuzumab; 5-FU, 5-Fluorouracil; wPTX, weekly Paclitaxel.

the distance between tumors and the cut surface were measured, and the shortest distance from multiple tumors was defined as a surgical margin. When one of the surgical margins was positive, the tumor was defined as having a positive surgical margin. Major hepatectomy was defined as the resection of ≥ 3 contiguous segments, according to Couinaud's classification (*11*).

Statistical analysis

Categorical variables are expressed as numbers (%). Continuous variables are expressed as the median and range. The TNM classification and stage were determined according to the International Union Against Cancer (version 7), when gastrectomy or synchronous gastric and liver resection were performed.

Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Overall survival (OS) was calculated from the day of liver resection in patients undergoing upfront resection, or the initiation of neoadjuvant chemotherapy in patients undergoing neoadjuvant chemotherapy. Loss to follow-up and death without recurrence were censored for the recurrence-free survival (RFS) analysis.

Factors with a p value < 0.05 using the Cox proportional-hazards model were considered as potential risk factors and were further analyzed using a multivariate Cox model. Factors with a p value < 0.05 using logistic regression in univariate analysis were considered as potential predictors and were further analyzed in a multiple logistic regression analysis. Hazard ratios (HR), odds ratio (OR), and 95% confidence interval (CI) were calculated for each factor. The cutoff level for estimated blood loss in our study was set at 1,000 mL, based on previous reports (12). Tumor markers were categorized by institutional upper limits: carcinoembryonic antigen (≥ 5 *vs*. < 5), carbohydrate antigen 19-9 (≥ 37 *vs*. < 37), and α-fetoprotein (≥ 9 *vs*. < 9). Other continuous variables were categorized using the median value. A *p* value < 0.05 was considered to indicate statistical significance.

Statistical analysis was performed using JMP software (version 11.0.6; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The median maximum GELM size was 3.1 (range, 0.8-22.0) cm. Histological outcomes of gastric cancer were intestinal type in 21 patients (67.7%) and diffuse type/other type in 10 patients (32.3%). Liver resection for synchronous and metachronous metastases were performed in 13 (41.9%) patients and 18 (58.1%) patients, respectively. Before liver resection for GELM, 45.2% of patients (*n* = 14) underwent chemotherapy with regimens that mainly included S-1 and/or cisplatin, including three patients (9.7%) who were treated with neoadjuvant chemotherapy.

Intraoperative, postoperative outcomes

Intraoperative and postoperative outcomes are summarized in Table 2. Major hepatectomy was performed in six patients (19.3%). The morbidity rate was 12.9% (*n* = 4) including no Clavien-Dindo III-V complications. Resection rates of R0, R1, and R2 were 71.0 % (*n* = 22), 22.5% (*n* = 7), and 6.5% (*n*

Table 2. Intraoperative and postoperative outcomes

Variables	Value
Number of patients	31
Intraoperative outcomes	
Operative time, min [range]	358 [146-724]
Estimated blood loss, mL [range]	690 [20-3270]
Blood transfusion, *n* (%)	10 (32.3)
Major hepatectomy, *n* (%)	6 (19.3)
Postoperative outcomes	
Morbidity rate	16.1%
Clavien-Dindo classification, *n* (%)	
≥ IIIA	0 (0.0)
I-II	4 (12.9)*
Length of hospital stay, days [range]	14 [5-49]
R1 and R2 resection, *n* (%)	9 (29.0)
Postoperative chemotherapy, *n* (%)	15 (48.4)

*Cholangitis in two patients (6.5%), congestive heart failure in one patient (3.2%), and ileus in one patient (3.2%).

