ORIGINAL ARTICLE

CrossMark

Prognostic analysis and liver metastases relevant factors after gastric and hepatic surgical treatment in gastric cancer patients with metachronous liver metastases: a population-based study

Yibin Xiao[1] · Bo Zhang[1] · Yulian Wu[1]

Abstract

Background The prognosis for patients with liver metastases from gastric cancer is very poor. Nevertheless, standard therapeutic strategies have not been established yet. The impact of hepatic surgical treatment on survival of patients with metachronous liver metastases from gastric cancer still remains controversial.

Methods We conducted a retrospective analysis on records of 436 patients who received radical gastrectomy (with D2 lymphadenectomy, regardless of hepatic surgical treatment) for gastric cancer with metachronous (≥ 3 months after gastrectomy) liver metastases in our center between 2001 and 2016. All patients were followed until 2017/10/31 or withdrawn from the follow-up because of death.

Results The median interval for non-hepatic metastases of the 436 patients who underwent radical gastrectomy is 14 months. T ($P = 0.041$), N ($P = 0.023$) and lymphovascular invasion ($P < 0.001$) were independent predictors affecting liver metastases-free interval. The overall survival rates for the 436 patients were 44.5, 29.7, 16.3, and 16.3% at 1, 2, 3, and 5 years respectively since treatment of hepatic metastases, with a median survival time of 11 months. N ($P = 0.025$), extent of liver metastases (H) (H2 vs. H1, $P = 0.036$; H3 vs. H1, $P < 0.001$), and treatment of liver metastatic lesions ($P < 0.001$) were significant independent prognostic factors for survival after presence of liver metastases. Among H1 and H2 patients, median survival in hepatic surgical treatment group was significantly longer than that in systemic chemotherapy alone group (25 vs. 11 months, $P = 0.015$).

Conclusions Liver examinations should be performed during the first 2 years after gastric surgery and continued for 5 years for high-risk patients. Active therapeutic strategies may prolong patients' survival compared with supportive treatment alone. Patients with H1, H2 metachronous liver metastases may be considered appropriate candidates for hepatic surgical treatment before embarking on systemic chemotherapy alone.

Trial registration ISRCTN Registry (Retrospectively registered; Reference number: 35067; Date: 02/04/2018).

Introduction

Gastric carcinoma (GC) is the fourth most common cancer [1] and the second leading cause of cancer-related death globally [2]. Although the incidence of gastric cancer has decreased in China [3, 4], there are a large amount of late-stage patients with distant metastases at initial diagnosis and 4–14% have

metastasis to the liver [5]. Approximately 2.0 to 9.9% of gastric cancer patients develop synchronous liver metastases, and up to 37% of gastric cancer patients develop liver metastases metachronously following radical gastrectomy [6]. Almost 80% of metachronous liver metastases appear within the first 2 years after hepatic surgical treatment [7].

The effect of surgical treatment has been identified for colorectal metastases from gastric cancer (GCCM) [8]. However, protocols about standard therapeutic strategies for gastric cancer with metachronous liver metastases (GCMLM) have not been reached a consensus. Treatment strategies dealing with GCMLM vary among different healthy institutions [9]. It has always been regarded as a systemic disease and traditionally been treated with systemic chemotherapy. Surgical treatment is

✉ Yulian Wu
yulianwu@zju.edu.cn

[1] Department of Surgery, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou 310009, Zhejiang, China

not always a prior option [10]. Although the clinical benefit of gastrectomy for liver metastases from gastric cancer (GCLM) has been previously studied [11], the prognostic benefit of hepatic surgical treatment has not been demonstrated [12]. Besides, the clinicopathological characteristics associated with the survival of GCMLM have not been comprehensively recognized.

In this study, we evaluated the significant risk factors for non-hepatic metastases interval after radical gastrectomy by analyzing the data of 436 patients with GCMLM. Besides, we analyzed the survival time after the presence of metachronous liver metastases and investigate the prognostic factors of major clinical relevance.

Materials and methods

Study subjects

We conducted a retrospective study by reviewing the data of patients with GCMLM at the Department of Surgery, the Second Affiliated Hospital, School of Medicine, Zhejiang University between January 2001 and May 2016. Those who did not receive D2 lymphadenectomy, developed liver metastases within 3 months after gastrectomy, had a history of other malignancies, had extra hepatic metastases before or during the admission for liver metastases, received laparotomy or bypass surgery, or had substantially incomplete data were excluded. Four hundred thirty-six gastric cancer patients with metachronous liver-only metastases following radical gastrectomy were included in this study. Institutional ethical committee (the ethical committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University) reviewed and approved this study. Because liver metastases could only be identified during surgical exploration under certain conditions, patients arranged for gastric cancer resection were informed of the chance of receiving hepatectomy, counseled on the procedure and alternative therapeutic options. Informed consent was obtained from all individual participants included in the study. The diagnosis of metachronous liver metastases relied on the findings during surgery and routine abdominal computed tomography/ ultrasonography before gastrectomy.

There were 368 males and 68 females, with a median age of 61 years old (29–85 years old). The following demographic and clinicopathological data was obtained. Patient-related factors included age, gender, and family history of malignancies (yes or no). Gastric cancer-related factors included tumor location, tumor size, histological differentiation, depth of tumor invasion (T), lymph node metastases (N), and lymphovascular invasion. Metastasis-related factors included liver metastases-free interval, size of the largest liver metastatic lesion, and degree of liver metastases (H). Treatment-related factors included adjuvant chemotherapy after radical gastrectomy (yes

or no), resection margin (positive or negative), therapeutic method of liver metastases, and type of postoperative digestive tract reconstruction. The pathologic classification of primary gastric cancer was based on the 7th edition of the TNM classification of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC). Degree of liver metastasis was evaluated according to the H classification of Japanese Research Society for Gastric Cancer (JRSGC): H1, solitary liver metastasis confined to one lobe of the liver; H2, solitary liver metastasis distributed to both lobes of the liver; H3, multiple liver metastases distributed to both lobes of the liver. We defined multiple liver metastases as more than five metastatic lesions.

