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Dynamic Change in Serum Alpha-fetoprotein Level Predicts Treatment Response and Prognosis of Alpha-fetoprotein-producing Gastric Cancer

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Abstract

Alpha-fetoprotein (AFP)-producing gastric cancer (AFPGC) is rare and associated with a suboptimal prognosis. The aim of this retrospective study was to identify prognostic factors, with a particular focus on the dynamics of serum AFP levels during treatment, in AFPGC patients.

Data of patients with pathologically diagnosed primary gastric cancer treated with various modalities electronically collected in the medical management systems of 2 hospitals (ie, Shihezi People's Hospital and Shihezi Hospital) in Shihezi city, northwest China, from January 2007 to October 2018 were reviewed. Patients with AFPGC were identified based on serum AFP levels. Associations of the change in serum AFP levels and clinicopathological parameters with treatment response, including the overall response rate and disease control rate, and outcomes, including overall survival (OS) and progression-free survival (PFS), were compared among different groups.

Of 2354 patients diagnosed with gastric cancer, 96 patients with AFPGC were identified. The objective response rate and disease control rate were significantly higher in patients whose AFP level decreased by ≥50% than in patients whose AFP level decreased by <50% (68.8% *vs.* 40.6%, and 87.5% *vs.* 53.1%, respectively, both $P < .05$). The median OS and PFS were 32.0 (4-74) and 24.0 (1-66) months, respectively, in patients with a ≥50% decline in AFP, and 12.5 (0-69) and 9.0 (0-63) months, respectively, in those with a <50% decline in AFP (both $P < .05$). On univariate and multivariate analyses, tumor, node, metastasis staging classification stage, liver metastasis, curable surgery, and the decline in the serum AFP level were associated with OS and PFS.

A significant decline in the serum AFP level was associated with good treatment response and prognosis in AFPGC. Along with a decline in the serum AFP level, tumor, node, metastasis staging classification stage, liver metastasis, and curable surgery were also independent factors associated with prognosis.

Abbreviations: AFP = alpha-fetoprotein, AFPGC = alpha-fetoprotein-producing gastric cancer, CR = complete response, DCR = disease control rate, FOLFOX = fluorouracil-oxaliplatin-folinic acid, GC = gastric cancer, LM = liver metastasis, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PD = progression disease, PR = partial response, SD = stable disease, TNM = tumor, node, metastasis staging classification.

Keywords: alpha-fetoprotein -producing gastric cancer, serum alpha-fetoprotein, treatment response, prognosis, curable surgery

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RW and JL authors contributed equally to this work.

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1. Introduction

Gastric cancer (GC) is the second leading cause of cancer-related death worldwide and 1 of the ten most common malignant tumors in China.[1] GC is a heterogeneous disease with poorly understood carcinogenesis at the molecular level. As a result, individual patients respond differently to various therapeutic modalities, including curable surgery, chemotherapy, and combined curable surgery and chemotherapy patients. Therefore, identification of biomarkers characterizing the disease and predicting its progression could facilitate the development of treatment plans.

Alpha-fetoprotein (AFP), a protein predominantly synthesized in the liver and the yolk sac of the human fetus,[2] was identified initially in serum from human fetuses.[3] The serum AFP level on average ranges from 2 to 4 ng/mL in healthy adults,[4] and an elevated serum level of AFP has been reported in several cancers, including testicular tumors, hepatocellular carcinoma, and GC.[5–9]

An abnormal serum level of AFP was first described in GC with liver metastasis (LM).[10] It has now been reported that an elevated level of AFP is present in 1.3%-15% of patients with GC.[7–9] Currently, a few studies have investigated the clinicopathological characteristics and prognosis of AFP-producing GC (AFPGC), and demonstrated that AFPGC has similar demographic and symptomatic characteristics, but is associated with more aggressive disease and worse prognosis, compared with non-AFP-producing GC.[7,11,12]

However, there has been no study on the response to various therapeutic modalities and the factors that predict the prognosis of AFPGC, especially the potential effects of the dynamic change in the serum AFP level during the various therapeutic modalities on the prognosis of the disease. Therefore, the aim of this retrospective study was to identify prognostic factors, with a focus on the change in serum AFP levels during treatment, in AFPGC patients treated with various therapeutic modalities.