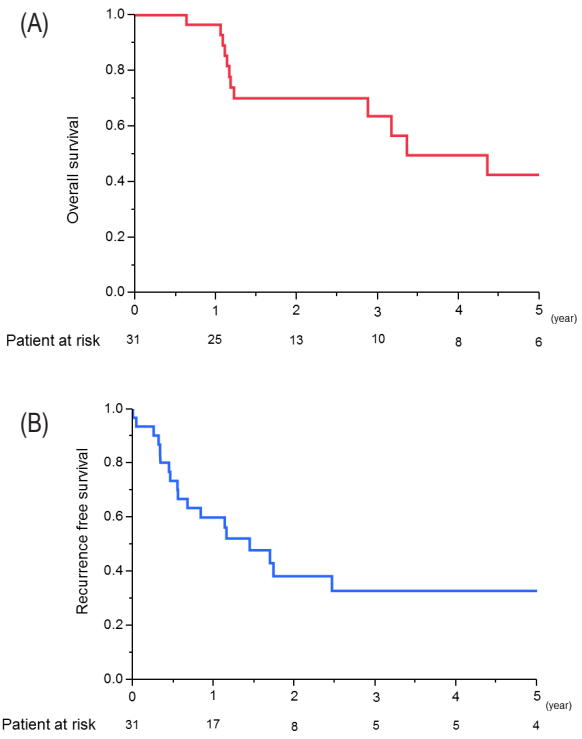

Figure 1. (A) Overall survival in patients with gastric/esophagogastric-junction liver metastasis. (B) Recurrence-free survival in patients with gastric/esophagogastric-junction liver metastasis.

= 2), respectively. Postoperative chemotherapy was prescribed in 15 patients (48.4%). All histopathological findings of GELM were consistent with those of a primary tumor.

Overall survival and recurrence-free survival

The median follow-up period was 3.3 (range, 0.3-8.4) years. The 1-, 3-, and 5-year OS rates were 92.8%, 56.2%, and 42.2%, respectively. The median OS was 3.2 years (Figure 1A). The 1-, 3-, and 5-year RFS rates were 58.5%, 31.3%, and 31.3%, respectively. The median RFS was 1.4 years (Figure 1B). Recurrence after liver resection for GELM occurred in 18 (58.1%) patients; this included the liver in eight (25.8%), the lung in two (6.5%), the bone in two (6.5%), the lymph nodes in one (3.2%), and the peritoneum in one (3.2%), including multiple site recurrence in four (22.2%).

Table 3. Univariate and multivariate analysis of overall survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors						
Sex,						
Male / Female	1.11	0.20-20.6	0.918			
Age						
≥ 70 years / ≤ 69 years	1.21	0.36-3.86	0.756			
BMI						
≥ 25.0 kg/m^2 / ≤ 24.9 kg/m^2	1.23	0.55-2.75	0.684			
ASA						
≥ 2 / ≤ 1	0.60	0.21-1.45	0.183			
AFP						
≥ 9.0 IU/mL / ≤ 8.9 IU/mL	0.41	0.06-1.80	0.251			
CEA						
≥ 5.0 IU/mL / ≤ 4.9 IU/mL	0.88	0.19-2.75	0.787			
CA19-9						
≥ 37.0 IU/mL / ≤ 36.9 IU/mL	0.91	0.19-3.40	0.902			
Preoperative chemotherapy	0.91	0.31-2.48	0.924			
Primary cancer-related factors						
Tumor location						
EGJ, Upper / Middle, Lower	1.78	0.55-4.84	0.314			
Maximum primary tumor size						
≥ 5 cm / ≤ 4.9 cm	1.72	0.59-5.52	0.312			
T classification						
≥ 3 / ≤ 2	1.17	0.73-2.94	0.240			
N classification						
≥ 1 / ≤ 0	1.35	0.50-3.94	0.552			
Histological type						
Intestinal / Diffuse and other	0.26	0.08-0.85	**0.027**	0.24	0.07-0.81	0.022
Liver metastases-related factors						
Timing of liver metastases						
Metachronous / Synchronous	0.68	0.63-4.94	0.284			
Tumor number						
Multiple / Single	1.06	0.33-2.86	0.914			
Tumor distribution						
Bilobular / Unilobular	1.34	0.42-3.68	0.586			
Maximum tumor size						
≥ 5 cm / ≤ 4.9 cm	0.66	0.15-2.09	0.518			
Operative procedures						
Synchronous hepatectomy	1.65	0.54-4.62	0.354			
Major hepatectomy	3.43	1.09-44.7	**0.044**			
Operating time						
≥ 360 min / ≤ 359 min	1.57	0.57-4.45	0.371			
Estimated blood loss						
≥ 1000 mL / ≤ 999 mL	1.26	0.44-3.46	0.648			
Resection						
≥ R1 / R0	4.86	1.32-17.9	**0.018**	5.31	1.40-20.5	0.015
Postoperative factors						
Clavien-Dindo classification						
≥ I / ≤ 0	0.81	0.59-2.00	0.786			
Duration of hospital stay						
≥ 14 days / ≤ 13 days	1.34	0.48-3.85	0.567			
Postoperative chemotherapy	1.12	0.41-3.09	0.815			

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; EGJ, esophagogastric junction; Por, undifferentiated adenocarcinoma; HR, hazard ratios; CI, confidence intervals.

