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Original Article

Development of a prognostic index for gastric cancer with liver metastasis at initial diagnosis: a single center retrospective study

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Abstract: Objective: Prognosis of gastric cancer patients with liver metastasis (GCLM) at initial diagnosis has been poor and the optimal treatment modality and prognostic factors have remained unclear. Therefore, we sought to investigate prognostic factors of GCLM at initial diagnosis. Methods: Medical records of 389 patients of GCLM at their initial diagnosis from 2005 to 2016 were examined. Univariate and multivariate analysis were conducted with log-rank tests and Cox proportional hazards model, respectively. Results: The median overall survival (OS) was 13.6 months (95% confidence interval (CI): 12.5-14.7 months). Four independent prognostic factors were identified by multivariate analysis: non-intestinal type of Lauren classification (Hazard Ratio (HR) = 1.921, 95% CI, 1.203-3.066), serum AFP level ≥ 20 ng/mL (HR = 1.691, 95% CI, 1.206-2.785), complicated with extrahepatic metastasis (HR = 1.700, 95% CI, 1.007-2.872), and good response to first-line chemotherapy (HR = 0.035, 95% CI, 0.219-0.560). A simple prognostic index was generated using three risk groups: good (0 or 1 risk factors, n = 61), moderate (2 risk factors, n = 53), and poor (3 or 4 risk factors, n = 33). The median overall survival (OS) for good, moderate, and poor risk groups was 10.5, 13.7 and 20.7 months, respectively. Survival differences among the groups were highly significant ($P < 0.001$). Conclusions: Four prognostic factors were identified for patients of GCLM at initial diagnosis. Using a simple prognostic index, the patients were divided into three different risk groups. This prognostic model could help clinicians in decision-making regarding treatment modality after first-line chemotherapy.

Keywords: Gastric cancer, liver metastasis, alpha-fetoprotein, Lauren classification, prognostic index

Introduction

Gastric cancer is the fourth most common cancer globally and is the second most common cause of death worldwide. As a leading cause of cancer-related deaths, gastric cancer has gained much more attention in China than in any other country due to its high incidence and mortality rate [1, 2]. However, at the time of diagnosis, 35% of patients are with distant metastasis and the liver is the most common organ of distant metastases in gastric cancer [3]. Synchronous liver metastasis is a known unfavorable prognostic factor representative of aggressive biology, especially gastric cancer with liver metastasis (GCLM) at initial diagnosis.

Unlike colorectal cancer, liver metastases arising from gastric cancer are usually associated with other non-curative factors such as peritoneal, distant lymph node, and extensive intrahepatic metastasis. Therefore, in clinical practice, systemic chemotherapy has been the standard therapy recommended by both the National Comprehensive Cancer Network (NCCN) Guidelines [4] and European Society For Medical Oncology (ESMO) Guidelines [5]. However, the lack of improvement in survival has been disappointing.

Recently, several studies have reported that D2 lymphadenectomy plus hepatic surgical treatment may provide hope for long-term survival of judiciously selected patients with hepatic metastases from gastric cancer [6-8]. Many studies have reported that potential patients should be good operative candidates with favorable tumor biology such as small (< 5 cm) or isolated disease, long disease free in-

Table 1. Clinical characteristics of 389 patients

Characteristics	No. Patients (%)
Gender	
Male	310 (79.7%)
Female	79 (20.3%)
Age (year)	
< 65	263 (67.6%)
≥ 65	126 (32.4%)
ECOG	
0-1	340 (87.4%)
2-3	49 (12.6%)
Primary lesion site	
EGJ	160 (42.4%)
Non-EGJ	217 (57.6%)
Remnant or not known	12
Histology type	
Well-differentiated adenocarcinoma	8 (2.1%)
Moderately-differentiated adenocarcinoma	124 (32.6%)
Poor-differentiated adenocarcinoma	201 (52.9%)
Signet-ring cell adenocarcinoma	38 (10.0%)
Hepatoid adenocarcinoma	9 (2.4%)
Unknown	9
Lauren classification	
Intestinal	145 (64.2%)
Diffuse	41 (18.1%)
Mixed	40 (17.7%)
Unknown	163
HER2 status	
Positive	77 (31.8%)
Negative	165 (68.2%)
Unknown	147
Serum AFP level	
≥ 20 ng/ml	63 (24.0%)
< 20 ng/ml	200 (76.0%)
Unknown	126
Number of LM	
> 3	316 (83.2%)
1-3	64 (16.8%)
Unknown	9
Extrahepatic metastasis	
Present	283 (72.8%)
Absent	106 (27.2%)
Peritoneal dissemination	
Present	56 (14.4%)
Absent	333 (85.6%)