2. Methods

2.1. Patients and data collection

Patients with pathologically diagnosed primary GC who were treated at Shihezi People's Hospital and Shihezi Hospital from January 2007 to August 2018 were identified in the medical management systems. Electronically entered demographic and clinicopathological data, including age, sex, the site of the primary tumor, tumor, node, metastasis staging classification (TNM) stage of disease according to the American Joint Committee on Cancer, tumor pathology classification, *Helicobacter pylori* infection, *etc.* were extracted from the hospital's records. Data on therapeutic modalities, including curable surgery, chemotherapy, and combined curable surgery and chemotherapy, and the outcomes, including response to treatment (ie, complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)), and prognosis (ie, progression-free survival (PFS), and overall survival (OS)), were collected.

Patients whose serum levels of AFP were detected at diagnosis, during the treatment, or at follow-up visits were screened and those with a serum level of >7 ng/mL at any time point were enrolled in the study.[13] Serum AFP was detected by electrochemiluminescence immunoassay, as previously described by Sturgeon.[13] Briefly, the venous blood of the patient's elbow was taken, and the serum was stored at -20 °C, and tested within 1 week. Electrochemiluminescence immunoassay was performed in strict accordance with the manufacturer's instructions. Patients were excluded from the study if they currently had or had a history of any disease that increases the serum AFP level, such as liver disease, yolk sac tumor, teratoma, or primary liver cancer.

2.2. Determination of the response to treatment and prognosis

The patients included in the study underwent treatment with various first-line regimens, including curable surgery, platinum-based double chemotherapy, fluorouracil-oxaliplatin-folinic acid (FOLFOX), and paclitaxel-based chemotherapy, or palliative symptomatic therapy for GC (Table 1). Enhanced computed tomography and/or gastroscopy were performed every 2 cycles (21–27 days per cycle) during treatment for patients who received chemotherapy, and at least every 6 months in patients who were not treated with chemotherapy.

Serum AFP was detected repeatedly throughout the treatment period for all patients, and the level was defined as "declined" if it decreased by 50% or more from the diagnosis to the end of the treatment.

Evaluation of response to treatment was based on the response criteria in solid tumors RECIST version 1.0 (before 2009) and RECIST 1.1. CR was defined as the disappearance of all target lesions with any pathological lymph nodes reduced in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. PD was defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum; and lastly, SD was defined as neither sufficient shrinkage to qualify as PR nor a sufficient increase to qualify as PD. Tumor shrinkage that met the criteria for CR or PR as defined above that lasted for at least 4 weeks was considered CR or PR in the present study. The overall response rate (ORR) was calculated as the sum of the CR rate and PR rate, whereas the disease control rate (DCR) was calculated as the sum of the CR rate, PR rate and SD rate.

OS, defined as the time from the diagnosis of GC to death from any cause, and PFS, defined as the time from diagnosis of GC to disease progression, were retrospectively calculated and analyzed according to patient records.

2.3. Statistical analysis

Mean ± standard deviation and median (range) were used to represent normally and abnormally distributed numerical data, respectively, and percentages were used for categorical data. Between-group comparisons were evaluated by using the Student's *t*-test or the Mann–Whitney U test, where appropriate, for numerical data, and Chi-squared test for categorical data. The Kaplan-Meier method was performed to analyze survival, and the log-rank test was used to compare differences in survival. In addition, multiple Cox regression analysis was performed to determine the factors independently associated with survival. A P value of <0.05 was considered significant. The statistical analyses were performed with SPSS software (version 21.0; SPSS, Chicago, IL), and GraphPad Prism 6 (GraphPad Software, Inc, La Jolla, CA) was used to generate Kaplan-Meier curves.

3. Results

3.1. Clinicopathological characteristics of AFPGC

Overall, 2354 patients were diagnosed with GC from January 2007 to August 2018 at the 2 hospitals. Of these patients, a serum

Table 1

Demographic and clinicopathological characteristics of patients with α-fetoprotein-producing gastric cancer as stratified by various therapeutic modalities.

Variable	Overall (n=96)	Surgery alone (n=4)	Chemotherapy alone (n=60)	Surgery and chemotherapy (n=16)	Palliative therapy (n=16)
Sex					
Male	66 (68.8)	3	42	11	10
Female	30 (31.2)	1	18	5	6
Age (yr)					
≥60	56 (58.3)	1	37	4	14
<60	40 (41.7)	3	23	12	2
Primary lesion site					
Antrum	54 (56.3)	3	24	8	9
Cardia	16 (16.7)	0	10	3	3
Corpus	26 (27.0)	1	16	5	4
Differentiation					
Well-moderately	18 (18.8)	3	7	6	2
Poorly	78 (81.2)	1	53	10	14
TNM stage					
I-II	21 (27.0)	4	6	11	0
III	40 (41.6)	0	29	5	6
IV	35 (36.4)	0	25	0	10
Liver metastasis					
Present	38 (39.6)	2	24	2	10
Absent	58 (60.4)	2	36	14	6
LNM					
Present	69 (71.9)	1	48	5	15
Absent	27 (28.1)	3	12	11	1
Other hematogenous metastasis					
Present	26 (27.1)	1	16	3	6
Absent	70 (72.9)	3	44	13	10

Data are expressed as number and (%).
LNM = lymph node metastasis, TNM = tumor node metastasis staging classification.

