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ORIGINAL ARTICLE

Clinical manifestations in patients with alpha-fetoprotein–producing gastric cancer

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ABSTRACT

Background

Patients with alpha-fetoprotein (AFP)–producing gastric cancer have a high incidence of liver metastasis and poor prognosis. There is some controversy about clinical manifestations in these patients.

Methods

Our study enrolled patients who, before surgery, had gastric cancer with serum AFP exceeding 20 ng/mL [AFP>20 (n = 58)] and with serum AFP 20 ng/mL or less [AFP≤20 (n = 1236)]. Clinical manifestations were compared between the groups.

Results

Early gastric cancer was more frequent (30.1% vs. 4%) and advanced gastric cancer was less frequent (69.9% vs. 96%) in the AFP≤20 group than the AFP>20 group ($p < 0.001$). Liver and lymph node metastasis occurred less frequently in the AFP≤20 group (4.4% vs. 27.6%, $p < 0.001$, and 60.7% vs. 91.4%, $p < 0.001$, respectively). The 1-, 3-, 5-, and 10-year survival rates of AFP≤20 patients were 75.2%, 53.4%, 45.8%, and 34.6% respectively. The 1-, 3-, 5-, and 10-year survival rates of patients with AFP greater than 20 ng/mL, but 300 ng/mL or less, were 46.7%, 28.9%, 17.8%, and 13.3% respectively. The 1-, 3-, and 5-year survival rates of patients with serum AFP greater than 300 ng/mL were 15.4%, 7.7%, and 0% respectively. The independent predictors for survival time were AFP concentration, age, peritoneal seeding, liver metastasis, lymph node metastasis, vascular invasion, TNM stage, curative surgery, serosal invasion, and Lauren classification.

Conclusions

Patients with high serum AFP had a high frequency of liver and lymph node metastasis and very poor prognosis. More aggressive management with multimodal therapy (for example, chemotherapy, radiotherapy) might be needed when treating such patients.

KEY WORDS

Gastric cancer, alpha-fetoprotein, early gastric cancer, metastasis

1. INTRODUCTION

Alpha-fetoprotein (AFP) is a glycoprotein that is normally produced during gestation by the fetal liver and yolk sac[1]. Elevation of serum AFP is considered to be abnormal in adults and is often used as a tumour marker in hepatocellular carcinoma and tumours of gonadal origin[2]. However, a variety of other malignancies also produce AFP, of which gastric cancer is the most common[3]. Elevated serum AFP can occur in patients without hepatocellular carcinoma but with chronic liver disease such as viral hepatitis or cirrhosis[4,5]. The influence of serum AFP on the prognosis of patients with gastric cancer remains unclear.

Alpha-fetoprotein–producing gastric cancer (AFPGC) is rare, constituting only about 1%–6% of all gastric cancers[6]. Poor prognosis is usually associated with AFPGC because of liver and lymph node metastasis[3,7].

Few studies to date have addressed the clinicopathologic features and long-term survival of patients with AFPGC. Controversy exists about the clinical manifestations in these patients. Therefore, in this retrospective study, we reviewed clinicopathologic findings for 58 Chinese patients with AFPGC and 1236 patients with normal serum AFP attending a single centre. We also correlated survival time with serum AFP concentration.

2. METHODS

We reviewed the medical records of 3172 consecutive patients with gastric adenocarcinoma who received surgical intervention at the Veterans General

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Hospital–Taipei between June 1988 and December 2011. Preoperative serum AFP was assessed by radioimmunoassay (normal value: <20 ng/mL) in 1331 patients. The analysis excluded 37 patients with acute or chronic hepatitis, cirrhosis, or hepatocellular carcinoma. Surgical and pathologic findings for the remaining 1294 patients were recorded using the Japanese classification of gastric carcinoma and the Lauren classification[8,9]. Nodal status and disease stage were assessed using the tumour–node–metastasis (TNM) system of the Union for International Cancer Control[10]. Sex, age, tumour size (mucosal size of the tumour), peritoneal seeding, liver metastasis, lymph node metastasis, location of the main tumour, lymphatic and vascular invasion, clinical staging, curative surgery, cause of death, morphologic appearance and depth of cancer involvement, cancer cell differentiation, and survival time were recorded.