Abbreviations: GHA, gastric hepatoid adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor-2; AFP, α-fetoprotein; LM, liver metastasis.

terval (> 1 year), lesions amenable to resection with negative margins, and with no extrahepatic disease [3]. However, in GCLM patients at initial diagnosis, who underwent a radical operation even combined with liver resection, intrahepatic recurrence would be expected for two thirds of patients within two years after surgery [9]. This may be partly attributed to the aggressive biology of this kind of tumor.

Therefore, elucidating prognostic factors of GCLM at initial diagnosis, including clinicopathological features and bio-behavior features, is critical to deciding treatment modality and improving patient prognosis. We aimed to better determine prognostic factors of survival for patients with GCLM at initial diagnosis, identify patients with different prognosis, and help clinicians choose candidates who are most likely to benefit from active treatments after systemic chemotherapy, such as gastrectomy with or without hepatic resection. This would also allow for risk stratification of patients in future clinical trials.

Materials and methods

Patient selection

Between 2005 and 2016, 2,047 patients were diagnosed in our institute with metastatic or recurrent gastric adenocarcinoma. Five hundred sixteen were diagnosed with liver metastasis (LM) including postoperative LM (n = 127) and LM at initial diagnosis (n = 389). We included subjects who had LM at initial diagnosis, leaving 389 patients for analysis.

Data collection

We collected age, gender, ECOG, primary lesion site, histological type, Lauren classification, human epidermal growth factor receptor-2 (HER2) status, serum α-Fetoprotein (AFP) level before treatment (pretreatment serum AFP was assessed by radioimmunoassay, normal value: < 7 ng/mL), first-line chemotherapy regimen, response, surgery treatment and local treatment for LM, and survival information.

Table 2. Treatment modality and response of first-line chemotherapy

Variables	No. patients (%)
First-line chemotherapy regimen	
Platinum-based doublet regimen	250 (64.3%)
Taxanes-based doublet regimen	78 (20.0%)
Triplet regimen	35 (9.0%)
Single-drug regimen	22 (5.7%)
Others	4 (1.0%)
Response of first-line chemotherapy	
PR	156 (50.0%)
SD + PD	156 (50.0%)
NA	77
Surgery treatment for GCLM	
Radical resection	13 (3.3%)
Palliative resection of primary lesion	13 (3.3%)
No	363 (93.4%)
Local treatment for LM[a]	
Yes	86 (31.1%)
No	303 (68.9%)

[a]Including TACE, ablation, radiotherapy, and liver resection. abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NA, not achievable; TACE, transcatheter arterial chemoembolization.

Follow up care

All patients were regularly followed up from the date of first hospitalization at our center. Objective response rate (ORR) was evaluated by RECIST version 1.0 (before 2009) and RECIST version 1.1. Overall survival (OS) was defined as the time from inspection of liver metastasis to death from any cause or the last follow up.

Statistics

To identify the prognostic factors GCLM at initial diagnosis, survival durations were calculated using the Kaplan-Meier method and were analyzed by log-rank test to compare cumulative survival durations. Cox proportional hazards model was used to determine univariate and multivariate hazards ratios for the study parameters. For all tests, a P value < 0.05 was considered significant. SPSS software (version 21.0; SPSS, Chicago, Illinois) was used for analyses. GraphPad Prism 6 (GraphPad Software, Inc, La Jolla, CA) was used for chart making.