AFP test was performed for 2182 patients during the disease course. Of these patients, 96 had an AFP level of >7 ng/mL, with a median value of 29.61 ng/mL (range, 7.2-40588 ng/mL) and 2086 had an AFP level of ≤7 ng/mL, with a median value of 2.12 ng/mL (range, 0-7.0 ng/mL). Thus, 96 patients with AFPGC were identified and included in the present study. Of the 96 patients, 4, 60, 16, and 16 patients received treatment with curable surgery alone, chemotherapy alone, curable surgery plus chemotherapy, and palliative therapy, respectively. The demographic and clinicopathological characteristics of these patients stratified by the various therapeutic modalities are summarized in Table 1.

Patients with AFPGC had high rates of LM (39.6%), lymph node metastasis (71.9%), and other hematogenous metastasis (27.1%). These metastases were significantly associated with the TNM stages; the rates were 23.8%, 14.3% and 19.0% in stage I-II, 25.0%, 90.0%, and 15.0% in stage III, and 65.7%, 45.7% and 77.1% in stage IV, respectively (all $P < 0.05$). Of the 96 patients with AFPGC, 4 (4.1%) patients underwent curable surgery alone, and 16 (16.7%) received curable surgery plus chemotherapy, giving a surgery rate of 20.8%. Notably, 62.5% (n=60) and 16.7% (n=16) received chemotherapy alone and palliative therapy, respectively (Table 1).

3.2. Response and prognosis in terms of therapeutic modalities

The ORRs and DCRs were 50.0%, 53.3%, 75.0% and 0%, and 50.0%, 71.6%, 75.0% and 0%, respectively, in AFPGC patients treated with the 4 types of therapeutic modalities (Table 2). No significant difference in DCR was noted among the 4 groups. It is worth noting that the ORR appeared to be higher in patients treated with curable surgery plus chemotherapy than in those with chemotherapy alone, although the difference was no statistically significant ($P = .10$).

The median OS and PFS were 16.5 (0-74) and 13 (0-66) months, respectively, and the 1-, 3-, and 5-year survival rates were 64.6% (62/96), 22.3% (21/94), and 7.8% (7/90) and 54.2% (52/96), 14.9% (14/94), and 2.2% (2/90), respectively, in patients with

Table 2

The overall response rate (ORR) and disease control rate (DCR) in AFPGC patients treated with various therapeutic modalities (n=94).

	Overall response rate (%)	Disease control rate (%)
Surgery alone (n=4)	50.0	50.0
Chemotherapy alone (n=60)	53.3	71.6
Monotherapy (n=10)	50.0	70.0
DCF (n=11)	54.5	72.7
FOLFOX (n=20)	55.0	75.0
XLOX (n=19)	52.6	68.4
Surgery plus chemotherapy (n=16)	75.0	75.0
Monotherapy (n=4)	25.0	25.0
DCF (n=2)	50.0	50.0
FOLFOX (n=5)	60.0	60.0
XLOX (n=5)	80.0	80.0
Palliative therapy (n=16)*	0	0

AFPGC, α-fetoprotein-producing gastric cancer; DCF, Docetaxel-cis-platinum-fluorouracil acid; FOLFOX, fluorouracil-oxaliplatin-folinic acid; XLOX, oxaliplatin-Xeloda (capecitabine).
* five of these patients received palliative surgery.

