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ORIGINAL ARTICLE

Survival Benefit of Surgical Treatment for Liver Metastases from Gastric Cancer

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Abstract
Background and Objectives Indications for the resection of liver metastases from gastric cancers (GLM) remain controversial, and few previous studies have reported subsequent surgical outcomes. Thus, the present retrospective study was designed to clarify the benefits of surgical treatment and identify prognostic factors.
Methods Outcomes of 47 patients with or without hepatectomy for GLM were retrospectively compared.
Results A total of 22 patients received surgical treatment for GLM, and overall 1-, 3-, and 5-year survival rates were 86, 26, and 26 %, respectively, and the median survival time (MST) was 22 months. Among 25 patients who did not receive hepatic surgical treatment, the overall survival rates were 24, 8.0, and 4.0 % at 1-, 3-, and 5-years, respectively, with an MST of 7 months. A significant difference was observed between patients with and without the liver surgical treatment ($P<0.001$). Univariate and multivariate analyses of recipients of surgery, only the number of liver metastases (solitary or multiple) was significantly predictive of survival (HR=0.26, $P=0.029$) following hepatic resection for GLM.
Conclusions Surgical treatment of GLM should be considered when complete excision including the primary tumor appears to be possible, particularly in cases of solitary hepatic metastases.

Keywords Gastric cancer liver metastases · Hepatectomy · Prognostic factors

Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death globally.[1] In Japan, gastric cancer is second only to lung cancer as a cause of cancer death. Early tumor detection, curative surgical resection including extended lymph node dissection (D2), and appropriate adjuvant therapy have led to the improved survival of patients with primary gastric cancer. In a previous study, the resection rate in patients with primary gastric cancers was 95.4 %, and the 5-year survival rate of resected patients was 70.7 %.[2] However, prognoses for patients with advanced or recurrent gastric cancer remain poor, with median survival time (MST) of approximately 1 year. The liver is one of the most common sites of advanced gastric cancer metastasis, and liver metastases from gastric cancer (GLM) are found in 4–14 % of patients with primary gastric cancer. Moreover, after the curative resection of primary gastric adenocarcinomas, 3.5–14 % of the patients experience intrahepatic recurrence.[3–7] GLM are often diagnosed as multiple intrahepatic nodules occupying both lobes and coexist with extrahepatic disease, including peritoneal carcinomatosis, lymph node metastases, and direct tumor invasions of other organs. Although systemic chemotherapy with or without new molecular targeting agents is the standard treatment modality for GLM, the 5-year survival of patients with GLM without surgical treatment is <10 %.[8] However, because outcomes in patients with noncurative resections for gastric cancer are extremely poor,[9,10] the benefits of surgery for GLM remain debatable.

Although several authors have reported 5-year survival rates of 0–39 % among selected surgically resected patients with GLM,[5,6,11–17] its significance is still controversial. Thus,

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given the severity of gastric cancer, surgical indications for GLM require careful investigation[18] to identify patients with GLM who are most likely to receive benefits from surgical treatment. In the present retrospective study, the benefits of surgical treatment were assessed among patients with and without hepatectomy for GLM, and prognostic factors were identified.

Materials and Methods

Patients

From 1995 to 2010, 857 patients with primary gastric cancer (adenocarcinoma) received surgery at the Department of Surgery, Hokkaido Cancer Center, Sapporo, Japan. Among these, a total of 47 patients (5.5 %) developed liver metastases, including 38 (4.4 %) with synchronous liver metastases and nine with metachronous liver metastases after resection of the primary gastric cancer. Liver resections were performed only in cases with curative potential. All possible alternative treatments were explained to the patients prior to surgery, and informed consent was obtained. Patients were excluded from analyses if they had received synchronous en bloc resections of gastric cancers that were directly invading the liver or no surgical treatment for metachronous liver metastases.