Statistical analysis was performed using the SPSS software application (SPSS for Windows, version 10.0: SPSS, Chicago, IL, U.S.A.). The chi-square test with Yates correction for continuity was used in comparisons of categorical data. The Fisher exact test was used when the numbers were less than 5. Survival curves were estimated by the Kaplan–Meier method, and differences were examined using the log-rank test. A multivariate analysis of prognostic factors was evaluated using the Cox proportional hazards model (forward stepwise method). Differences were considered significant when the p value was less than 0.05.

3. RESULTS

Of the 1294 eligible patients, 58 (4.5%) were found to have high serum AFP (>20 ng/mL), with preoperative concentrations ranging from 20.6 ng/mL to 9999.9 ng/mL (median: 90.4 ng/mL). Median follow-up was 43.2 months.

Table I compares the clinicopathologic features of patients with a serum AFP of 20 ng/mL or less [AFP≤20 (n = 1236)] and those with a serum AFP exceeding 20 ng/mL [AFP>20 (n = 58)]. Sex, age, tumour size, peritoneal seeding, and tumour location were similar in the two groups. Compared with the AFP≤20 group, the AFP>20 group had higher incidences of vascular invasion (17.2% vs. 3.8%, $p < 0.001$), lymphatic invasion (70.7% vs. 59.7%, $p < 0.001$), liver metastasis (27.6% vs. 4.4%, $p < 0.001$), and lymph node metastasis (91.4% vs. 60.7%, $p < 0.001$). Compared with patients having normal serum AFP, those in the AFP>20 group had more stage IV disease and less stage I or II disease ($p < 0.001$). Fewer patients in the AFP>20 group received curative surgery (10.3% vs. 37.9% in the AFP≤20 group, $p < 0.001$). More patients in the AFP>20 group died of their gastric cancer (58.6% vs. 27.1% in the AFP≤20 group, $p < 0.001$).

Table II analyzes the depth of cancer involvement in the gastric wall. The AFP>20 group included fewer cases of early gastric cancer (EGC: 4% vs. 30.1%; $p < 0.001$) and more cases of advanced gastric cancer (96% vs. 69.9%, $p < 0.001$). In the 2 EGC patients of the AFP>20 group, cancer cells had involved the intramucosal and muscularis mucosa layers. In the AFP≤20 group, 349 patients (30.1%) had EGC, with cancer cells confined to the intramucosa in 97 cases (27.8%), to the muscularis mucosa in 94 cases (26.9%), and to the submucosal layer in 158 cases (45.3%). Cancer cells penetrated to serosal layer and beyond in more patients of the AFP>20 group [40 patients (80%) vs. 628 patients (54.2%) in the AFP≤20 group, $p < 0.001$].

Table III summarizes the histologic classification of cancer cells in the two groups. Poorly differentiated cancers (por 1, por 2, signet-ring cell, mucinous adenocarcinoma) were not statistically different between the groups (AFP≤20: n = 558, 48.7%; AFP>20: n = 23, 50%; p = 0.87). The Lauren classification was

TABLE I Serum alpha-fetoprotein (AFP) and clinicopathologic features in patients with gastric cancer