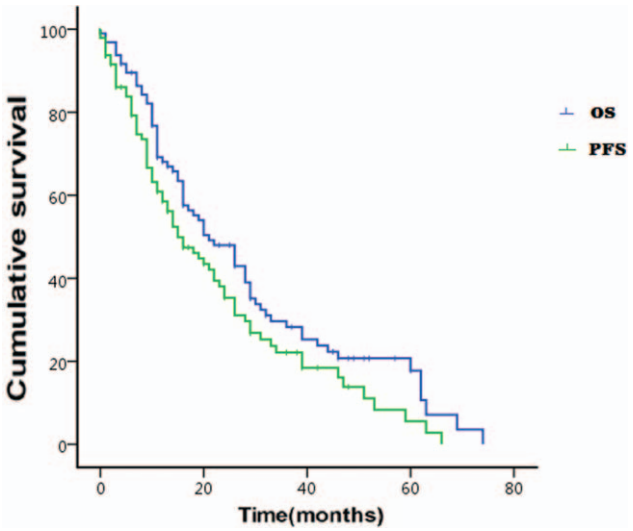

Figure 1. The 1-, 3-, and 5-year overall survival (OS) and progression-free survival (PFS) rates of all 96 cases with alpha-foetoprotein-producing gastric caner.

AFPGC (Fig. 1). The median OS and PFS were longer in those who received curable surgery, alone or in combination with chemotherapy, than in those who did not receive curable surgery (47.0 (20-74) *vs.* 13.5 (0-60) months, and 37.0 (1-66) *vs.* 10.0 (0-51) months, respectively, both $P < 0.05$) (Fig. 2A and 2B). When different chemotherapies (ie, monotherapy, docetaxel-cis-platinum-fluorouracil acid, FOLFOX, and oxaliplatin-xeloda [capecitabine]), regardless of combination with curable surgery, were taken into the analysis, there was no significant difference in survival among them. In addition, palliative surgery was performed in 5 of the 16 patients who received palliative treatment, and all these patients had stage III AFPGC. There were no significant differences in OS and PFS between these 5 patients and the other patients who received palliative treatment.

3.3. Association of the serum AFP changes with the response to various therapeutic modalities and prognosis

The ORR and DCR were significantly higher in patients whose AFP decreased by ≥50% than in patients whose serum AFP levels decreased by <50% (68.8% vs 40.6%, and 87.5% vs 53.1%, respectively, both $P < .05$).

The median OS and PFS were 32.0 (4-74) and 24.0 (1-66) months, respectively, in patients whose serum AFP level decreased by ≥50%. In contrast, the median OS and PFS were 12.5 (0-69) and 9.0 (0-63) months, respectively, in patients whose AFP decreased by <50%.

Furthermore, the 1-, 3-, and 5-year survival rates were significantly higher in patients whose serum AFP level decreased by ≥50% than in the patients whose AFP decreased by <50% (90.6% vs 51.5%, 46.8% vs 9.7% and 13.8% vs 4.9%, respectively, all $P < .05$) (Fig. 3A and B).

Factors associated with prognosis

In the univariate analysis, age, sex, primary lesion site and differentiation degree were not predictors of survival (Table 3). However, TNM stage, LM, curable surgery, and the decline in the serum AFP level were significantly associated with OS and PFS (Table 3). The multiple Cox regression analysis demonstrated that age, TNM staging, and serum AFP decline were independent factors associated with OS (Table 4).

4. Discussion

The present retrospective study investigated the serum AFP level as a prognostic factor for GC during various therapeutic modalities. We found that, compared with that for patients with non-AFPGC, the prognosis was worse for patients with AFPGC whose AFP level was greater than 7 ng/mL, with a lower ORR and DCR and shorter OS and PFS. These results are consistent with previous findings that AFP production predicts worse outcomes in patients with GC.[7,14–17]

Although the mechanism by which an increased serum AFP level is associated with worse outcomes is not fully understood, it has been demonstrated that AFP positivity is often observed in patients with LM of AFPGC and hepatocellular carcinoma, and thus, AFP has been a key biomarker in the management of patients with these diseases.[18,19] The present study showed that the serum AFP level can be a useful biomarker for treatment response and prognosis of patients with AFPGC. Moreover, we further observed that a greater than 50% decline in serum AFP level during the treatment was associated with greater survival benefits, which was consistent with the findings obtained in a previous study in which Wang *et al.* enrolled GC patients with serum AFP ≥ 20 ng/mL at diagnosis or recurrence and observed that a serum AFP decline ≥ 50% during the treatment was associated with an increased median OS.[20] Thus, continued monitoring the serum AFP levels could predict the efficacy of a treatment for an individual patient with AFPGC and provide information for modification of the treatment plan for the particular patient.

From both the univariate and multivariate analyses, we found that TNM stage, LM, curable surgery, and the decline in the serum AFP level were significantly associated with clinical outcomes, including OS and PFS.