Risk factors for OS and RFS

Intestinal-type adenocarcinoma, major hepatectomy, and R1/R2 resection were found to be significantly associated with OS (Table 3). Of these factors, intestinal-type adenocarcinoma was associated with a significantly lower risk of OS (HR, 0.24; 95% CI, 0.07-0.81; p = 0.022). In contrast, R1/R2 resection (HR, 5.31; 95% CI, 1.40-20.5; p = 0.015) was an independent risk factor for OS. Primary gastric location (esophagogastric junction and upper stomach) and intestinal-type adenocarcinoma were found to be significantly associated with RFS (Table 4). Of the two factors, intestinal-type adenocarcinoma was associated

Table 4. Univariate and multivariate analysis of recurrence-free survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors						
Sex						
Male / Female	1.08	0.32-6.72	0.938			
Age						
≥ 70 years / ≤ 69 years	1.02	0.41-2.59	0.949			
BMI						
≥ 25.0 kg/m^2 / ≤ 24.9 kg/m^2	0.73	0.38-1.30	0.307			
ASA						
≥ 2 / ≤ 1	0.91	0.28-2.20	0.460			
AFP						
≥ 9.0 IU/mL / ≤ 8.9 IU/mL	1.68	0.54-5.09	0.356			
CEA						
≥ 5.0 IU/mL / ≤ 4.9 IU/mL	4.88	0.53-4.85	0.447			
CA19-9						
≥ 37.0 IU/mL / ≤ 36.9 IU/mL	2.65	0.89-8.16	0.077			
Preoperative chemotherapy	0.89	0.44-2.99	0.821			
Primary cancer-related factors						
Tumor location						
EGJ, Upper/ Middle, Lower	3.03	1.08-8.12	**0.039**			
Maximum primary tumor size						
≥ 5 cm / ≤ 4.9 cm	1.93	0.71-4.86	0.183			
T classification						
≥ 3 / ≤ 2	1.28	0.51-3.45	0.596			
N classification						
≥ 1 / ≤ 0	1.03	0.41-2.62	0.934			
Histological type						
Intestinal /Diffuse and other	0.25	0.10-0.68	**0.006**	0.34	0.09-0.72	**0.008**
Liver metastases-related factors						
Timing of liver metastases						
Metachronous / Synchronous	0.88	0.24-2.25	0.786			
Tumor number						
Multiple / Single	1.61	0.59-4.02	0.329			
Tumor distribution						
Bilobular / Unilobular	1.24	0.43-3.16	0.661			
Maximum tumor size						
≥ 5 cm / ≤ 4.9 cm	1.93	0.71-4.86	0.183			
Portal vein thrombosis	2.18	0.60-6.30	0.210			
Operative procedures						
Synchronous hepatectomy	0.73	0.17-1.83	0.650			
Major hepatectomy	3.16	0.77-9.98	0.093			
Operating time						
≥ 360 min / ≤ 359 min	1.23	0.48-3.17	0.654			
Estimated blood loss						
≥ 1000 mL / ≤ 999 mL	1.05	0.64-2.71	0.922			
Blood transfusion	0.92	0.32-2.39	0.881			
Resection						
≥ R1 / R0	1.82	0.62-4.82	0.256			
Postoperative factors						
Clavien-Dindo classification						
≥ I / ≤ 0	1.16	0.56-2.14	0.646			
Duration of hospital stay						
≥ 14 days / ≤ 13 days	0.86	0.31-2.26	0.776			
Postoperative chemotherapy	0.79	0.29-1.98	0.631			

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; EGJ, esophagogastric junction; Por, undifferentiated adenocarcinoma; HR, hazard ratios; CI, confidence intervals.

with a lower risk of RFS (HR,0.34; 95% CI, 0.09-0.72; $p = 0.008$).