Treatment for primary gastric cancer and hepatic metastases

As for the method of radical gastrectomy, we used D2 lymphadenectomy as the standard nodal dissection. Three hundred ninety-two patients received adjuvant systemic chemotherapy after surgery. As for the chemotherapeutic strategy, we gave priority to 5-fluorouracil combined with tetrahydrofolic acid. Some patients were treated with platinum, taxane, or camptothecin on the basis of the former strategy [13]. TNM classification of the 44 patients without systemic chemotherapy was as follows: T1N0M0 in 24 patients and other 20 patients were T1N1M0, T2N0M0, T4N0M0, T4N2M0, and T4N3M0 respectively. After the presence of metachronous liver metastases, 60 patients underwent hepatic surgical treatment (resection and radiofrequency ablation) (13.8%), 220 patients underwent transcatheter arterial chemoembolization (TACE) (50.5%), 20 patients underwent microwave coagulation therapy (MCT) (4.6%), 92 patients underwent chemotherapy alone (21.1%), and 44 patients underwent supportive or palliative therapy (10.1%).

Follow-up

Patients' follow-up lasted until death or the cut-off date of December 31, 2016. Evaluation of patients' survival was by follow-up contact using telephone, outpatient records, or mail. Among the patients lost to follow-up, those whose status were very poor at the last discharging from hospital and who had been hospitalized repeatedly were considered as deaths. Other patients who were lost to follow-up were censored at their last outpatient follow-up time. Patients who were still alive at the follow-up deadline were censored at the cut-off date of follow-up. The last censored ratio was 24.8%. The median follow-up period for the 436 patients was 11 months (1–53 months) since the presence of metachronous liver metastases.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM, Chicago, IL, USA) were used for statistical analyses. The clinicopathological characteristics between groups were analyzed using the chi-square test. Overall survival and liver metastases-free interval were calculated according to the Kaplan-Meier method and were compared and analyzed univariatly with a log-rank test. Multivariate analysis was performed using the Cox proportional hazards model for survival analysis. A P value of < 0.05 was considered statistically significant.

Data availability statement No additional data are available.

Results

Analysis of interval time for liver metastases originating from gastric cancer after radical gastrectomy and related clinicopathological characteristics

Interval time for liver metastases

The median liver metastases-free interval time for 436 gastric cancer patients with metachronous liver metastases in our group was 14 months (6–293 months), with liver metastases-free survival rates at 1, 2, 3, 5, and 10 years were 57.5, 28.1, 22.3, 12.0, and 5.3% respectively. For most of these patients (68.5%), liver metastases were diagnosed metachronously within 2 years after radical gastrectomy.

Univariate and multivariate analysis of interval time for liver metastases

Clinicopathological and treatment-related factors were analyzed for prognostic significance in the 436 patients. Five factors were found to be associated with liver metastases-free interval by univariate analysis: size of primary tumor ($P = 0.012$), lymphovascular invasion ($P < 0.001$), T ($P = 0.003$), N ($P < 0.001$), and primary tumor location ($P = 0.004$) (Table 1). The following factors were not significant prognostic indicators: gender ($P = 0.480$), age ($P = 0.650$), family history of malignancies ($P = 0.125$), histological differentiation ($P = 0.210$), resection margin ($P = 0.269$), size of the largest liver metastatic lesion ($P = 0.074$), and H ($P = 0.145$).

Multivariate analysis was performed to determine the independent prognostic factors. Variables displaying a P value of less than 0.05 by univariate analysis were included in the Cox regression model (Table 2); T ($P = 0.041$), N

($P = 0.023$), and lymphovascular invasion ($P < 0.001$) were shown to be significantly independent indicators influencing interval time for liver metastases from gastric cancer after radical gastrectomy.

Analysis of survival and prognostic factors after presence of liver metastases

Overall survival after presence of liver metastases

The overall survival rates for the 436 patients were 44.5, 29.7, 16.3, and 16.3% at 1, 2, 3, and 5 years respectively since the presence of metachronous liver metastases, with a median survival time (MST) of 11 months (1–46 months) (Fig. 1).

Univariate and multivariate analysis of overall survival after presence of liver metastases

Table 3 shows the outcomes of univariate analysis after the presence of metachronous liver metastases. MST of patients between different age groups were 13 months (≤ 65) and 8 months (> 65) respectively ($P = 0.017$). The survival time of group N0–2 (MST 13 months) was significantly longer than that of group N3 (MST 6 months) ($P = 0.001$); non-T4b patients had better survival outcome than that of T4b patients (MST 13 vs. 5 months, $P = 0.007$). MST of patients in group H1, H2, and H3 were 18, 13, and 6 months after presence of metachronous liver metastases (Pairwise comparisons: H1 vs. H2, $P = 0.24$; H1 vs. H3, $P < 0.001$; H2 vs. H3, $P = 0.025$). Comparing to supportive or palliative therapy only, active treatment of hepatic metastases (hepatic surgical treatment, TACE, MCT, or systemic chemotherapy) might prolong patients' survival after occurrence of hepatic metastases.

The following factors were not significant prognostic indicators for overall survival after presence of liver metastases: gender ($P = 0.778$), family history of malignancies ($P = 0.603$), size of primary gastric cancer ($P = 0.306$), location of primary gastric cancer ($P = 0.478$), histological differentiation of primary gastric cancer ($P = 0.202$), lymphovascular invasion ($P = 0.566$), adjuvant chemotherapy after radical gastrectomy ($P = 0.591$), liver metastases-free interval ($P = 0.822$), and size of the largest liver metastatic lesion ($P = 0.216$).