The findings obtained in the present study have significant clinical implications. First, there is currently no treatment algorithm that is specifically tailored for this subpopulation of GC patients, and clinical treatment guidelines including the National Comprehensive Cancer Network guideline have not incorporated the assessment of the serum AFP concentration into the work-up for GC.[14,21] The associations of the serum AFP level and its change during the treatment with treatment response and outcomes observed in the present study indicate that this biomarker should be used in the management of patients with AFPGC. Second, in the present study, ORR and DCR of curable surgery alone, curable surgery plus chemotherapy, and chemotherapy alone were compared. No significant differences in ORR and DCR were found among patients treated with these different modalities, although the ORR appeared to be higher with curable surgery plus chemotherapy than with chemotherapy alone. More importantly, the present study clearly demonstrated that curable surgery plus chemotherapy achieved better OS than chemotherapy alone and palliative therapy and better PFS than the 3 other modalities.

At present, there is no particular recommendation for chemotherapy for AFPGC treatment in the NCCN Clinical Practice Guidelines in Oncology: GC,[20] and determination of the effective treatment plan for AFPGC remains in the exploration stage. Some studies have found that regimens with apatinib or gimeracil and oteracil potassium plus cisplatin are

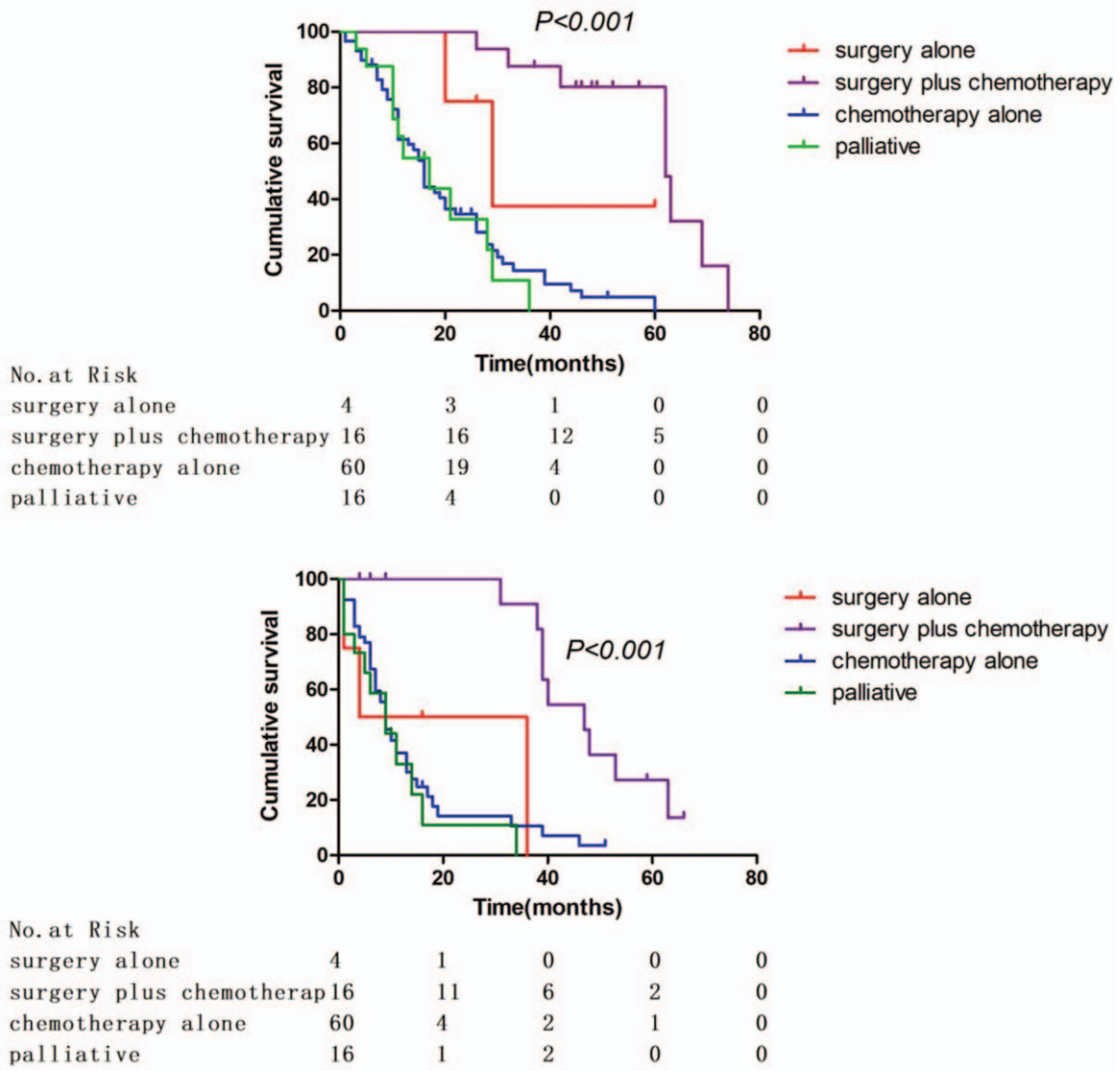

Figure 2. Overall survival (A) and progression-free survival (B) in relation to various therapeutic modalities. There was a significant difference in the overall survival between surgery plus chemotherapy and chemotherapy alone ($P < .001$) and between surgery plus chemotherapy and palliative therapy ($P < .001$). Also, there was a significant difference in the progression-free survival between surgery plus chemotherapy and surgical alone ($P = .010$), between surgery plus chemotherapy and chemotherapy alone ($P < .001$), and between surgery plus chemotherapy and palliative therapy ($P < .001$).