Results

Clinical characteristics

A total of 389 patients of GCLM at initial diagnosis were evaluated. Median age was 60 years and 263 (67.6%) patients were under 65. The majority of patients (n = 310, 79.7%) were male. Concerning primary lesion site, 160 (42.4%) tumors were located at the gastroesophageal junction (GEJ). The distribution of patients according to histology type were as follows: 8 (2.1%) were identified as well-differentiated adenocarcinoma, 124 (32.6%) were moderately-differentiated adenocarcinoma, 201 (52.9%) were poor-differentiated adenocarcinoma, and 38 (10.0%) of signet-ring cell adenocarcinoma. Notably, 9 (2.4%) were identified as hepatoid adenocarcinoma, which is defined as a special subtype of primary gastric adenocarcinoma characterized by the histologic structures of "hepatocellular carcinoma (HCC) like differentiation" with or without excessive production of AFP [10]. In addition, AFP-producing gastric cancer, a special subtype of gastric cancer, only accounts for 2.3~7.1% of all gastric cancers.

It has gained much attention in recent years due to its high incidence of liver metastasis and poor prognosis [11]. In the patient population of our present study, 63 (24.0%) patients had serum AFP levels ≥ 20 ng/mL at diagnosis. However, 145 (64.2%) patients were intestinal type of Lauren classification and 77 (31.8%) patients were confirmed as human epidermal growth factor receptor-2 (HER2) positive. The majority of patients were complicated with extrahepatic metastasis, 106 (27.2%) had liver metastasis only. Peritoneal dissemination rate was rather low in this population (n = 56, 14.4%). Also, most of the patients were diagnosed with multiple liver metastasis, only 64 (16.8%) patients had a liver metastasis number of 1-3. The clinicopathological features of all 389 patients are detailed in **Table 1**.

Treatment and response

Systemic chemotherapy is the recommended treatment for GCLM. The standard treatment regimen has been a matter of debate for a long time. In the analysis of first-line chemotherapy, 250 (64.3%) patients received platinum-based doublet regimen, 78 (20.0%) patients received

Table 3. ORR of different regimens as first-line chemotherapy

Regimens	Platinum-based doublet regimen (n = 205)	Taxanes-based doublet regimen (n = 66)	Triplet regimen (n = 28)	Single-drug regimen (n = 10)	P^a
PR	105 (51.2%)	33 (50.0%)	16 (57.1%)	2 (20.0%)	0.121
SD + PD	100 (48.8%)	33 (50.0%)	12 (42.9%)	8 (80.0%)	

[a]By Pearson's Chi-square test.

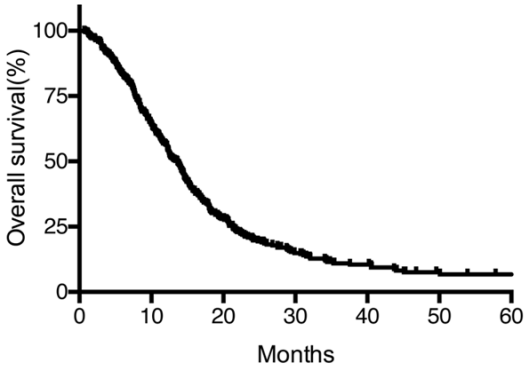

Figure 1. Kaplan-Meier survival curves of overall survival for all patients (n = 389): Median OS was 13.6 months (95% CI, 12.5-14.7 months).

taxanes-based doublet regimen, 35 (9.0%) patients received triplet regimen, and 22 (5.7%) patients received single-drug regimen. Among the original 389 patients, only 312 were evaluable for their response. Overall, the objective response rate (ORR) was 50%. Other than systemic chemotherapy, 13 (3.3%) patients received radical resection of both primary lesion and liver metastasis and 13 (3.3%) received palliative resection of the primary lesion. Also, 86 (31.1%) received local treatment for liver metastasis (**Table 2**).

Next, we analyzed the ORR of different regimens with results showing that ORR of doublet regimen, including platinum-based doublet regimen and taxanes-based doublet regimen, was similar to triplet regimen (51.2%, 50.0%, and 57.1%, respectively). Statistical analysis showed no significant difference (P = 0.121) (**Table 3**).