Thirteen of 38 patients with synchronous liver metastases received gastrectomy with concomitant hepatic resection or intraoperative radiofrequency ablation (RFA). The other 25 patients received laparotomy without surgical treatment for GLM. All nine patients with metachronous liver metastases received hepatic resection after curative primary tumor resection. A total of 22 patients with liver metastases received liver resection or RFA. Among these, three were noncurative, and two patients with metachronous liver metastases received repeat hepatectomy. Preoperative chemotherapy was performed in 14 cases (29.8 %), and eight patients received oral S1, including four patients who received S1 plus cisplatin and docetaxel (DCS), five patients received intravenous 5-fluorourcil (5-FU), and one patient received hepatic arterial infusions of 5-FU. Outcomes in these 47 patients with liver metastases were retrospectively reviewed, and patients were followed until death or until January 2014.

Study Design

A total of 47 patients were classified into groups according to surgical treatment for GLM. The following clinicopathological factors were retrospectively analyzed, and patients were divided to subgroups according to age, gender, status of serosa invasion (T4), lymph node metastases, and histological differentiation in the primary gastric cancer, status of extrahepatic metastasis, time between primary disease and liver metastasis (synchronous or metachronous), tumor number, size and location of liver metastases, types of liver surgical procedures, and receipt of systemic chemotherapy (preoperative and postoperative chemotherapy).

The depth of tumor penetration into the gastric wall (T parameter) and the number of metastatic regional lymph nodes involved (N parameter) were classified according to the 7th edition of the Union for International Cancer Control (UICC) at the time of gastric resection. Synchronous liver metastases were defined by detection before or during surgery or within 3 months of primary tumor resection. Operative death was defined as that occurring within 30 days of surgery. Morbidity included any type of complication, including surgical and nonsurgical events. The overall survival time was measured from the date of hepatic resection or other surgical operation in patients without hepatectomy until the date of death.

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, 2012), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria version 2.13.0). This modified version of R commander (version 1.6-3) was designed to add statistical functions that are frequently used in biostatistics. Univariate analyses of categorical data were performed using cross-linked tables and Fisher's exact test. Differences were considered significant when $P<0.05$. Survival analyses were performed using the Kaplan–Meier method. Prognostic factors were identified using univariate and multivariate analyses with log-rank tests and Cox's proportional hazard models.

Results

Patients and Tumor Characteristics

The baseline characteristics of eligible patients are presented in Table 1. The study group comprised 38 men and nine women with an average age of 66.7 years (range 29–81). A total of 22 patients received surgery for GLM. At the time of diagnosis, 13 patients had synchronous metastases and nine had metachronous liver metastases. Surgical procedures for GLM included anatomic resection in six patients (27 %), limited resection in 12 patients (56 %), and RFA in four patients (18 %). The other 25 patients had synchronous liver metastases and did not receive hepatic surgery. The distribution of surgical procedures included primary gastric resection in 21 patients (84 %) and exploratory laparotomy in four patients only (16 %).

Table 1 Characteristics of patients with and without hepatic surgical treatment for liver metastases of gastric cancer

	With hepatic surgical treatment (n=22)	Without hepatic surgical treatment (n=25)	Odd ratio	95 % CI	*P* value
Age					
<65	8	12	1.599	0.433–6.147	0.556
≧65	14	13			
Gender					
Male	19	19	1.971	0.356–13.99	0.47
Female	3	6			
T classification of primary					
T1, T2, T3	19	3	0.025	0.002–0.146	<0.001
T4	3	22			
N classification of primary					
N0	6	0	0	0–0.643	0.007
N1, N2, N3	16	25			
Degree of histological differentiation in primary					
Well-moderate	18	13	4.026	0.941–21.16	0.063
Poorly	4	12			
Extrahepatic metastases					
Absent	20	12	0.097	0.009–0.541	0.002
Present	2	13			
Timing of liver metastases					
Synchronous	13	25	0	0–0.325	<0.001
Metachronous	9	0			
Number of liver metastases					
Solitary	11	7	2.518	0.659–10.30	0.144
Multiple	11	18			
Maximum tumor size of liver metastases					
<4 cm	17	23	3.296	0.470–38.569	0.228
≧4 cm	5	2			
Distribution of liver metastases					
Unilobar	17	8	6.882	1.68–33.31	0.003
Bilobar	5	17			
Liver treatment method					
Liver resection	18				
Liver segmentectomy	6				
Atypical resection	12				
Radiofrequency ablation	4				
None		25			
Curability					
Yes	19	2	60.994	8.980–798.197	<0.001
No	3	23			
Gastrectomy					
Distal gastrectomy	13	12			
Total gastrectomy	9	9			
None		4			
Systemic chemotherapy					
Received	16	20	0.673	0.135–3.20	0.732
Not received	6	5			
Preoperative chemotherapy					
Received	6	8	0.801	0.184–3.329	0.76
Not received	16	17			