helpful in improving the prognosis of AFPGC.[22–24] Recently, Wang *et al.* suggest that triplet chemotherapy regimens may be a better choice for GC patients with markedly elevated AFP.[20] The present study compared 4 general chemotherapy regimens, including monotherapy, docetaxel-cis-platinum-fluorouracil acid, FOLFOX, and oxaliplatin-xeloda (capecitabine), with palliative therapy, in terms of OS and PFS, and demonstrated that compared with palliative treatment, there was no significant difference in the OS and PFS between the 4 chemotherapy regimens ($P > 0.05$).

It has been reported that LM occurs in 4.0%-17.0% of patients with GC.[25,26] Moreover, a previous study demonstrated that LM was a major feature of AFPGC and an important factor for worsening the prognosis.[27] In the present study, LM was present in 39.6% of the 96 patients with AFPGC. According to the NCCN Clinical Practice Guidelines in Oncology: GC,[20] LM of GC should be directly classified as stage IV, which is associated with poor prognosis,[28] as confirmed in the present study. It is recommended that for patients with operable GC, radical gastrectomy is the preferred treatment.[20] A recent study reported that patients with AFPGC also benefited from surgery in terms of survival.[29] In the present study, 20 patients received curable surgery, and their prognosis was much better than that of patients not treated with surgery. However, it should be mentioned that palliative surgery was performed in 5 patients with stage III AFPGC in the present study, but no significant difference in prognosis was observed between these patients and other patients receiving palliative therapy, likely due to the small number of cases. Therefore, whether palliative surgery or non-radical surgery can improve the prognosis of patients with advanced AFPGC remains to be elucidated in the future.

It should be emphasized that there is not a consensus on the definition of AFPGC in terms of the serum AFP level to date. The definition of AFPGC varies in different studies; whereas some studies applied an AFP greater than 20 ng/mL to define AFPGCs,[14,15] one study applied an APF serum level greater than