Entering variables with a P value less than 0.05 by univariate analysis into a Cox regression model for multivariate analysis, the outcomes showed that N ($P = 0.025$, Fig. 2), H (H2 vs. H1, $P = 0.036$; H3 vs. H1, $P < 0.001$, Fig. 3), and treatment of hepatic metastases ($P < 0.001$, Fig. 4) were independent prognostic factors for survival after the presence of metachronous liver metastases from gastric cancer (Table 4).

Table 1 Univariate analysis of interval time for liver metastases

Variables	No. of patients	Liver metastases-free interval[a]	Liver metastases-free rate (%)				P
			1 year	2 years	3 years	10 years	
Primary tumor location							
Distal 1/3	236	17	63.3	36.2	19.2	9.3	0.004
Non-distal 1/3	200	14	53.1	23.1	11.1	0	
Primary tumor size							
≤ 5 cm	284	18	65.1	35.5	14.4	7.4	0.004
> 5 cm	152	12	45.8	19.3	3.7	0	
T							
T1	52	57	91.2	75.8	45.1	29.7	0.003
T2–T4b	384	15	55.3	25.1	7.3	3.2	
N							
N0, N1, N2	340	17	66.0	34.2	13.0	6.9	< 0.001
N3a, N3b	96	10	30.3	13.6	0	0	
Lymphovascular invasion							
Absent	376	17	68.9	32.8	10.6	5.3	< 0.001
Present	60	9	7.8	7.5	7.8	0	

Only significant results at univariate analysis are shown

[a] Median value (months)

Analysis of the therapeutic effect of different treatment methods on metachronous liver metastases from gastric cancer

Comparison of baseline data of patients receiving different treatment methods

We further analyzed the survival difference of the 436 patients after appearance of hepatic metastases stratified by therapeutic strategies of the metastatic lesions. Forty-four patients without any treatment and 20 patients undergoing microwave coagulation therapy were not included in this study. Table 5 showed the clinicopathological characteristics of the 372 patients.

We separated our patients into three groups, including surgical treatment group (liver resection and RFA), TACE group, and systemic chemotherapy group. The three groups had significant difference in gender ($P = 0.033$), lymphovascular invasion ($P = 0.006$), and degree of liver metastases (H) ($P = 0.015$). Systemic chemotherapy group had more female patients compared to the other two groups. The proportion of

patients with lymphovascular invasion in TACE group (1.8%) was lower than that of surgical treatment group (20.0%) and systemic chemotherapy group (21.7%). As for the degree of liver metastases, patients with H1 and H2 metastases accounted for 86.7 and 13.3% separately of all patients in surgical treatment group and there was no H3 patients in this group. Proportion of H2 and H3 liver metastases patients in TACE group and systemic chemotherapy group was significantly higher than that in surgical treatment group.

Survival of patients receiving different treatments after the presence of liver metastases

Median survival time (MST) of patients with different treatments was compared according to different liver metastases degrees (H1/ H2 and H3). Because there were no H3 patients receiving surgical treatment of hepatic metastases, survival difference was compared between patients with TACE and systemic chemotherapy only.

Table 2 Multivariate analysis of interval time for liver metastases

Variables	Multivariate P values	OR	95% CI
Primary tumor location (non-distal 1/3 vs. distal 1/3)	0.208	1.425	0.838–2.127
Primary tumor size (> 5 cm vs. ≤ 5 cm)	0.139	1.513	0.936–2.182
T (T2, T3, T4 vs. T1)	0.041	3.140	1.573–6.283
N (N3a, N3b vs. N0, N1, N2)	0.023	1.714	1.027–2.891
Lymphovascular invasion (present vs. absent)	< 0.001	4.208	2.274–7.892

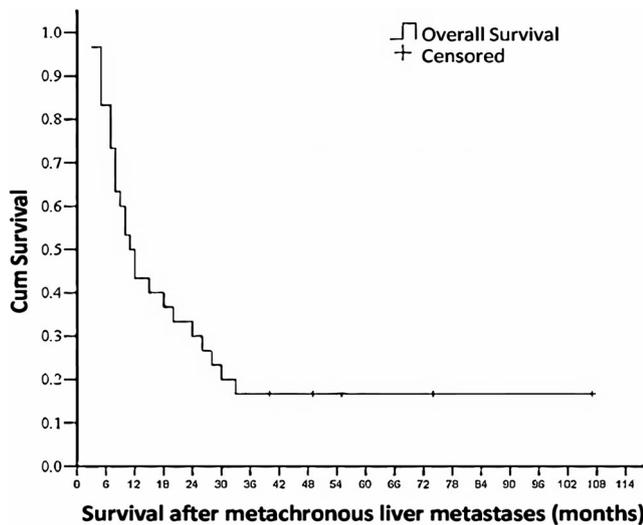OR odds ratio, CI confidential interval

Fig. 1 Median survival in 436 patients. Kaplan-Meier survival curve of the 436 gastric cancer patients in this study showed a median survival of 11.0 months (1–46 months) after the presence of metachronous liver metastases

Figure 5 showed the overall survival stratified according to different treatments in H1/ H2 group. MST for surgical treatment, TACE, and systemic chemotherapy groups was 25, 15, and 11 months respectively (Pairwise comparisons: surgical treatment vs. systemic chemotherapy, $P = 0.015$; surgical treatment vs. TACE, $P = 0.417$; systemic chemotherapy vs. TACE, $P = 0.093$). However, no significant difference was observed between TACE (MST 9 months) and systemic chemotherapy (MST 6 months) groups ($P = 0.165$) in H3 patients (Fig. 6).