Survival analysis

During the follow up time, 310 out of 389 patients died, 35 were lost to follow up, and 44 remained alive. The median overall survival (OS) was 13.6 months (**Figure 1**). Prognostic factors including patient general status, primary lesion factors, metastasis factors, and treatment modality and response were examined. Among the factors related to overall survival time, ECOG (10.1 vs. 14.1 m, P = 0.001), HER2 status (16.1 vs. 14.1 m, P = 0.040), serum AFP level (10.9 vs. 14.9 m, P = 0.016), extrahepatic metastasis (12.2 vs. 16.1 m, P = 0.010), peritoneal dissemination (10.1 vs. 14.1 m, P < 0.001), and response to first-line chemotherapy (10.6 vs. 17.6 m, P < 0.001) were significant predictors (**Table 4**). Factors including age, gender, and primary lesion site had no significant differences.

In general treatment of inoperable locally advanced and/or metastatic (stage IV) GC, palliative chemotherapy has been suggested by most guidelines. Other treatment modalities beyond chemotherapy vary mainly based on patient response to chemotherapy. So, all factors readily available to clinicians before deciding whether to give active treatment were analyzed in our multivariate analysis, including primary tumor factors, metastasis factors, and response to first-line chemotherapy. Parameters of P < 0.200 by univariate analysis were included in multivariate analysis. Among these parameters, Lauren classification (P = 0.006), serum AFP level (P = 0.039), complicated with extrahepatic metastasis (P = 0.047), and response to first-line chemotherapy (P < 0.001) were independent factors for overall survival (**Table 5**).

Prognostic index and risk group

Four prognostic factors were identified from GCLM at initial diagnosis. A simple prognostic model was developed: prognostic index = Lauren classification (0 or 1) + serum AFP level at diagnosis (0 or 1) + complicated with extrahepatic metastasis (0 or 1) + response to first-line chemotherapy (0 or 1). Patients with a 0 or 1 prognostic index were categorized as the good risk group (n = 61), those with a prognostic index of 2 were categorized as moderate risk group (n = 53), and those with a prognostic index of 3 or 4 were categorized as the poor

Table 4. Prognostic factors associated with survival of GCLM at initial diagnosis

Factors	No. patients (%)	Median OS (months)	*P*[a]
Patient general condition and primary lesion factors			
Gender			
Male	310 (79.7%)	12.2	0.257
Female	79 (20.3%)	13.8	
Age			
≥ 65	263 (67.6%)	13.0	0.934
< 65	126 (32.4%)	13.8	
ECOG			
0-1	340 (87.4%)	14.1	0.001
2-3	49 (12.6%)	10.1	
Primary lesion site			
EGJ	160 (42.4%)	13.8	0.875
Non-EGJ	217 (57.6%)	12.7	
Differentiation degree			
Well-differentiated[a]	132 (34.7%)	14.1	0.055
Poor-differentiated[b]	248 (65.3%)	12.5	
Lauren classification			
Intestinal	145 (64.2%)	15.1	0.052
Non-intestinal	81 (35.8%)	11.4	
HER2 status			
Positive	77 (31.8%)	16.1	0.040
Negative	165 (68.2%)	14.1	
Serum AFP level			
≥ 20 ng/ml	63 (24.0%)	10.9	0.016
< 20 ng/ml	200 (76.0%)	14.9	
Metastasis lesion factors			
Number of LM			
> 3	316 (83.2%)	12.4	0.068
1-3	64 (16.8%)	16.1	
Extrahepatic metastasis			
Present	283 (72.8%)	12.2	0.010
Absent	106 (27.2%)	16.1	
Peritoneal dissemination			
Present	56 (14.4%)	10.1	< 0.001
Absent	333 (85.6%)	14.1	
First-line chemotherapy and response factors			
Regimen			
Doublet regimen	277 (91.7%)	14.1	0.158
Triplet regimen	25 (8.3%)	10.9	
Response			
PR	156	17.6	< 0.001
SD + PD	156	10.6	

[a]Including well differentiated and moderately differentiated adenocarcinoma. [b]Including poorly differentiated, signet ring cell adenocarcinoma, and GHA.

risk group (n = 33). Highly significant survival differences were observed among the three risk groups (P < 0.001, **Table 6**, **Figure 2**), where median overall survival for good, moderate, and poor risk groups was 20.7, 13.7 and 10.5 months, respectively.