Factors predicting extra-hepatic recurrence

Intestinal-type adenocarcinoma and a maximum tumor size ≥ 5 cm were found to be significantly associated with extra-hepatic recurrence after liver resection for GELM (Table 5). Subsequent multiple logistic regression analysis revealed that intestinal-type adenocarcinoma (OR, 0.13; 95% CI, 0.02-0.66; $p = 0.012$) was associated with a lower incidence of extra-hepatic recurrence. Extra-hepatic recurrence rates after liver resection were significantly lower in patients

Table 5. Univariate and multivariate analysis of extra-hepatic recurrence

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors						
Sex						
Male / Female	0.56	0.02-5.13	0.630			
Age						
≥ 70 years / ≤ 69 years	0.57	0.11-2.52	0.463			
BMI						
≥ 25.0 kg/m^2 / ≤ 24.9 kg/m^2	0.82	0.16-3.26	0.363			
ASA						
≥ 2 / ≤ 1	1.03	0.52-2.82	0.623			
AFP						
≥ 9.0 IU/mL / ≤ 8.9 IU/mL	3.00	0.46-26.7	0.256			
CEA						
≥ 5.0 IU/mL / ≤ 4.9 IU/mL	0.53	0.09-2.64	0.449			
CA19-9						
≥ 37.0 IU/mL / ≤ 36.9 IU/mL	1.50	0.31-7.66	0.610			
Preoperative chemotherapy	2.66	0.57-15.0	0.213			
Primary cancer-related factors						
Tumor location						
EGJ, Upper/ Middle, Lower	0.30	0.05-1.48	0.140			
Maximum primary tumor size						
≥ 5 cm / ≤ 4.9 cm	1.67	0.26-2.46	0.253			
T classification						
≥ 3 / ≤ 2	1.54	0.33-7.11	0.568			
N classification						
≥ 1 / ≤ 0	0.47	0.09-2.06	0.318			
Histological type						
Intestinal /Diffuse and other	0.14	0.02-0.67	**0.006**	0.13	0.02-0.66	**0.012**
Liver metastases-related factors						
Timing of liver metastases						
Metachronous / Synchronous	3.03	0.69-14.5	0.141			
Tumor number						
Multiple / Single	1.07	0.20-6.27	0.943			
Tumor distribution						
Bilobular / Unilobular	2.30	0.42-18.1	0.345			
Maximum tumor size						
≥ 5 cm / ≤ 4.9 cm	1.08	1.02-5.06	**0.049**			
Operative procedures						
Synchronous hepatectomy						
Major hepatectomy	1.77	0.27-11.4	0.531			
Operating time						
≥ 360 min / ≤ 359 min	1.08	0.20-4.14	0.919			
Estimated blood loss						
≥ 1000 mL / ≤ 999 mL	1.23	0.13-4.07	0.803			
Blood transfusion	1.55	0.32-8.91	0.589			
Resection						
≥ R1 / R0	2.67	0.54-14.0	0.221			
Postoperative factors						
Clavien-Dindo classification						
≥ I / ≤ 0	0.72	0.20-3.08	0.654			
Duration of hospital stay						
≥14 days / ≤13 days	1.94	0.43-9.61	0.387			
Postoperative chemotherapy	2.40	0.55-11.1	0.241			

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; EGJ, esophagogastric junction; Por, undifferentiated adenocarcinoma; OR, odds ratio; CI, confidence intervals.