Discussion

Hematogenous metastasis is the main way of metastasis for gastric cancer patients [14]. Because liver is a parenchymal organ in upper abdomen with the most abundant blood supply and portal vein receives most of the venous reflux of the gastrointestinal tract, gastric cancer cells could translocate to the liver via bloodstream easily [15]. Hepatic metastases account for 77.8% of all hematogenous metastases [16]. Approximately 2.0–9.9% patients were found to have liver metastases before or at the definite diagnosis of primary gastric cancer and 13.5–30.0% were presented with liver metastases after radical gastrectomy [17]. All cases in this study were identified with metachronous liver metastases more than 3 months after D2 radical gastrectomy because metastases occurred within 3 months were usually micro-metastases undetected by clinicians at the definite diagnosis of gastric cancer.

In our analysis, the median non-hepatic metastases interval time was 14 months for 436 gastric cancer patients with metachronous liver metastases and liver metastases occurred within 2 years in 68.5% of them, which was consistent with previous study [18]. Marrelli et al. [19] conducted a prospective cohort study among 208 patients after radical gastrectomy, 13.5% of whom had liver metastases during postoperative follow-up with 82.1% presented with metastases within 2 years after surgery. Therefore, whether there are liver metastases during the follow-up after radical gastrectomy should be examined regularly. In addition, it will be of great help for clinicians to identify patients who are prone to have liver metastases after gastric surgery in a short period of time if they are familiar with

Table 3 Univariate analysis of overall survival after the presence of liver metastases

Variables	No. of patients	Median OS after liver metastases (months)	OS rate after liver metastases (%)			P
			1 year	2 years	3 years	
Age (years)						
≤ 65	260	14	55.1	24.8	7.3	0.015
> 65	176	7	34.0	11.3	6.9	
T						
Non-T4b	324	13	51.6	22.3	9.8	0.005
T4b	112	6	32.4	7.8	0	
N						
N0, N1, N2	340	14	53.6	22.8	10.3	0.003
N3a, N3b	96	5	20.1	4.9	0	
Extent of liver metastases (H)						
H1	176	19	64.5	41.1	13.8	< 0.001
H2	120	12	51.7	7.2	6.9	
H3	140	5	18.3	0	0	
Hepatic surgical treatment						
Absent	44	3	0	0	0	< 0.001
Present	392	14	51.3	20.3	7.9	

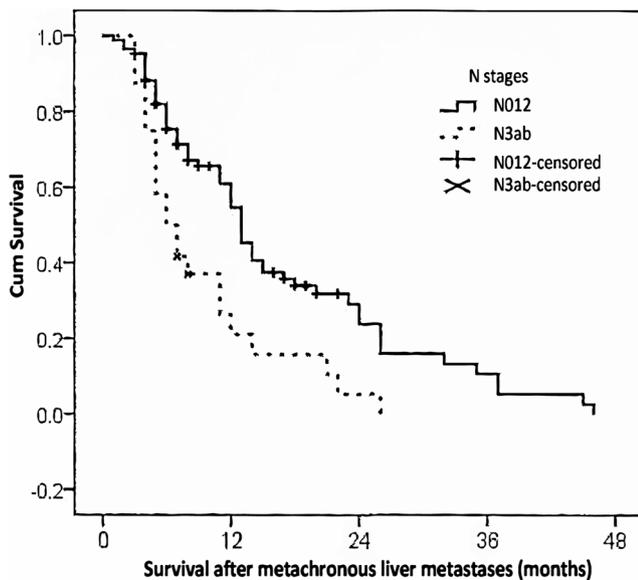Only significant results at univariate analysis are shown. *OS* overall survival

Fig. 2 Overall survival for gastric cancer patients of different N stages after the presence of metachronous liver metastases ($P = 0.025$)

the factors related to the non-hepatic metastases interval time [20]. Consequently, these patients should be monitored and followed up carefully in order to improve their prognosis.

This study showed that N stage, T stage, and lymphovascular invasion were independent factors affecting interval for non-hepatic metastases after radical gastrectomy. This interval were 17 and 10 months ($P = 0.025$) respectively in patients with N0–2 and N3 metastases, which is in accordance with the study of Kumagai et al. [21] Many studies pointed out that there was close relationship between N stage and hematogenous metastasis in gastric cancer [22, 23]. Patients with higher N stage were more likely to develop metastatic lesions because of the large amount
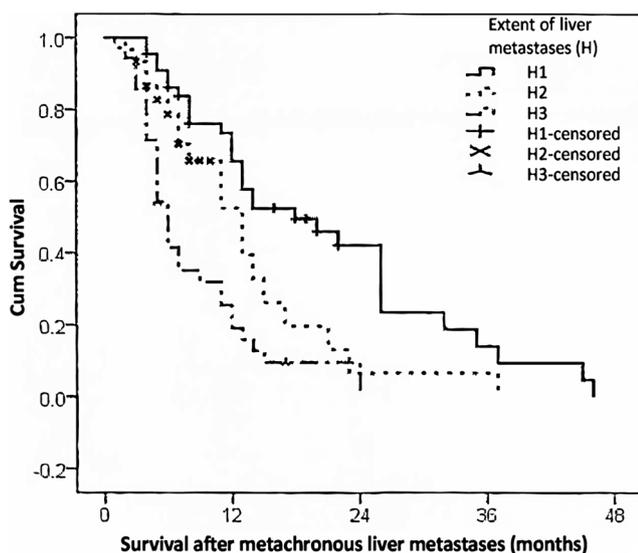