Discussion

GCLM at initial diagnosis has a poor prognosis. Palliative chemotherapy, with various regimens, has been widely used as the main treatment choice. However, long term survival has been rarely observed and specific prognostic factors remain unclear. In our present study, we revealed that complicated with extrahepatic metastasis, non-intestinal type of Lauren classification, poor response to first-line chemotherapy, and serum AFP level ≥ 20 ng/mL at diagnosis are unfavorable independent prognostic factors of overall survival. Also, we tried first to develop a simple prognostic index model for GCLM at initial diagnosis, resulting in different risk groups with varying survival.

In general treatment of inoperable locally advanced and/or metastatic (stage IV) GC, doublet combinations of platinum and fluropyrimidines are generally used, with an ORR of 52.2%-58.7% [12, 13]. There remains controversy regarding utility of triplet regimes, especially in China and Japan [14]. GCLM patients at initial diagnosis received first-line systemic chemotherapy in our study and reached an overall ORR of 50%, which was similar to all advanced gastric cancers. Despite the ORR of triplet regimen seeming higher than doublet regimen in the present study (57.1% vs. 50.0~51.2%), OS turned out to be shorter in the triplet regimen group (10.9 vs. 14.1 m). This phenomenon could be partly attributed to the bias of patient selection for different regimens. In clinical practice, triplet regimen is always

Table 5. Multiple Cox regression analysis of prognostic factors associated with survival of GCLM at first diagnosis

Factors	HR	95% CI	P[a]
ECOG ≥ 2	1.147	0.059-2.201	0.681
Well-differentiated	0.772	0.402-1.483	0.438
Non-intestinal type of Lauren classification	1.921	1.203-3.066	0.006
HER2 negative	1.261	0.773-2059	0.353
Serum AFP ≥ 20 ng/ml	1.691	1.026-2.785	0.039
LM number of 0-3	0.714	0.394-1.294	0.267
Extrahepatic metastasis	1.700	1.007-2.872	0.047
Peritoneal dissemination	1.484	0.749-2.940	0.258
Triplet regimen	1.492	0.510-4.363	0.465
Response of PR	0.035	0.219-0.560	< 0.001

[a]Cox Regression abbreviations: HR, hazard ratio; CI, confidence interval; PR, partial response.

Table 6. Comparison of survival stratified into three risk groups according to prognostic risk

Risk group	Prognostic index	No. patients (%)	Median OS (months)	95% CI	P[a]
Good	0-1	61 (41.5%)	20.7	17.8-23.6	< 0.001
Moderate	2	53 (36.1%)	13.7	10.2-17.2	
Poor	3-4	33 (22.4%)	10.5	9.1-11.9	

[a]Log-rank test.

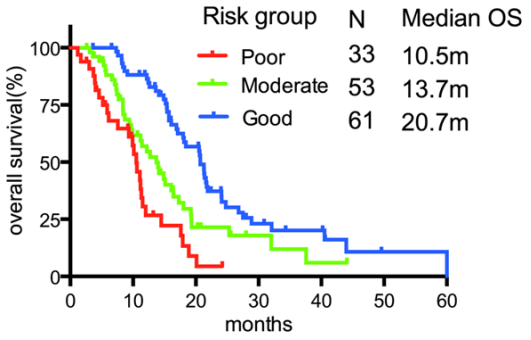

Figure 2. Overall survival curves according to prognostic index: Median survival time for the good-risk, moderate-risk, and poor-risk groups were 10.5, 13.7, and 20.7 months, respectively. ($P < 0.001$).

used in patients with a heavy tumor burden, which may be associated with poor prognosis. More work needs to be done in the future regarding the optimal treatment regimen for GCLM at initial diagnosis.