Table 1 (continued)

	With hepatic surgical treatment (n=22)	Without hepatic surgical treatment (n=25)	Odd ratio	95 % CI	*P* value
Postoperative chemotherapy					
Received	16	18	1.036	0.239–4.604	1
Not received	6	7			
Mortality	0	3			
Morbidity	4	7			

Six of 14 patients who received preoperative chemotherapy also received surgical treatment for liver metastases. Gastrectomy was performed in eight patients. Three patients (DCS, $n=2$; S1 plus various drugs, $n=1$) achieved complete clinical responses for liver tumors before surgery. One patient received gastrectomy with partial liver resection and survived for >5 years without further recurrence. Two patients who received gastrectomy without liver resection were recorded as curable and were included in the no hepatic surgery group. One of these patients survived for >5 years, and the other died of systemic recurrence at 39 months after surgery.

Characteristics of primary gastric cancers, such as the status of T4 factor, lymph node metastasis, and extrahepatic metastasis, significantly differed between patients who did and did not receive surgery for GML. The states of liver metastases also significantly differed, with differing distributions of metastatic nodules. However, no differences in numbers or sizes of lesions were observed.

Operative Outcomes in All Patients

Among the 22 patients who received surgical treatment for liver metastases, the overall 5-year survival rate was 26 % and MST was 22 months (range 15–35). Among the 25 patients without aggressive treatment, the overall survival rate was 4.0 % at 5 years with an MST of 7 months (range 5–9). A significant difference was observed between patients with and without the liver surgical treatment ($P<0.001$, Fig. 1). Three patients in the treatment group and one in the no treatment group were still alive at the end of the cutoff date.

Univariate analyses of all 47 patients revealed that the curability of gastric cancer (hazard ratio=0.113), surgical treatment for GLM (0.273), T4 factor (0.3), degree of histological differentiation in the primary gastric cancer (0.512), distribution of liver metastases (0.362), solitary liver metastasis (0.388), and status of extrahepatic metastases (0.45) significantly influenced prognoses for GLM (Table 2). Multivariate analyses of all 47 patients revealed that surgical treatment for liver metastasis (0.239), solitary liver metastasis (0.423), and the degree of histological differentiation (0.486) were significant prognostic factors for GLM (Table 3).

Operative Results of Hepatic Surgical Treatment

Among the 19 patients who achieved curative resection (R0), the 1-, 3-, and 5-year survival rates were 83.3, 31.7, and 31.7 %, respectively, with an MST of 27 months (range 15–35). The 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 42.0, 26.0, and 26.0 %, respectively (Fig. 2). Factors for poor prognosis were identified in univariate and multivariate analyses and are shown in Tables 4 and 5. The number of liver metastasis (solitary or multiple) was the only significant prognostic factor for survival in patients with hepatic resection for GLM. There was not a significant difference between patients with liver resection and those who received RFA treatment for GLM. Systemic chemotherapy did not influence prognoses.

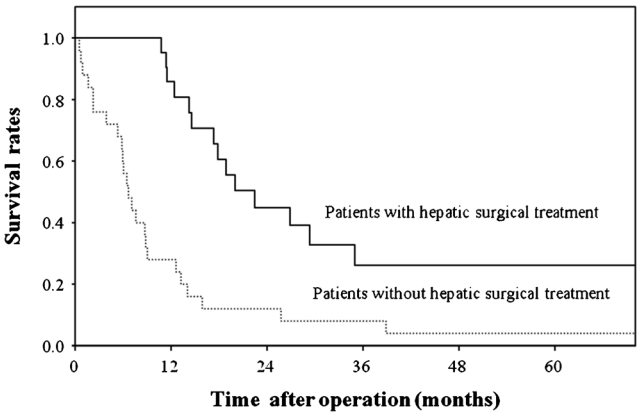

Fig. 1 Overall survival of patients with and without hepatic surgical treatment. For the 22 patients in the surgical treatment for liver metastases (*solid line*), the overall 1-, 3-, and 5-year survival rates were 86, 26, and 26 %, respectively. The median survival time (MST) was 22 months (range 15–35). In the 25 patients without hepatic surgical treatment (*dotted line*), the overall survival rate was 24, 8.0, and 4.0 % at 1-, 3-, and 5-years, respectively, with the MST of 7 months (range 5–9). A significant difference was observed between patients with and without the liver surgical treatment ($P<0.001$)