Fig. 3 Overall survival for H1, H2, and H3 gastric cancer patients after the presence of metachronous liver metastases (Pairwise comparisons: H2 vs. H1, $P = 0.036$; H3 vs. H1, $P < 0.001$)
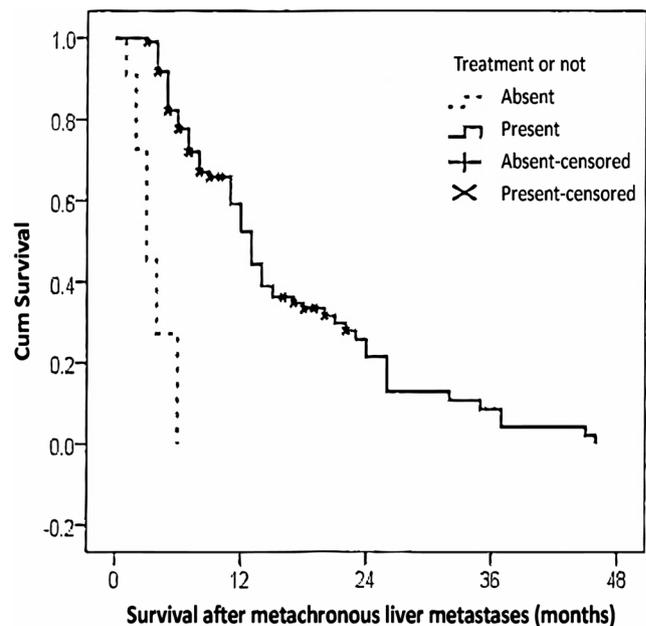

Fig. 4 Overall survival for gastric cancer patients with and without treatment after the presence of metachronous liver metastases ($P < 0.001$)

of tumor cells in lymphatic system and blood circulation [24]. T stage is an important parameter indicating the progression of primary gastric cancer [25]. In this study, the median non-hepatic metastases interval time of T1 patients was significantly longer than those with T2, T3, T4a, and T4b metastases (57 months vs. 17, 15, 14, and 10 months, $P = 0.041$) respectively. Our study showed that patients with lymphovascular invasion had shorter median interval for non-hepatic metastases (9 vs. 17 months, $P < 0.001$) due to the fact that lymphovascular tumor thrombus might be able to reach secondary organs through blood circulation and developed into metastatic lesions [26]. Okano K et al. indicating that the size of primary gastric cancer was of independent prognostic value for non-hepatic metastases interval [27]. However, in our study, it was only found to be significant by univariate analysis and was not an independent prognostic factor suggesting that volume of primary gastric cancer might

Table 4 Multivariate analysis of overall survival after the presence of liver metastases

Variables	Multivariate P values	OR	95% CI
Age (≤ 65 vs. > 65)	0.078	1.515	0.928–2.327
T (Non-T4b vs. T4b)	0.059	1.647	0.963–2.758
N (N0, N1, N2 vs. N3a, N3b)	0.025	2.083	1.097–3.596
Extent of liver metastases (H)			
H2 vs. H1	0.036	1.916	1.133–3.379
H3 vs. H1	< 0.001	2.979	1.633–5.369
Hepatic surgical treatment (absent vs. present)	< 0.001	0.192	0.081–0.457

OR odds ratio, *CI* confidential interval

Table 5　Clinicopathological characteristics of GCMLM patients receiving different treatment

Variables	Hepatic surgical treatment	TACE	Systemic chemotherapy	Total	P
Age					
≤ 65	28 (46.7)	148 (67.3)	64 (69.6)	240 (64.5)	0.275
> 65	32 (53.3)	72 (32.7)	28 (30.4)	132 (35.5)	
Gender					
Male	52 (86.7)	196 (89.1)	60 (65.2)	308 (82.8)	0.033
Female	8 (13.3)	24 (10.9)	32 (34.8)	64 (17.2)	
Family history of malignancies					
Present	12 (20.0)	72 (32.7)	20 (21.7)	268 (72.0)	0.453
Absent	48 (80.0)	148 (67.3)	72 (78.3)	104 (28.0)	
Primary tumor size					
≤ 5 cm	32 (53.3)	136 (61.8)	72 (78.3)	240 (64.5)	0.257
> 5 cm	28 (46.7)	84 (38.2)	20 (21.7)	132 (35.5)	
Primary tumor location					
Proximal 1/3	20 (33.3)	80 (36.4)	20 (21.7)	120 (32.3)	0.837
Middle 1/3	4 (6.7)	12 (5.5)	8 (8.7)	24 (6.5)	
Distal 1/3	32 (53.3)	108 (49.1)	56 (60.9)	196 (52.7)	
Whole	4 (6.7)	20 (9.1)	8 (8.7)	32 (8.6)	
Histology classification					
Well/Moderately differentiated	24 (40.0)	84 (38.2)	32 (34.8)	140 (37.6)	0.930
Poorly/Undifferentiated	36 (60.0)	136 (61.8)	60 (65.2)	232 (62.4)	
T					
T1	0 (0)	24 (10.9)	24 (26.1)	48 (12.9)	0.083
T2, T3	24 (40.0)	40 (18.2)	16 (17.4)	80 (21.5)	
T4	36 (60.0)	156 (70.9)	52 (56.5)	244 (65.6)	
N					
N0	16 (26.7)	48 (21.8)	36 (39.1)	100 (26.9)	0.745
N1	16 (26.7)	64 (29.1)	20 (21.7)	100 (26.9)	
N2, N3	28 (46.7)	108 (49.1)	36 (39.1)	172 (46.2)	
Lymphovascular invasion					
Present	12 (20.0)	4 (1.8)	20 (21.7)	36 (9.7)	0.006
Absent	48 (80.0)	216 (98.2)	72 (78.3)	336 (90.3)	
Chemotherapy following primary gastrectomy					
Present	60 (100)	192 (87.3)	84 (91.3)	336 (90.3)	0.330
Absent	0 (0)	28 (12.7)	8 (8.7)	36 (9.7)	
Liver metastases-free interval					
≤ 12 months	28 (46.7)	76 (34.5)	36 (39.1)	140 (37.6)	0.831
12–36 months	24 (40.0)	84 (38.2)	40 (43.5)	148 (39.8)	
36–60 months	4 (6.7)	32 (14.5)	8 (8.7)	44 (11.8)	
> 60 months	4 (6.7)	28 (12.7)	8 (8.7)	40 (10.8)	
Diameter of the largest metastasis					
≤ 3 cm	24 (40.0)	100 (45.5)	60 (65.2)	184 (49.5)	0.187
> 3 cm	36 (60.0)	120 (54.5)	32 (34.8)	188 (50.5)	
Extent of liver metastases (H)					
H1	52 (86.7)	80 (36.4)	28 (30.4)	160 (43.0)	0.015
H2	8 (13.3)	60 (27.3)	32 (34.8)	100 (26.9)	
H3	0 (0)	80 (36.4)	32 (34.8)	112 (30.1)	