Variable	*AFP concentration*		p *Value*
	≤20 ng/mL	*>20 ng/mL*	
Patients (n)	1236	58	
Sex [n (%) men]	976 (78.2)	51 (87.9)	0.099[a]
Mean age (years)	66.2±11.7	68.0±9.5	0.257
Mean tumour size (cm)	5.7±4.1	6.7±3.4	0.063
Peritoneal seeding [n (%) yes]	179 (14.5)	8 (13.8)	1.000[a]
Peritoneal seeding present [n (%)]			0.728[b]
Proximal to transverse colon	83 (46.4)	3 (37.5)	
Distal to transverse colon	96 (53.6)	5 (62.5)	
Metastasis [n (%) yes]			
Liver	53 (4.4)	16 (27.6)	<0.001[a]
Lymph nodes	750 (60.7)	53 (91.4)	<0.001[a]
Location of main tumour			0.932[a]
Cardia	195 (15.8)	10 (17.2)	
Body	395 (32.0)	19 (32.8)	
Antrum	646 (52.3)	29 (50.0)	
Invasion [n (%) yes]			
Lymphatic	738 (59.7)	41 (70.7)	<0.001[a]
Vascular	47 (3.8)	10 (17.2)	<0.001[a]
Stage			<0.001[a]
IA	319 (25.2)	2 (3.3)	
IB	114 (9.0)	1 (1.6)	
II	158 (12.5)	3 (4.9)	
IIIA	190 (15.0)	12 (19.7)	
IIIB	153 (12.1)	11 (18.0)	
IV	333 (26.3)	32 (52.5)	
Curative surgery [n (%)]	468 (37.9)	6 (10.3)	<0.001
Cause of death [n (%) cancer]	330 (27.1)	34 (58.6)	<0.001[a]

[a] By chi-square test.
[b] By Fisher exact test.

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TABLE II Serum alpha-fetoprotein (AFP) and depth of cancer involvement of the gastric wall

Variable	*AFP concentration [n (%)]*		p *Value*
	≤20 ng/mL	*>20 ng/mL*	
Patients[a]	1158	50	<0.001[b]
Gastric cancer			
Early	349 (30.1)	2 (4.0)	
Advanced	809 (69.9)	48 (96.0)	
Depth of involvement			<0.001[c]
Intramucosa	97 (8.4)	1 (2.0)	
Muscularis mucosa	94 (8.1)	1 (2.0)	
Submucosa	158 (13.6)	0 (0)	
Muscularis propria	133 (11.5)	2 (4.0)	
Subserosa α	10 (0.9)	2 (4.0)	
Subserosa β	18 (1.6)	3 (6.0)	
Subserosa γ	20 (1.7)	1 (2.0)	
Serosal penetration	518 (44.7)	32 (62.7)	
Invasion of adjacent structures	110 (9.5)	8 (16)	

[a] Data not available for 78 patients in the ≤20 ng/mL group, and 7 in the >20 ng/mL group.
[b] By Fisher exact test.
[c] By chi-square test.

TABLE III Serum alpha-fetoprotein (AFP) and cell differentiation in gastric cancer

Variable	*AFP concentration [n (%)]*		p *Value*
	≤20 ng/mL	*>20 ng/mL*	
Patients[a]	1145	46	0.002[b]
Papillary adenocarcinoma	19 (1.7)	1 (2.2)	
Tubular adenocarcinoma			
Well-differentiated	113 (9.9)	1 (2.2)	
Moderately differentiated	446 (39.0)	18 (39.1)	
Adenocarcinoma, poorly differentiated			
Solid type	43 (3.8)	4 (8.7)	
Non-solid type	387 (33.8)	16 (34.8)	
Signet-ring cell carcinoma	89 (7.8)	3 (6.5)	
Mucinous adenocarcinoma	39 (3.4)	0 (0)	
Adenosquamous carcinoma	1 (0.1)	1 (2.2)	
Undifferentiated	3 (0.3)	1 (2.21)	
Miscellaneous	5 (0.4)	1 (2.2)	
Lauren classification			0.802[b]
Intestinal	590 (51.5)	25 (54.3)	
Diffuse	350 (30.6)	16 (34.8)	
Mixed	205 (17.9)	5 (10.9)	

[a] Data not available for 91 patients in the ≤20 ng/mL group, and 12 in the >20 ng/mL group.
[b] By chi-square test.

not statistically significantly different between the AFP≤20 and AFP>20 groups.

Survival time was further analyzed by various levels of high serum AFP. In 45 patients, serum AFP was greater than 20 ng/mL but less than or equal to 300 ng/mL (20<AFP≤300); in 13 patients, serum AFP exceeded 300 ng/mL (AFP>300). The 1-, 3-, 5-, and 10-year survival rates for patients in the AFP≤20 group were 75.2%, 53.4%, 45.8%, and 34.6% respectively. The 1-, 3-, 5-, and 10-year survival rates for 20<AFP≤300 patients were 46.7%, 28.9%, 17.8%, and 13.3% respectively. The 1-, 3-, and 5-year survival rates for patients with AFP>300 were 15.4%, 7.7%, and 0% respectively. The patients in the AFP≤20 group had the best survival time, and the patients in the 20<AFP≤300 group had the poorest survival ($p < 0.001$, Figure 1).