Table 2 Univariate analysis of survival of all registered patients with liver metastases from gastric cancer

	Number	Median survival time (months)	Hazard ration	95 % CI	*P* value
Curability					
Yes	21	29(18-)	0.113	0.049–0.267	<0.001
No	26	7(5–9)			
Hepatic surgical treatment					
Present	22	22(15–35)	0.273	0.139–0.538	<0.001
Absence	25	7(5–9)			
Age					
<65	20	10(7–18)	1.203	0.632–2.288	0.573
≧65	27	15(6–26)			
Gender					
Male	38	14(9–18)	0.556	0.260–1.189	0.13
Female	9	9(1–22)			
T classification of primary					
T1, T2, T3	22	19 (12-)	0.3	0.151–0.596	<0.001
T4	25	7(6-13)			
N classification of primary					
N0	6	18(11-)	0.557	0.171–1.818	0.332
N1, N2, N3	41	13(7–17)			
Degree of histological differentiation in primary					
Well-moderate	31	15(12–26)	0.512	0.261–1.003	0.05
Poorly	16	6(4–11)			
Extrahepatic metastases					
Absence	32	14(11–22)	0.45	0.234–0.867	0.0169
Present	15	7 (2–15)			
Timing of liver metastases					
Synchronous	38	12(7–15)	2.398	0.932–6.166	0.07
Metachronous	9	20(11-)			
Number of liver metastases					
Solitary	18	22(11-)	0.388	0.189–0.794	0.01
Multiple	29	11(6–15)			
Maximum tumor size of liver metastases					
<4 cm	40	13(9–18)	0.913	0.379–2.203	0.84
≧4 cm	7	12(1–29)			
Distribution of liver metastases					
Unilobar	25	17(11–35)	0.362	0.187–0.700	0.003
Bilobar	22	9(5–13)			
Hepatic surgical method					
Liver segmentectomy	6	24(12-)			
Atypical resection	12	19(12-)			
Radiofrequency ablation	4	27(11-)			
None	25	7(5–9)			
Systemic chemotherapy					
Received	36	13(9–19)	0.768	0.350–1.688	0.511
Not received	11	15(1-)			
Preoperative chemotherapy					
Received	14	13(2–20)	1.022	0.513–2.036	0.951
Not received	33	14(7–22)			
Postoperative chemotherapy					
Received	34	14(9–20)	0.634	0.3047–1.321	0.224
Not received	13	9(2-)			

Table 3 Multivariate analysis of prognostic factors for survival in all patients with liver metastases from gastric cancer

Clinical variable	Hazard ration	95 % CI	*P* value
Hepatic surgical treatment	0.239	0.102–0.561	0.001
Number of liver metastases (solitary)	0.423	0.203–0.881	0.022
Degree of histological differentiation (well-moderate)	0.486	0.237–0.997	0.049
Present of extrahepatic metastases	1.022	0.470–2.222	0.956
Received preoperative or postoperative systemic chemotherapy	0.434	0.179–1.051	0.064

Morbidity and Mortality

At 30 days, postoperative mortality was 0 in the hepatic surgery group, and due to the progression of cancer in three patients, it was 12 % in the no hepatic surgery group. The overall morbidity rate was 19 % (four patients) in the hepatic surgery group and included intestinal leakage, bile leakage, pulmonary infarction, bleeding, and intra-abdominal abscess. The overall morbidity was 28 % (seven patients) in the no surgery group and included liver failure, liver dysfunction, gastric emptying disorder, urinary tract infection, and wound infection.