only function as a synergistic factor for non-hepatic metastases interval to some extent. There were studies showing that gastric cancer patients with higher degree of differentiation tended to have liver metastases [28], but others held the opposite opinion [29]. Differentiation in our study group had nothing to do with the non-hepatic metastases interval ($P = 0.289$).
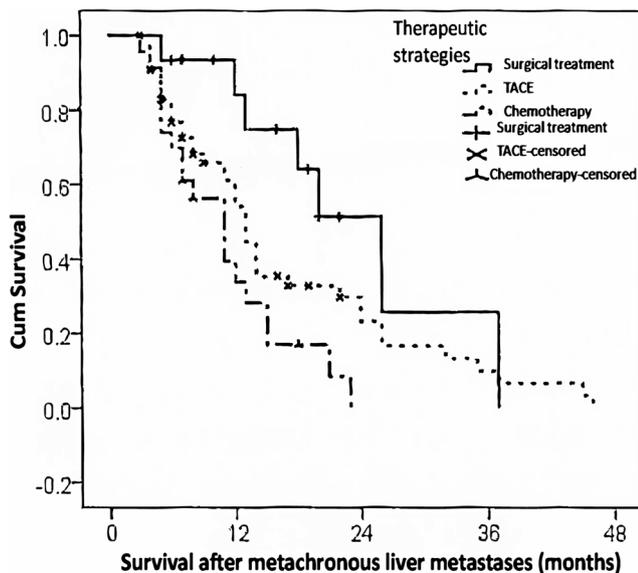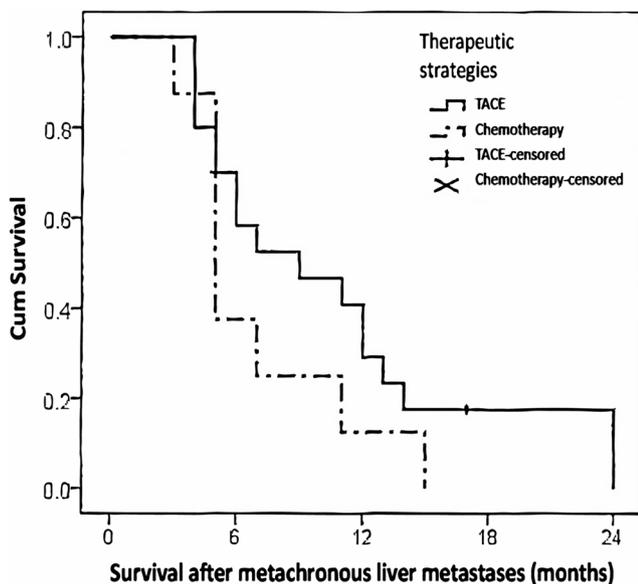
Fig. 5 Overall survival for H1 and H2 gastric cancer patients receiving different therapeutic strategies after the presence of metachronous liver metastases (Pairwise comparisons: surgical treatment vs. systemic chemotherapy, $P = 0.015$; surgical treatment vs. TACE, $P = 0.417$; systemic chemotherapy vs. TACE, $P = 0.093$)

The overall survival rates for 436 patients were 44.5, 29.7, 16.3, and 16.3% at 1, 2, 3, and 5 years, respectively, with an MST of 11 months (1–46 months). Multivariate analysis showed that N stage, H type, and treatment of hepatic metastases were independent prognostic factors for survival of GCMLM patients after presence of liver metastases. Ueda K et al. [30] indicated that N stage was an independent prognostic factor for survival among H1 and H2 patients without peritoneal metastases. Median survival for H1, H2, and H3 patients in

Fig. 6 Overall survival for H3 gastric cancer patients receiving different therapeutic strategies after the presence of metachronous liver metastases ($P = 0.165$)

our study were 19, 12, and 5 months respectively ($P < 0.001$), which was in accordance with previous reports [31]. Univariate analysis indicated that age (≤ 65 or > 65 years old) was a prognostic factor after liver metastases but did not have independent prognostic value. The proportion of untreated patients > 65 years old was significantly higher than those ≤ 65 years old. The lower proportion of elder patients receiving active treatment might be the main reason for the significance of age in univariate analysis. The development of liver metastases was a fatal event for gastric cancer patients and always be a major cause of cancer-related death [32]. If no specific treatment was given, the prognosis was extremely poor, with an MST of 3–5 months [33]. At present, standard treatment for GCLM has not been established. Even though, the survival of patients receiving active treatment (including hepatic metastasectomy, TACE, microwave coagulation, and systematic chemotherapy) significantly improved compared with those without any treatment or with palliative treatment only ($P < 0.001$).