In univariate analysis, serum AFP greater than 20 ng/mL, male sex, age greater than 60, tumour size greater than 7 cm, peritoneal seeding, liver metastasis, lymph node metastasis, lymphatic and vascular invasion, tumour stage IV, no curative surgery, serosal invasion, and poorly differentiated and diffuse cell types were associated with poor survival time (Table IV).

In multivariate analysis, the independent prognostic factors for survival were serum AFP, patient age, peritoneal seeding, liver metastasis, lymph node metastasis, vascular invasion, TNM stage, curative surgery, serosal invasion, and Lauren classification (Table V).

4. DISCUSSION

In our study, 58 patients with AFPGC had a high percentage of lymph node and liver metastasis and a poor prognosis. The prevalence of AFPGC is reported to be

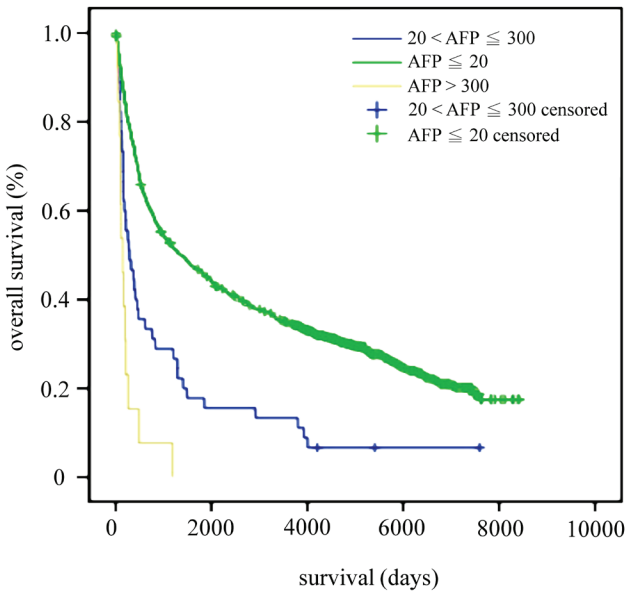

FIGURE 1 Overall survival by serum alpha-fetoprotein (AFP) concentration in nanograms per milliliter.

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TABLE IV Univariate analysis of all patients by the Kaplan–Meier method

Variable	*Pts (n)*	*5-Year survival*	*Log-rank p value*
Alpha-fetoprotein			
≤20 ng/mL	1236	0.458	<0.001
>20 ng/mL	58	0.138	
Sex			
Men	1018	0.423	<0.001
Women	276	0.519	
Age			
<60 Years	281	0.535	<0.001
≥60 Years	1013	0.418	
Tumour size			
<7 cm	862	0.577	<0.001
≥7 cm	431	0.176	
Peritoneal seeding			
Yes	187	0.032	<0.001
No	1107	0.513	
Liver metastasis			
Yes	71	0.042	<0.001
No	1223	0.467	
Lymph node metastasis			
Yes	803	0.228	<0.001
No	491	0.849	
Location of main tumour			
Cardia	205	0.402	0.056
Body	414	0.488	
Antrum	675	0.429	
Lymphatic invasion			
Yes	803	0.321	<0.001
No	491	0.795	
Vascular invasion			
Yes	57	0.140	< 0.001
No	1237	0.457	
TNM stage			
I	314	0.843	<0.001
II	280	0.687	
III	299	0.313	
IV	400	0.055	
Curative surgery			
Yes	474	0.790	<0.001
No	820	0.243	
Serosal invasion			
Yes	754	0.206	<0.001
No	540	0.775	
Differentiation			
Papillary adenocarcinoma	20	0.450	<0.001
Tubular adenocarcinoma	578	0.569	
Poorly differentiated[a]	554	0.403	
Mucinous	39	0.237	
Lauren classification			
Intestinal	614	0.558	0.004
Diffuse	367	0.392	
Mixed	208	0.403	

[a] Includes signet-ring cell carcinoma.
Pts = patients.