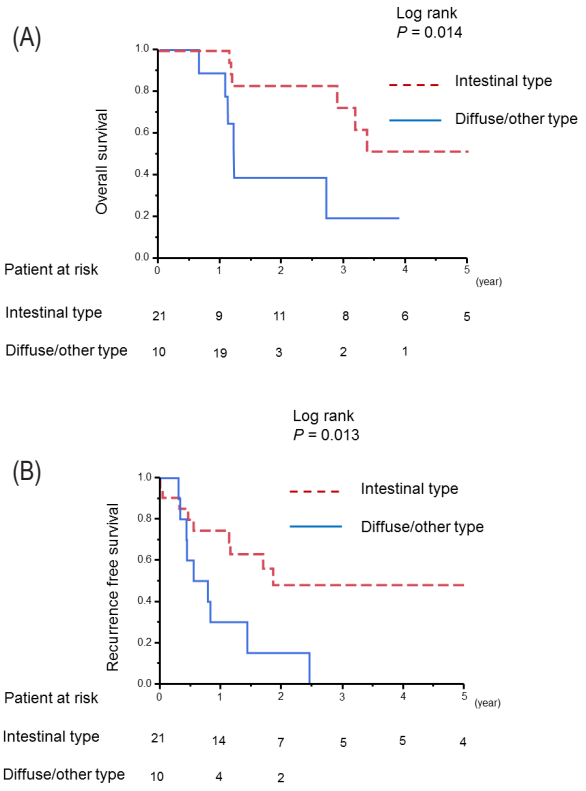

Figure 2. (A) Overall survival in patients with intestinal-type adenocarcinoma and with diffuse-type adenocarcinoma/other type in GELM. (B) Recurrence-free survival in patients with intestinal-type adenocarcinoma and with diffuse-type adenocarcinoma/other type in GELM. GELM, gastric/esophagogastric-junction liver metastasis.

with intestinal-type adenocarcinoma than in those with diffuse-type adenocarcinoma/other type (23.8% [5/21] *vs*. 60.0% [6/10]; $p = 0.002$).

OS and RFS in patients with intestinal-type adenocarcinoma

OS ($p = 0.014$) and RFS ($p = 0.013$) differed significantly between patients with intestinal-type adenocarcinoma and patients with diffuse-type adenocarcinoma/other type (Figure 2). The 1-, 3-, and 5-year OS rates in patients with intestinal-type adenocarcinoma were 100.0%, 72.9%, and 52.0%, respectively, whereas diffuse-type adenocarcinoma/other type were 88.8%, 19.4%, and 19.4%, respectively. The 1-, 3-, and 5-year RFS rates in patients with intestinal-type adenocarcinoma were 74.5%, 48.0%, and 48.0%, respectively, while those in patients with diffuse-type adenocarcinoma/other type were 30.0%, 0.0%, and 0.0%, respectively. Recurrence after liver resection occurred in nine of 10 (90%) patients with diffuse-type adenocarcinoma/other type, including in the liver in three, in the lymph nodes in one, in the peritoneum in one, in the bone in one, and in multiple sites in three.

Summary of outcomes for GELM resection in previous study

Table 6 shows Indication, long-term outcomes, and prognostic factors of patients undergoing GELM resection in previous studies that included > 30 patients in recent years.

Discussion

Our study demonstrated that the 5-year OS and RFS rates in selected patients who underwent liver resection for GELM were 42.2% and 31.3%, respectively. Intestinal-type adenocarcinoma was associated with a lower risk for both OS and RFS, and with a lower incidence for extra-liver recurrence after liver resection for GELM.

The 5-year OS and RFS rates in our study are similar to those reported in previous studies. The OS and RFS rates reportedly ranged from 9.3% to 42.1% and from 8.6% to 27.7%, respectively (*3-7,12-18*). The median OS time was 38.0 months for selected patients in our study, which was also comparable to previous studies, where it ranged from 11 to 36 months (*3,6,15,16,18,19*). In contrast, according to a recent phase III clinical trial for GELM (*20*), the median OS was 9.5-14.1 months without liver resection. However, to address appropriate selection criteria for GELM resection, factors for poor prognosis concerning GELM resection and predictors for extra-hepatic recurrence after liver resection should be investigated; this is because gastric cancer develops peritoneal dissemination and lymph node metastases more frequently than colorectal cancer (*21*). In the present study, intestinal-type adenocarcinoma reduced a risk for OS and RFS. Additionally, intestinal-type adenocarcinoma was associated with a lower incidence of extra-hepatic recurrence. This finding is reasonable because diffuse-type histology is associated with infiltrative growth and peritoneal dissemination (*22*). Actually, the peritoneal dissemination rate is reported to be higher in patients with diffuse-type adenocarcinoma than those with intestinal-type adenocarcinoma (31% *vs*. 6%) (*23*). In our study, extra-hepatic recurrence rates after liver resection were significantly higher in patients with diffuse-type adenocarcinoma/other type than in those with intestinal-type adenocarcinoma (60% [6/10] *vs*. 23.8% [5/21]; $p = 0.002$). Accordingly, GELM resection is preferable for patients with intestinal-type adenocarcinoma. It would be reasonable to limit solitary GELM and/or to use a mandatory neoadjuvant chemotherapy strategy for non-intestinal-type histology, instead of upfront liver resection, although the effect of perioperative chemotherapy for GELM remains unclear. Additionally, the use of a strong adjuvant chemotherapy regimen can be recommended for GELM with diffuse-type adenocarcinoma/other type.