Generally speaking, the therapeutic methods for advanced or metastatic gastric cancer referred to palliative chemotherapy and the reported MST was approximately 7 months [34]. Hepatic metastatic lesions of gastric cancer were characterized by disseminated [35]. Moreover, liver metastases from gastric cancer were often distributed in two hepatic lobes. Most patients presented with H2 and H3 metastasis and sometimes accompanied by extrahepatic metastases [36]. These contributed to the small number of patients suitable for hepatic metastasectomy.

Different medical institutes [11, 12] showed that selected patients, accounting for 0.2 to 37.9% of all cases with hepatic metastases, were suitable for liver resection, with the survival rates ranging from 15 to 77% at 1 year, 0 to 42% at 5 years, and an MST of 8.8–34 months. In our analysis, 13.8% of the 436 patients with metachronous liver metastases received surgical treatment and there were no H3 patients. Currently, we considered patients with solitary liver metastasis, with multiple metastases confined to one hepatic lobe and patients with less than three metastatic lesions scattered in half liver could benefit from liver resection. Among patients with H1 and H2 liver metastases, the median survival time (MST) was 25, 15, and 11 months in surgical treatment group, TACE group, and systemic chemotherapy group respectively after the presence of liver metastases. Surgical treatment brings about more survival benefits for patients with H1 and H2 liver metastases than systemic chemotherapy. However, whether surgical treatment is superior to TACE still needs large sample studies to further evaluate its efficacy and safety. Patients with H3 metastases were not suitable for hepatic resection while TACE combined with systemic chemotherapy could be considered as an alternative therapy. TACE, as one of the promising therapeutic strategies, took advantage of the first pass effect to make drugs concentrate in the liver, helping to kill tumor cells from gastric cancer. Besides, TACE had little toxicity and side effects compared to systemic chemotherapy [37]. Hirasawa et

al. [38] have shown that the efficacy rate for GCLM patients undergoing TACE combined with intravenous chemotherapy was 62.5%, with the median survival of 36.1 months. Patients in TACE group and systemic chemotherapy group were stratified into two subgroups (H1, H2, and H3). The survival of patients receiving TACE was slightly better than that of systemic chemotherapy without showing significant difference ($P = 0.091$ for H1H2 patients and $P = 0.180$ for H3 patients respectively). TACE was not suitable when volume of the hepatic metastases accounted for more than 75% of the liver because of the limitation of curative effect and the probability of increased complications [38].

Admittedly, this study also has some limitations. First of all, as a retrospective study, selection bias is possible. Patients in the resection group may have presented with a more acceptable oncologic burden for surgical resection. Secondly, the timing, regimen, and dosage of chemotherapy were not recorded in the database and could not therefore be determined. Some patients might have received chemotherapy without being admitted. However, we believed that even in patients who received aggressive chemotherapy for metastatic gastric cancer, liver resection still had a role. Thirdly, only a relatively small sample size of patients could be identified in this study and the data were secondary and administrative in nature. Consequently, this study had limited statistical and inferring power because of this constraint. Fourthly, other important parameters, such as the details of each operation, quality of life after curative resection, and some details, including the initial stage, extent, and pathological characteristics of the primary tumor were not recorded and therefore could not be obtained in the current study.

Conclusion

Metachronous liver metastasis from gastric cancer often occurs within 2 years. T stage, N stage, and lymphovascular invasion were independent factors influencing the liver metastases-free interval after radical gastrectomy. The occurrence of liver metastases should be closely monitored 2 years after radical gastrectomy, in particular for patients with T2-T4b, N3, or those with lymphovascular invasion. N stage, extent of liver metastases (H), and hepatic surgical treatment were independent prognostic factors for survival after liver metastases. For H1 and H2 patients, hepatic metastasectomy may be able to prolong survival, while surgical treatment is not recommended for H3 patients. TACE is a promising local therapy. However, its efficacy and safety compared with single systemic chemotherapy still need to be explored in future prospective studies.

Compliance with ethical standards

Abbreviations GC, gastric carcinoma; GCCM, colorectal metastases from gastric cancer; GCMLM, gastric cancer with metachronous liver metastases; GCLM, liver metastases from gastric cancer; TACE, transcatheter arterial chemoembolization; MCT, microwave coagulation therapy; MST, median survival time

References

1. Thun MJ, DeLancey JO, Center MM, Center MM, Jemal A, Ward EM (2010) The global burden of cancer: priorities for prevention. Carcinogenesis 31:100–110
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
3. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr (1991) Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 265:1287–1289
4. Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137–2150
5. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS (2004) Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 240:808–816
6. Sakamoto Y, Sano T, Shimada K, Esaki M, Saka M, Fukagawa T et al (2007) Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. J Surg Oncol 95:534–539
7. Tiberio GA, Coniglio A, Marchet A, Marrelli D, Giacopuzzi S, Baiocchi L et al (2009) Metachronous hepatic metastases from gastric carcinoma: a multicentric survey. Eur J Surg Oncol 35: 486–491
8. Slupski M, Wlodarczyk Z, Jasinski M, Masztalerz M, Tujakowski J (2009) Outcomes of simultaneous and delayed resections of synchronous colorectal liver metastases. Can J Surg 52:E241–E244
9. Saiura A, Umekita N, Inoue S, Maeshiro T, Miyamoto S, Matsui Y et al (2002) Clinicopathological features and outcome of hepatic resection for liver metastasis from gastric cancer. Hepato-Gastroenterology 49:1062–1065

10. Kunisaki C, Makino H, Takagawa R, Oshima T, Nagano Y, Fujii S et al (2008) Impact of palliative gastrectomy in patients with incurable advanced gastric cancer. Anticancer Res 28:1309–1315

11. Cheon SH, Rha SY, Jeung HC, Im CK, Kim SH, Kim HR et al (2008) Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. Ann Oncol 19:1146–I 153

12. Sakamoto Y, Ohyama S, Yamamoto J, Yamaka K, Seki M, Ohta K et al (2003) Surgical resection of liver metastases of gastric cancer: an analysis of a 17-year experience with 22 patients. Surgery 133: 507–511