Discussion

The surgical resection of GLM is rarely indicated because prognoses for patients with noncurative resection for advanced gastric cancers remain poor,[9,10] and most patients with GLM remain incurable, even after extended surgery. Among these patients, incurable features include bilobar multinodular liver tumor spread, gross peritoneal dissemination, extensive lymph node metastasis, distant metastasis, and unresectable primary tumor spread. In the present study, we retrospectively reviewed outcomes in 47 patients and compared patients who received surgical treatment for GLM with those who did not. Patients who were inoperable at the time of diagnosis of GLM were excluded. Nonetheless, the serous invasions, extensive lymph node metastases, and extrahepatic metastases significantly disturbed surgical liver resections in the present patients. As a result, the TNM stage of primary gastric cancers considerably influenced the indication for surgical resection of GLM. In addition, the number and distribution of liver metastases significantly differed between the two treatment groups. Especially, bilobar tumor spread within the liver appears more frequently in gastric cancers than in other gastrointestinal malignancies.[15] These results showed poorer biologic nature in gastric cancer. Thus, even in cases of potentially resectable gastric liver metastases, the surgical procedure for GLM may be avoided.

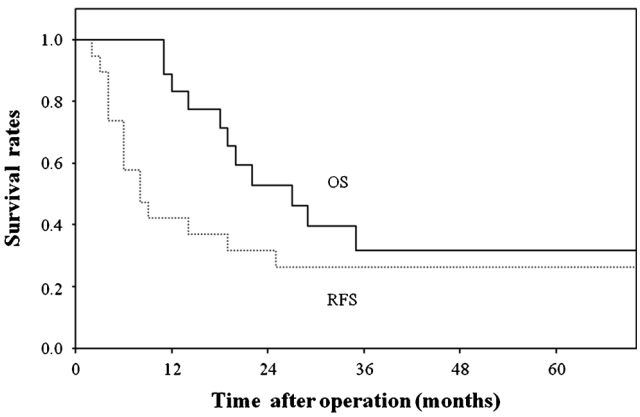

Fig. 2 Overall survival (OS, *solid line*) and recurrence-free survival (RFS, *dotted line*) in the 19 patients in whom curative resection (R0) was achieved. The 1-, 3-, and 5-year OS rates were 83.3, 31.7, and 31.7 %, with MST of 27 months. The 1-, 3-, and 5-year RFS rates were 42.0, 26.0, and 26.0 %, respectively

Patients receiving curative surgical resection for GLM are expected to have better prognosis. Among 19 patients with curative surgical treatment for GLM in the present study, MST was 27 months, and the 5-year survival rate was 31.7 %. Moreover, the present univariate analyses of patients with GLM identified status of serosa invasion and degree of histological differentiation in the primary gastric cancer, distribution of liver metastases, solitary liver metastasis, and status of extrahepatic metastases as good prognostic factors. Similarly, according to univariate and multivariate analyses of patients who received hepatic resection for GLM, solitary nodule of liver metastases was the only factor with a significant impact on the survival.

Among previous studies of GLM, the 5-year survival rates ranged from 0 to 39 %, and MST ranged from 9 to 48 months.[5,6,11–17] In earlier studies, the cumulative survival rates were generally poor and reflected generalized disease, with a 5-year survival in <20 % of the cases after hepatic resection.[4,5] In contrast, more recent studies show the 5-year survival rates of 11–39 %, with eight trials exceeding 30 %.[6,11–17] Kerkar et al.[19] performed meta-analyses of 19 studies of survival following liver resection for GLM and showed a median survival for all 436 patients of 17 months, with a 5-year survival of 26.5 % of the cases. Similar studies have compared surgical outcomes between patients with and without hepatic resection.[6,13,15,20] In agreement with the present date, these studies suggest that hepatic resection should always be considered as an option for patients with GLM when complete excision appears to be possible.