Besides palliative chemotherapy, whether other surgery treatments, including radical and palliative surgery, could benefit GCLM at initial diagnosis remains controversial. Several retrospective studies have revealed that curative resection might offer a chance for long-term survival in carefully selected patients of GCLM at initial diagnosis [6, 9] and active treatment modality was reported to benefit candidates with a favorable prognosis, especially those who had a lesser number of liver metastases [7, 15]. The number of LM was not significantly associated with OS in our study, indicating that tumor bio-behavior may play a more important role in survival prognosis. On the other hand, whether palliative gastrectomy could improve survival in patients with metastatic gastric cancer still remains controversial [16]. A prospective randomized controlled phase III study REGATTA failed to show that gastrectomy followed by chemotherapy can bring any survival benefit for advanced gastric cancers with a single non-curable factor [17]. In another study of GC with peritoneal metastasis, results showed that patients who gained disease control after chemotherapy had a longer median OS in the gastrectomy group than patients in the non-gastrectomy group [18]. All of these results suggest that response to first-line chemotherapy needs to be a factor for consideration when discriminating the subgroup of patients most likely to benefit from radical or palliative surgery.

Moreover, in our present study, we elucidated the correlation between response to chemotherapy and survival prognosis in GCLM at initial diagnosis. This may be partially because those patients with good tumor control could get more treatment chances after first-line chemotherapy, further improving overall survival. Regrettably, the number of patients in our study that received surgery was rather small. Although our results showed that patients who received surgery for a primary tumor with or without resection of liver metastasis could harvest a significant survival benefit, we still cannot draw

a definite conclusion. The benefit of surgery for this subgroup of gastric cancer needs be confirmed in future prospective clinical trials.

Intestinal type of Lauren classification has already been accepted as one of the most important prognostic factors for all gastric cancers, representing a more favorable biology as compared with diffuse type [19]. Although the Lauren classification system dates back to 1965, it is still widely accepted and employed by pathologists and physicians today and represents a simple but robust classification approach, providing the basis for individualized treatment for advanced cancer [20]. The importance of the Lauren classification also grabbed our attention in the present study. Nearly two thirds of GCLM patients at initial diagnosis in the present study were intestinal type, obviously higher than the 43.7% reported in a study enrolling all gastric cancers [19]. Also, our results demonstrate that it is an independent prognostic factor for survival of GCLM patients at initial diagnosis, in accordance with previous studies [21]. We know that the two Lauren types have several distinct clinical characteristics, molecular characteristics, and response to chemotherapy [22-24], which may partly explain their biological heterogeneity and different prognosis.

Another new finding of our study was that serum AFP $\geq$ 20 ng/mL is an unfavorable prognostic factor for GCLM at initial prognosis. AFP is a fetal serum protein produced by fetal and yolk sac cells and by some fetal gastrointestinal cells [25]. After birth, levels of AFP rapidly decrease. Elevation of AFP in serum of people older than one year is indicative of either HCC or yolk sac tumor. In addition, some reports have shown that AFP could also be produced by other tumors including gastric cancer, rectal cancer, pancreas cancer, gallbladder cancer, lung cancer, and bladder cancer, etc. [12]. In 1970, Bourreille Haimeiy first reported a case of AFP-producing GC, which refers to a type of gastric cancer in which AFP is positive in the immunohistochemical staining of pathological specimen [26]. AFP is already widely accepted as one of the most important tumor markers for GCLM, as many previous reports have shown that AFP-producing gastric cancer has a poorer prognosis and much higher LM rate than AFP-negative gastric cancer [27-29]. The significance of this marker was further confirmed in our present study. Our study reveals that serum AFP level is an independent prognostic factor for GCLM at initial diagnosis. It has been frequently reported that AFP-producing gastric cancer has a high rate of liver metastasis, an aggressive behavior, and poor response to chemotherapy [29-31] indicating that serum AFP-elevated GCLM should be treated carefully and distinctively from AFP-negative patients.

Finally, a simple prognostic index was developed and we identified three different risk groups. Although this was a retrospective observational study, since all four prognostic factors can easily be evaluated, these results could be helpful in designing future treatment approaches for GCLM at initial diagnosis. In the future, molecular markers predictive of survival could be incorporated into the proposed model to better deicide treatment modality. Our proposed prognostic index still requires further validation.

In conclusion, for GCLM patients at initial diagnosis, we found that Lauren classification, extrahepatic metastasis, different response to first-line chemotherapy, and serum AFP level are independent prognostic factors for survival. This prognostic model could help clinicians in decision-making regarding treatment modalities after first-line chemotherapy, based on the estimated prognosis. Discovering the optimal chemotherapy modality for GCLM at initial diagnosis still requires further research.

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Disclosure of conflict of interest

None.

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