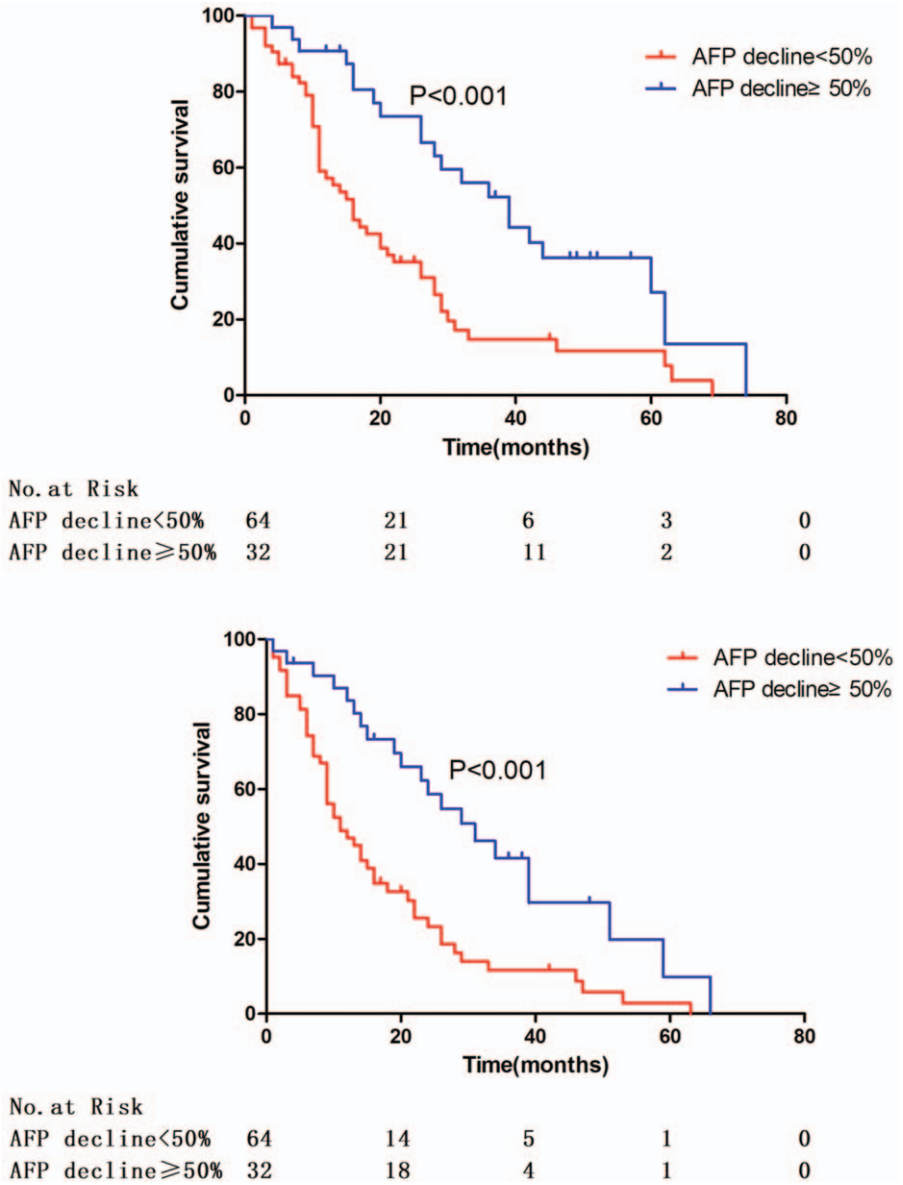

Figure 3. Decline in the serum α-fetoprotein (AFP) level is associated with improved overall survival (A) and progression-free survival (B).

10 ng/mL.[7] In the present study, we used a cut-off serum AFP concentration of 7 ng/mL to identify patients with AFPGC.[13] We found that although false-positive results may be possible with the reduction of the AFP level, the prognosis did not seem to shift substantially from that reported in previous studies.[30] Therefore, we propose that in clinical practice, a serum AFP level set lower than 7 ng/mL can be used to distinguish patients with AFPGC from those with non-AFPGC in order to identity more patients at risk.

Theoretically, it would be better to examine the AFP expression in gastric tissues and the corresponding liver tissues to determine the prognosis. However, AFP immunohistochemical examination is not a routine examination for GC at our hospital. Due to the retrospective nature of the present study, we are not able to examine the AFP expression in gastric tissues and the corresponding liver tissues to determine the prognosis and the association between AFP level in GC tissues and GC patient survival time. In a retrospective study, Liu *et al.* observed that among 111 patients with an elevated serum level of AFP (≥10 ng/mL), 104 were positive for immunohistochemical staining of AFP in gastric cancerous tissues. Moreover, these 104 AFPGC patients had a higher incidence of LM (60.6% vs 11.5%), and lower 1-, 3-, and 5-year survival rates (53%, 35%, and 28% vs 95%, 57%, and 38%, respectively), compared with 208 stage-matched GC patients with normal serum AFP levels [7]. These findings indicate that AFPGC patients have a poorer prognosis than AFP-negative GC patients. The purpose of the present study was to identify prognostic factors, with a focus on the change in serum AFP levels during treatment, in AFPGC patients treated with various therapeutic modalities, because the detection of AFP in serum is fast, convenient, economical, and acceptable by patients, and the AFP levels can be measured several times during the disease course, including the follow-up process.

Table 3

Univariate analysis of factors associated with overall survival and progression-free survival in patients with α-fetoprotein-producing gastric cancer.