Table 4 Univariate analysis affecting survival of 22 patients with hepatic surgical treatment: impact of factors on survival

	Number	Median survival time (months)	Hazard ration	95 % CI	*P* value
Age					
<65	8	29(11-)	1.479	0.398–5.525	0.559
≧65	14	20(12-29)			
Gender					
Male	19	20(14-)	1.558	0.516–4.703	0.431
Female	3	22(19-)			
T classification of primary					
T1, T2, T3	19	19(14-)	1.299	0.354–4.768	0.693
T4	3	22(20-)			
N classification of primary					
N0	6	18(11-)	1.493	0.404–5.348	0.559
N1, N2, N3	16	22(15-)			
Degree of histological differentiation in primary					
Well-moderate	4	17(11-)	1.625	0.358–7.368	0.529
Poorly	18	22(14-35)			
Extrahepatic metastases					
Absence	20	22(14-)	0.641	0.141–2.907	0.565
Present	2	22(15-)			
Timing of liver metastases					
Synchronous	13	22(12-)	1.156	0.384–3.481	0.797
Metachronous	9	20(11-)			
Number of liver metastases					
Solitary	11	35(11-)	0.301	0.096–0.943	0.039
Multiple	11	18(12-20)			
Maximum tumor size of liver metastases					
<4 cm	17	22(15-)	0.65	0.120–2.119	0.475
≧4 cm	5	19(11-)			
Distribution of liver metastases					
Unilobar	17	29(14-)	0.349	0.108–1.125	0.078
Bilobar	5	18(12-)			
Systemic chemotherapy					
Received	16	21(12-)	0.921	0.254–3.341	0.901
Not received	6	26(15-)			
Preoperative chemotherapy					
Received	6	16(11-)	2.146	0.708–6.501	0.177
Not received	16	27(15-)			
Postoperative chemotherapy					
Received	16	21(12-)	0.921	0.25–3.341	0.901
Not received	6	26(15-)			

Multiple factors are associated with outcomes following liver resection for GLM and can hamper the establishment of indications for surgery. However, indications for liver resection could be based on analyses of prognostic factors. The first study of GLM prognostic factors was performed by Ochiai et al.[4], who described serosal perforation by the

Table 5 Multivariate analysis to determine prognostic factors for survival after hepatic surgical treatment

Clinical variable	Hazard ration	95 % CI	*P* value
Number of liver metastases (solitary)	0.264	0.080–0.872	0.029
Present of extrahepatic metastases	1.603	0.281–9.166	0.596
T4 factor of primary	1.512	0.325–7.034	0.598
Received postoperative chemotherapy	0.76	0.173–3.32	0.716

primary tumor, lymphangiosis, and venangiosisas negative prognostic factors. Several subsequent studies have described novel prognostic factors, including the size of the primary gastric tumor,[12,13] D2 lymphadenectomy,[13] serosal invasion,[4,7,12] lymph node metastasis,[5,19] histological type,[6] number of GLM,[6,7,13,16,17,20] maximum size of GLM,[12,18] distribution[12,20] and timing of hepatectomy,[6,12] surgical margins,[14] and absence of peritoneal dissemination.[16,19] In addition, the number of liver metastases is often described as an important prognostic factor, and solitary liver metastases are a favorable prognostic factor according to previous univariate and multivariate analyses.[13,16,17] Consequently, the present and previous data indicate that the number of liver metastases (solitary or multiple) may be the most significant prognostic factor for survival after initial hepatic resection for GLM.

RFA is widely used to treat primary and secondary liver tumors.[21] However, few studies have evaluated outcomes following RFA for GLM. Kim et al.[22] treated 20 patients with synchronous GLM using RFA and gastrectomy and achieved an MST of 30.7 months and a median progression-free survival time of 6.8 months. This procedure was performed in four of the present patients, and the resulting MST of 27 months indicates at least the same efficacy as that of liver resection. However, high recurrence rates are commonly associated with RFA.

Systemic chemotherapy is a standard treatment approach for most patients with GLM. However, the specification of appropriate regimens remains controversial.[23] Moreover, the efficacy of preoperative and postoperative chemotherapy in patients with GLM after liver resection has not been fully evaluated.[12,13,20,23] Nonetheless, systemic chemotherapy before and after liver resection may provide significant benefits to future patients.

Conclusions

Although curative liver resection is rarely achieved in patients with GLM, this surgical option may produce survival benefits. Therefore, the present data suggest that liver resection should be considered when complete excision including the primary tumor appears to be possible, particularly in cases of solitary hepatic metastases.

Conflict of Interest The authors have no conflict of interest to declare.

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