TABLE V Independent prognostic factors by Cox modelling

Variable	*Coefficient*	*HR*	*95% CI*	p *Value*
AFP group	0.575	1.777	1.297 to 2.437	<0.001
Sex	–0.0.87	0.917	0.759 to 1.717	0.366
Age	0.028	1.029	1.021 to 1.036	<0.001
Tumour size	0.003	1.003	0.989 to 1.017	0.656
Peritoneal seeding	0.628	1.874	1.490 to 2.356	<0.001
Liver metastasis	0.575	1.776	1.253 to 2.519	0.001
Lymph node metastasis	0.267	1.306	1.035 to 1.649	0.025
Lymphatic invasion	0.003	1.003	0.809 to 1.244	0.979
Vascular invasion	–0.313	0.731	0.550 to 0.974	0.032
TNM stage	0.417	1.518	1.310 to 1.759	<0.001
Curative surgery	0.265	1.304	1.054 to 1.612	0.015
Serosal invasion	0.356	1.427	1.142 to 1.783	0.002
Differentiation	0.070	1.073	0.928 to 1.240	0.343
Lauren classification	–0.122	0.885	0.789 to 0.992	0.037

HR = hazard ratio; CI = confidence interval; AFP = alpha-fetoprotein.

0.17%–8.4% in patients with gastric cancer[3,6,11–14]. Clinical manifestations in patients with AFPGC have rarely been observed because of that small incidence[15]. Furthermore, controversy exists about those manifestations.

We observed that 4.5% of gastric cancer patients (58 of 1294) had an abnormal serum AFP reading (>20 ng/mL), a proportion that is comparable with those in other reports. To avoid confounding factors in patients with AFPGC, we excluded 37 patients with liver disease (cirrhosis, hepatoma, acute hepatitis) from the analysis.

Liver metastasis (14.3%–75.6%) is one of the main features of AFPGC or hepatoid adenocarcinoma of the stomach (HAS)[12–14,16]. In our series, 16 patients (27.6%) in the AFPGC group were found to have liver metastasis during follow-up. That group more frequently had liver metastasis than did patients with normal serum AFP (n = 53, 4.4%, $p < 0.001$). However, the related literature describes some different observations. Nakajima *et al.*[17] reported that there was no correlation between preoperative AFP values and histopathology, lymph node metastasis, vessel invasion, and liver metastasis.

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Lymph node involvement has been reported to be present in 62.9%–100% patients with AFPGC[11–15]. Lymph node metastasis was found more often in our AFPGC patients than in patients with normal serum AFP (91.4% vs. 60.7%, $p < 0.001$). Vascular invasion is very common in AFPGC, occurring in 63.5%–75.6% patients with AFPGC or HAS[3,6,11,16]. In our series, it occurred in 10 patients (17.2%) with AFPGC and in 47 patients (3.8%) with normal serum AFP ($p < 0.001$). Lymphatic invasion has been reported to occur in 71.4%–86.7% of patients with AFPGC or HAS[11,12,16,18]. In our series, it occurred in 41 patients (70.7%) with AFPGC and in 738 (59.7%) patients with normal serum AFP ($p < 0.001$).

The lower one third of the stomach is most common location for AFPGC or HAS, in the range 40%–61.5%[3,6,11–13,16]. Our observation was similar. In our series, the primary cancer was above the antrum in 29 patients with AFPGC (50%) and in 646 patients (52.3%) with normal serum AFP.

With respect to clinical staging, the literature reports a number of different observations. In one large series (270 patients), Adachi *et al.*[15] showed that most patients with AFPGC had serosal invasion, lymph node metastasis, and liver metastasis; three quarters had stage III or IV disease. Those authors found that the 5-year survival rate after gastrectomy was only 22%. The poor prognosis was attributable mostly to simultaneous metastases or early recurrence in the liver. However, Chun *et al.*[13] reported that 74% (n = 26) of their AFPGC patients had stage I or II disease. In our study, patients with normal serum AFP were observed to have more stage I disease (25.2% vs. 3.3% in patients with AFPGC) and less stage IV disease (27.1% vs. 58.6% in patients with AFPGC, $p < 0.001$).