Variable	Overall survival (mo)	Progression-free survival (mo)
Sex		
Male (n=66)	20 (10.5-30.0)	14.0 (7.7-20.3)
Female (n=30)	21 (12.3-29.7)	16.0 (7.4-24.6)
Age, years		
<60 (n=40)	26.0 (13.1-38.9)	19.0 (9.1-28.9)
≥60 (n=61)	18.0 (10.3-25.7)	13.0 (8.3-17.7)
Primary lesion site		
Antrum (n=54)	26.0 (15.4-36.5)	16.0 (5.7-26.3)
Cardia (n=16)	15.0 (0.8-29.2)	10.0 (1.6-18.4)
Corpus (n=26)	20.0 (15.4-24.6)	18.0 (10.6-23.4)
Differentiation degree		
Well-moderately (n=18)	31.0 (22.0-40.0)*	26.0 (17.2-34.8)*
Poor (n=78)	19.0 (14.4-23.6)	14.0 (10.6-17.4)
TNM stage		
I-II (n=21)	62.0 (36.7-87.3)**	47.0 (24.9-69.1)**
III (n=40)	28.0 (18.7-37.3)	16.0 (9.5-22.5)
IV (n=35)	11.0 (9.2-12.8)	8.0 (5.4-10.6)
Liver metastasis		
Present (n=38)	16.0 (7.9-24.1)**	9.0 (5.8-12.2)**
Absent (n=58)	29.0 (19.0-36.0)	26.0 (16.3-35.7)
LNM		
Present (n=69)	17 (12.3-21.7)*	13.0 (9.8-16.2)*
Absent (n=27)	33 (14.8-51.1)	28.0 (18.3-37.7)
Other hematogenous metastasis		
Present (n=26)	22 (6.4-37.6)	19.0 (8.2-29.8)
Absent (n=70)	20 (13.1-26.9)	15.0 (9.5-20.5)
Curable surgery		
Yes (n=20)	62.0 (39.0-85.0)**	53.0 (39.4-66.6)**
No (n=76)	16.0 (13.2-18.8)	12.0 (8.5-15.5)
α-fetoprotein decline		
≥50% (n=32)	39.0 (28.0-50.0)**	31.0 (19.9-42.1)**
<50% (n=64)	16.0 (11.0-21.0)	11.0 (8.0-14.0)

Data are expressed as median (95% confidence interval).

TNM, tumor, node, metastasis staging classification; LNM, lymph node metastasis.

* $P < .05$.

** $P < .001$.

Table 4

Multiple Cox regression analysis of factors associated with overall survival and progression-free survival in patients with α-fetoprotein-producing gastric cancer.

Variables	Overall survival	Progression-free survival
Differentiation degree (well-moderate vs poor)	1.164 (0.585-2.316)	1.139 (0.578-2.246)
TNM stage (I/II *vs.* III/IV)	2.616 (1.597-4.286)**	2.423 (1.498-3.919)**
Liver metastasis (Yes vs no)	0.538 (0.315-0.920)8	0.394 (0.231-0.672)**
LNM (Yes vs no)	0.750 (0.410-1.371)	0.637 (0.317-1.280)
Curable surgery (Yes *vs.* no)	6.211 (2.141-18.182)**	5.988 (2.262-15.873)**
α-fetoprotein decline (≥50% vs <50%)	2.105 (1.211-3.650)*	2.193 (1.266-3.802)*

Data are expressed as the hazard ratio (95% confidence interval).

TNM, tumor, node, metastasis staging classification; LNM, lymph node metastasis.

* $P < .05$.

** $P < .001$.

The present study has a few limitations. First, the population size included in the study was relatively small; however, as shown in previous studies,[7,16] AFPGC is a rare condition and we could manage to identify only 96 patients with AFPGC among 2354 GC patients during a period of 20 months. Future research with a larger population size is required to confirm the findings of the present study. Second, for the same reason described above, it is difficult to make a meaningful comparison on the survival benefits in patients who received different treatments, and thus, to make a conclusion regarding which treatment offers the greatest survival benefit to patients with AFPGC. Third, as LM and stage IV disease are known to be closely associated with advanced GC and poor prognosis, further analysis of data obtained in a study with a large sample size and a long-term follow-up period would help distinguish these 2 factors in the prognosis of AFPGC.

In conclusion, a significant decline in the serum AFP level is associated with good treatment response and prognosis of AFPGC. Along with a decline in the serum AFP level, TNM stage, LM, and curable surgery are also independent factors associated with prognosis. These findings indicate that serum AFP is a useful biomarker predicting treatment response and prognosis and that curable surgery can be used as a first-line treatment for AFPGC.

Author contributions

Conceptualization: Ruhan Wang, Ping Gong.
Data curation: Ruhan Wang, Jing Li, Dan Xu, Ruiyang Li.
Investigation: Ruhan Wang, Jing Li, Dan Xu, Ruiyang Li.
Writing – original draft: Ruhan Wang.
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