According to previous studies that included > 30

Table 6. Surgical indication, long-term outcomes, and prognostic factors reported in the previous and present studies

Author	Year	*n*	Surgical indication	Median OS (month)	5-year RFS rate (%)	5-year OS rate (%)	Prognostic factors for poor survival
Shildberg *et al*.	2012	31	Without other distal metastasis	NS	NS	13	Multiple liver metastases R1/R2 resection Synchronous
Takemura *et al*.	2012	64	Three or fewer GELMs (More liver metastases at the surgeon's discretion) Only R0 resection	34	27	37	≥ 5 cm in size pT4 of primary tumor
Wang *et al*.	2012	30	Without other distal metastasis preoperatively Synchronous GELMs Only R0 resection	11	NS	16.7	Peritoneal dissemination Multiple distal metastases
Kinoshita *et al*.	2014	256†	Three or fewer GELMs (More liver metastases at the surgeon's discretion) Only R0 resection	31	30.1	31.1	pT4 of primary tumor ≥ 5 cm in size ≥ 3 GELMs
Tiberio *et al*.	2014	53†	Without other distal metastasis	34	NS	31.5	≥ 6 cm in size D2 dissection
Wang *et al*.	2014	39	Without other distal metastasis	14	7.7	10.3	Lymph node metastasis Multiple distal metastases
Guner *et al*.	2015	68†	Not stated in detail (case by case)	24	26.0	30.0	≥ 3 cm in size
Liu *et al*.	2015	35	Without other distal metastasis	33	NS	14.3	Lymphovascular invasion Multiple liver metastasis
Oki *et al*.	2015	94†	Without other distal metastasis	34	27.7	42.3	≥ 3 cm in size Multiple GELMs ≥ N2 of primary tumor
Present study	2018	31	Three or fewer GELMs Controllable after chemotherapy Only R0 resection	38	31.3	42.2	Diffuse/other type R1/R2 resection

Abbreviations: OS, overall survivals; RFS, recurrence-free survivals; GELM, gastric/esophagogastric-junction liver metastasis; NS, not stated. †, Multicenter cohort study.

patients in the past 5 years, multiple liver metastases, R1/R2 resection, synchronous metastases, maximum size of liver metastases, pT4 of primary tumor, and other distant metastases were reported to be risk factors for OS (*3,5,6,16,18,19*). Unlike the previously reported covariates, the diffuse-type adenocarcinoma in our study is one of the prognostic factors for OS and RFS, and it is a predictor of extra-liver metastasis development. This is most likely because the previous series included advanced-stage patients with GELM and other organ metastases, and patients with four or more GELMs. These factors tempered the influence of the diffuse/other-type adenocarcinoma of primary gastric cancer in the analysis. In contrast, our indication criteria are more restrictive than the previous series, namely three or fewer GELMs without any distant metastases; in addition, the diffuse-type carcinoma was found to be a factor for poor prognosis.

The present study had several limitations. Its retrospective nature and the small number of patients enrolled may weaken the reliability of the statistical analyses. Genomic expressions including α-fetoprotein and human epidermal growth factor receptor-related 2 (HER2) were not evaluated in the study. Further investigations with a large number of patients in a well-designed multicenter study are needed to evaluate appropriate patient selection criteria for GELM resection.

In conclusion, intestinal-type adenocarcinoma was associated with a lower risk for OS and RFS; it was also associated with a lower incidence of extra-hepatic recurrence, under the GELM resection criteria involving three or fewer tumors without distant metastases. Therefore, GELM resection is preferable for patients with intestinal-type histology. A strict indication such as solitary GELM and/or the use of mandatory neoadjuvant chemotherapy, and the use of a strong adjuvant chemotherapy regimen, can be recommended for GELM with diffuse-type adenocarcinoma/other type.

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**Address correspondence to*:
Yoshikuni Kawaguchi and Kiyoshi Hasegawa, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail: yokawaguchi-tky@umin.ac.jp and kihase-tky@umin.ac.jp