13. Ajani JA (2005) Evolving chemotherapy for advanced gastric cancer. Oncologist 10(Suppl 3):49–58

14. Shin A, Kim J, Park S (2011) Gastric cancer epidemiology in Korea. J Gastric Cancer 11:135–140

15. Li C, Yan M, Chen J, Xiang M, Zhu ZG, Yin HR et al (2010) Survival benefit of non-curative gastrectomy for gastric cancer patients with synchronous distant metastasis. J Gastrointest Surg 14: 282–288

16. Zacherl J, Zacherl M, Scheuba C, Steininger R, Wenzl E, Mühlbacher F et al (2002) Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. J Gastrointest Surg 6:682–689

17. Markar SR, Mikhail S, Malietzis G, Athanasiou T, Mariette C, Sasako M et al (2016) Influence of surgical resection of hepatic metastases from gastric adenocarcinoma on long-term survival: systematic review and pooled analysis. Ann Surg 263:1092–1101

18. Tsujimoto H, Ichikura T, Ono S, Suqasawa H, Hiraki S, Sakamoto N et al (2010) Outcomes for patients following hepatic resection of metastatic tumors from gastric cancer. Hepatol Int 4:406–413

19. Marrelli D, Roviello F, De Stefano A, Fotia G, Giliberto C, Garosi L et al (2004) Risk factors for liver metastases after curative surgical procedures for gastric cancer: a prospective study of 208 patients treated with surgical resection. J Am Coll Surg 198:51–58

20. Takemura N, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y et al (2012) Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. Langenbeck's Arch Surg 397:951–957

21. Kumagai K, Tanaka T, Yamagata K, Yokoyama N, Shimizu K (2001) Liver metastasis in gastric cancer with particular reference to lymphatic advancement. Gastric Cancer 4:150–155

22. Koga S, Takebayashi M, Kaibara N, Nishidoi H, Kimura O, Kawasumi H et al (1987) Pathological characteristics of gastric cancer that develop hematogenous recurrence, with special reference to the site of recurrence. J Surg Oncol 36:239–242

23. Maehara Y, Orita H, Okuyama T, Moriguchi S, Tsujitani S, Korenaga D et al (1992) Predictors of lymph node metastasis in early gastric cancer. Br J Surg 79:245–247

24. Saito H, Tsujitani S, Kondo A, Ikeguchi M, Maeta M, Kaibara N (1999) Expression of vascular endothelial growth factor correlates with hematogenous recurrence in gastric carcinoma. Surgery 125: 195–201

25. Hyung WJ, Lee JH, Choi SH, Min JS, Noh SH (2002) Prognostic impact of lymphatic and/or blood vessel invasion in patients with node-negative advanced gastric cancer. Ann Surg Oncol 9:562–567

26. Dicken BJ, Graham K, Hamilton SM, Andrews S, Lai R, Listgarten J (2006) Lymphovascular invasion is associated with poor survival in gastric cancer: an application of gene-expression and tissue array techniques. Ann Surg 243:64–73

27. Okano K, Maeba T, Ishimura K, Karasawa Y, Goda F, Wakabayashi H et al (2002) Hepatic resection for metastatic tumors from gastric cancer. Ann Surg 235:86–91

28. Kwok CM, Wu CW, Lo SS, Shen KH, Hsieh MC, Lui WY (2004) Survival of gastric cancer with concomitant liver metastases. Hepato-Gastroenterology 51:1527–1530

29. Lim S, Muhs BE, Marcus SG, Newman E, Berman RS, Hiotis SP (2007) Results following resection for stage IV gastric cancer; are better outcomes observed in selected patient subgroups? J Surg Oncol 95:118–122

30. Ueda K, Iwahashi M, Nakamori M, Nakamura M, Naka T, Ishida K et al (2009) Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer. Langenbeck's Arch Surg 394:647–653

31. Saito H, Yamada Y, Tsujitani S, Ikeguchi M (2009) Clinicopathologic characteristics of gastric cancer patients who underwent noncurative gastrectomy with long-term survival. Langenbeck's Arch Surg 394: 99–103

32. Morise Z, Sugioka A, Hoshimoto S, Kato T, Ikeda M, Uyama I et al (2008) The role of hepatectomy for patients with liver metastases of gastric cancer. Hepato-Gastroenterology 55:1238–1241

33. Leong T (2005) Chemotherapy and radiotherapy in the management of gastric cancer. Curr Opin Gastroenterol 21:673–678

34. Samarasam I, Chandran BS, Sitaram V, Perakath B, Nair A, Mathew G (2006) Palliative gastrectomy in advanced gastric cancer: is it worthwhile? ANZ J Surg 76:60–63

35. Koga R, Yamamoto J, Ohyama S, Saiura A, Seki M, Seto Y et al (2007) Liver resection for metastatic gastric cancer: experience with 42 patients including eight long-term survivors. Jpn J Clin Oncol 37:836–842

36. Miyagaki H, Fujitani K, Tsujinaka T, Hirao M, Yasui M, Kashiwazaki M et al (2008) The significance of gastrectomy in advanced gastric cancer patients with non-curative factors. Anticancer Res 28:2379–2384

37. Hwang SE, Yang DH, Kim CY (2009) Prognostic factors for survival in patients with hepatic recurrence after curative resection of gastric cancer. World J Surg 33:1468–1472

38. Hirasawa T, Asahara S, Fujisaki S, Kuraoka K, Takano K, Kamei A et al (2008) Transcatheter arterial chemoembolization (TACE) using degradable starch microspheres (DSM) for metastatic liver tumors in patients with gastric cancer. Nippon Shokakibyo Gakkai Zasshi 105:367–372