In our study, more patients died of gastric cancer in the AFPGC group than in the AFP≤20 group (58.6% vs. 27.1%, $p < 0.001$), an observation that might be explained by a low rate of curative surgery and greater rates of recurrent gastric cancer and liver metastasis in the patients with AFPGC. In patients with HAS or AFPGC, the rate of EGC has been reported to be 0%–42.9%[3,6,11–14,16,19], with most publications reporting rates of less than 10%[6,12,14]. However, different observations have also been published. Chun *et al.*[13] found that 42.9% of their patients with AFPGC (n = 15) had early-stage disease. In our series, EGC was found in 4% of patients with AFPGC (2 of 50), which is a rate lower than that seen in the patients with normal AFP (349 of 1158, 30.1%, $p < 0.001$). Our finding is compatible with those in most other reports (0%–19.4%)[6,11,14], which found that advanced gastric cancer was present in most patients with HAS or AFPGC[3,6,12,14]. In our study, patients with AFPGC more often had advanced gastric cancer than did patients with normal serum AFP (96% vs. 69.9%, $p < 0.001$).

Poorly differentiated cancer cells have been reported to predominate in patients with AFPGC or HAS (48.6%–64.4%)[3,12,13,16]; however, different findings have also been reported. In one large analysis of pooled data from Japan, Adachi *et al.*[15] found that well-differentiated cancers was predominated in patients with AFPGC (n = 218, 87.2%). In our study, the incidence of poorly differentiated cancer cells (por 1, por 2, signet-ring cells, mucinous adenocarcinoma) was similar in both patient groups [50% in the AFPGC group (n = 23) and 48.7% in the normal serum AFP group (n = 558), $p = 0.87$].

Surgery is the currently the main therapy for gastric cancer. However, radical surgery was successful in only 6 patients of our AFPGC group (10.3%). In contrast, radical surgery was much more successful in patients with normal serum AFP (n = 468, 37.9%, $p < 0.001$). That difference might explain why the AFPGC group had more liver metastasis and a worse prognosis than did patients with normal serum AFP.

The 5-year survival rate in patients with AFPGC has been reported to be 9%–66%[6,12,13,16]. However, there has been some controversy about the link between AFP and survival duration. Survival duration after surgery has been found not to be linked to preoperative serum AFP[6]. Inoue and colleagues observed that 1 patient with high serum AFP (25,400 ng/mL) was still living 12 years after diagnosis of gastric cancer[6]. The large Japanese study using pooled data also showed similar results: Adachi *et al.*[15] found that 5-year survival rates were not different for patients with gastric cancer and a serum AFP less than 1000 ng/mL (42.7%) or greater than 1000 ng/mL (39.4%). Nagai *et al.*[20] also reported that the 5-year survival rate was 40% in patients with lower AFP and 38% in patients with higher AFP.

Other authors found that patients with AFPGC had a shorter survival duration. In one large series, Liu *et al.*[3] found that the 1-, 3-, and 5-year survival rates for patients with AFPGC were 53%, 35%, and 28% respectively. Those authors also found that patients with AFPGC or HAS had a poorer prognosis than did patients who had lower AFP concentrations ($p < 0.01$) or non-HAS disease ($p < 0.05$)[3]. Chun *et al.*[13] found that the 5-year survival rate in patients with AFP-producing disease was significantly poorer than that in non-AFP-producing group (66% vs. 80%, $p = 0.002$); however, their reported 5-year survival rate was extremely high compared with that in other reports. In our study, we found that 1-, 3-, 5-, and 10-year survival rates for 20<AFP≤300 patients were 46.7%, 28.9%, 17.8%, and 13.3% respectively. The 1-, 3-, and 5-year survival rates for AFP>300 patients were 15.4%, 7.7%, and 0% respectively. Patients in the AFP≤20 group had the best survival time, and patients in the 20<AFP≤300 group had the poorest survival time ($p < 0.001$, Figure 1).

5. CONCLUSIONS

Patients with AFP-producing gastric cancer had a low rate of successful surgery, a high rate of liver

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and lymph node metastasis, and very poor prognosis. More aggressive management with multimodal therapy (for example, chemotherapy, radiotherapy) might be needed when treating such patients.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors declare that they have no financial conflicts of interest.

8. REFERENCES

1. Bergstrand CG, Czar B. Demonstration of a new protein fraction in serum from the human fetus. *Scand J Clin Lab Invest* 1956;8:174.
2. El-Bahrawy M. Alpha-fetoprotein–producing non-germ cell tumours of the female genital tract. *Eur J Cancer* 2010;46:1317–22.
3. Liu X, Cheng Y, Sheng W, *et al.* Clinicopathologic features and prognostic factors in alpha-fetoprotein-producing gastric cancers: analysis of 104 cases. *J Surg Oncol* 2010;102:249–55.
4. Sterling RK, Wright EC, Morgan TR, *et al.* Frequency of elevated hepatocellular carcinoma (HCC) biomarkers in patients with advanced hepatitis C. *Am J Gastroenterol* 2012;107:64–74.
5. Collier J, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998;27:273–8.
6. Inoue M, Sano T, Kuchiba A, Taniguchi H, Fukagawa T, Katai H. Long-term results of gastrectomy for alpha-fetoprotein-producing gastric cancer. *Br J Surg* 2010;97:1056–61.
7. Chang YC, Nagasue N, Kohno H, *et al.* Clinicopathologic features and long-term results of alpha-fetoprotein-producing gastric cancer. *Am J Gastroenterol* 1990;85:1480–5.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011;14:101–12.
9. Lauren PA, Nevalainen TJ. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. *Cancer* 1993;71:2926–33.
10. Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours*. 6th ed. Hoboken, NJ: John Wiley and Sons; 2002.
11. Baek SK, Han SW, Oh DY, Im SA, Kim TY, Bang YJ. Clinicopathologic characteristics and treatment outcomes of hepatoid adenocarcinoma of the stomach, a rare but unique subtype of gastric cancer. *BMC Gastroenterol* 2011;11:56.
12. Zhang JF, Shi SS, Shao YF, Zhang HZ. Clinicopathological and prognostic features of hepatoid adenocarcinoma of the stomach. *Chin Med J (Engl)* 2011;124:1470–6.
13. Chun H, Kwon SJ. Clinicopathological characteristics of alpha-fetoprotein–producing gastric cancer. *J Gastric Cancer* 2011;11:23–30.
14. Ucar E, Semerci E, Ustun H, Yetim T, Huzmeli C, Gullu M. Prognostic value of preoperative CEA, CA 19-9, CA 72-4 and AFP levels in gastric cancer. *Adv Ther* 2008;25:1075–84.
15. Adachi Y, Tsuchihashi J, Shiraishi N, Yasuda K, Etoh T, Kitano S. AFP-producing gastric carcinoma: multivariate analysis of prognostic factors in 270 patients. *Oncology* 2003;65:95–101.
16. Liu X, Cheng Y, Sheng W, *et al.* Analysis of clinicopathologic features and prognostic factors in hepatoid adenocarcinoma of the stomach. *Am J Surg Pathol* 2010;34:1465–71.
17. Nakajima K, Ochiai T, Suzuki T, *et al.* Impact of preoperative serum carcinoembryonic antigen, CA 19-9 and alpha-fetoprotein levels in gastric cancer patients. *Tumor Biol* 1998;19:464–9.
18. Ishikura H, Fukasawa Y, Ogasawara K, Natori T, Tsukada Y, Aizawa M. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. *Cancer* 1985;56:840–8.
19. Kinjo T, Taniguchi H, Kushima R, *et al.* Histologic and immunohistochemical analyses of α-fetoprotein–producing cancer of the stomach. *Am J Surg Pathol* 2012;36:56–65.
20. Nagai E, Ueyama T, Yao T, Tsuneyoshi M. Hepatoid adenocarcinoma of the stomach. A clinicopathologic and immunohistochemical analysis. *Cancer* 1993;72:1827–35.

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