**Influence of high serum alpha fetoprotein on patients with gastric cancer**

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**Acknowledgement: This study was supported by the Tomorrow Medical Foundation. The authors expressed their gratitude to Wallace company for English revision.**

**Abstract**

**Background**

Patients with alpha-fetoprotein (AFP)-producing gastric cancer (AFPGC) have a high incidence of liver metastasis and poor prognosis. However, the clinical manifestation of AFPGC remains controversial.

**Methods**

We enrolled patients who, before surgery, had gastric cancer with serum AFP levels of > 100 ng/mL (n = 30) and of ≤ 20 ng/mL (n= 1236). Clinical manifestations were compared between these two groups.

**Results**

Compared with in the AFP> 100 group, early gastric cancer was more frequent (30.1% vs. 0%) and advanced gastric cancer was less frequent (69.9% vs. 100%) in the AFP ≤ 20 ng/mL group (*p* < 0.001). Moreover, the incidence of liver and lymph node metastases was lower in the AFP ≤ 20 ng/mL group than in the AFP > 100 ng/mL group (4.4% vs. 43.3%, *p* < 0.001 and 60.7% vs. 93.3%, *p* < 0.001, respectively). More patients had stage IV AFPGC in the AFP > 100 ng/mL group than in the ≤ 20 ng/mL group (66.7% vs 27.1%, *p* < 0.001). Furthermore, fewer patients underwent curative surgery in the AFP > 100 ng/mL group (6.7% vs 37.9%, *p* < 0.001). More patients in the AFP > 100 ng/mL group died because of gastric cancer (66.7% vs 27.1%, *p* < 0.0001).

**Conclusions**

Patients with very high serum AFP levels have a high incidence of liver and lymph node metastases and extremely poor prognosis.

**Introduction**

Alpha-fetoprotein (AFP) is a glycoprotein produced by the fetal liver and yolk sac during gestation **〔1〕** However, an increase in the serum AFP level is frequently observed in patients with hepatocellular carcinoma and in those with tumors of gonadal origin [2]. In addition, various other malignancies, including gastric cancer, produce AFP [3]. Moreover, the serum AFP level is increased in patients with chronic liver diseases such as viral hepatitis and cirrhosis [4, 5].

AFP-producing gastric cancer (AFPGC) is rare, accounting for less than 6% of all gastric cancers [6]. Poor prognosis is usually linked to AFPGC because of liver and lymph node metastases [3, 7]. However, controversy exists about the clinical manifestations in these patients. Some studies have reported favorable prognosis for patients with high serum AFP levels [8, 9]. To date, few studies have investigated the clinicopathological characteristics of and long-term survival in patients with AFPGC in Taiwan and worldwide. Moreover, the pathogenesis of AFPGC remains unclear. Therefore, in this single-center retrospective study, we reviewed the clinicopathological findings of 30 Chinese patients with gastric cancer and high serum AFP levels (> 100 ng/mL).

**Methods**

We reviewed the medical records of 3172 consecutive patients with gastric adenocarcinoma who received surgical intervention at the Taipei Veterans General Hospital between June 1988 and December 2011. The preoperative serum AFP level was measured in 1331 patients through radioimmunoassay (normal value: < 20 ng/mL). We excluded 37 patients with acute or chronic hepatitis, cirrhosis, or hepatocellular carcinoma. Furthermore, we recorded the surgical and pathological findings of the remaining 1294 patients by using the Japanese Classification of Gastric Carcinoma and Lauren classification [10, 11]. The nodal status and disease stage were assessed using the tumor–node–metastasis (TNM) system of the Union for International Cancer Control [12]. In addition, sex, age, tumor size (mucosal size of the tumor), liver and lymph node metastases, main tumor location, lymphatic and vascular invasion, clinical staging, curative surgery, and cause of death were recorded. Statistical analyses were performed using the SPSS software (SPSS for Windows, Version 10.0, SPSS, Chicago, IL, U.S.A.). The chi-square test with Yates’ correction for continuity was used to compare categorical data. The Fisher’s exact test was used when numbers were less than 5. Differences were considered significant when the *p* value was < 0.05.

We compared clinical parameters among patients with serum AFP>100 ng/mL, AFP 20-100 ng/mL and AFP <20 ng/mL.

**Results**

Of the 1294 eligible patients, 30 (2.3%) had high serum AFP levels (> 100 ng/mL), with preoperative levels ranging from 107 to 9999.9 ng/mL (mean, SD: 1660, 2635). We compared the clinicopathological characteristics of the patients with a serum AFP level of ≤ 20 ng/mL (n= 1236) with those of the patients with a serum AFP level of > 100 ng/mL (n = 30; table). Sex, age, tumour size, peritoneal seeding, and tumour location were similar in both groups. The incidence of liver and lymph node metastases was higher in the AFP > 100 ng/mL group than in the AFP ≤ 20 ng/mL group (43.3% vs. 4.4%, *p* < 0.001 and 93.3% vs. 60.7%, *p* < 0.001, respectively). Furthermore, compared with the patients in the AFP ≤ 20 ng/mL group, more patients had stage IV AFPGC (66.7% vs. 26.3%) and fewer had stage I AFPGC ( 3.3% vs. 34.2%) or II disease (6.7% vs. 37.9%; *p* < 0.001) in the AFP > 100 ng/mL group. Fewer patients in the AFP > 100 ng/mL group underwent curative surgery (6.7% vs. 37.9% in the AFP ≤ 20 ng/mL group, *p* < 0.001). Compared with the patients in the AFP ≤ 20 ng/mL group, more patients in the AFP > 100 ng/mL group died of gastric cancer (66.7% vs.27.1%, *p* < 0.001).

Compared with the AFP>100 ng/mL group, the AFP 20-100 ng/mL group had a lower incidence of liver metastasis (15.6% versus 43.3%, *p*=0.0247) (Table 2). The other parameters were not statistically different between both groups.

**Discussion**

The prognosis of patients with gastric cancer and abnormal serum AFP levels is poor [13]. In this study, we investigated patients with extremely high serum AFP levels (> 100 ng/mL). To the best of our knowledge, this is the first study investigating a large number of patients with gastric cancer and extremely high serum AFP levels. AFPGC is rare, and its clinical manifestation remains controversial [3, 6, 9, 14-16]. In our study, we observed that 2.3% of patients with gastric cancer (30 of 1294) had extremely high serum AFP levels (> 100 ng/mL). To avoid confounding factors in patients with AFPGC, we excluded 37 patients with liver diseases (cirrhosis, hepatoma, or acute hepatitis).

Liver metastasis (14.3%–75.6%) is one of the main characteristics of AFPGC or hepatoid adenocarcinoma of the stomach [9, 15, 16, 18]. In our study, 13 patients (43.3%) in the AFPGC group had liver metastasis at enrolment. Liver metastasis was more frequently observed in the patients with AFPGC than in the patients with AFP between 20 and 100 ng/mL (15.6%, *p*=0.0247) and in patients with a normal serum AFP level (n = 53, 4.4%, *p* < 0.001). However, differing observations have been reported. Nakajima et al. [8] reported no correlation between preoperative AFP levels and histopathology, lymph node and liver metastases, and vessel invasion. Studies have reported that lymph node involvement is high (62.9%–100%) in patients with AFPGC [9, 14-16]. In our study, compared with in the patients with a normal serum AFP level, lymph node metastasis was more frequently observed in the patients having a high serum AFP level (93.3% vs. 60.7%, *p* < 0.001).

The lower one-third of the stomach is the most common tumor location in AFPGC, accounting for 40%–61.5% of AFPGC cases [3, 6, 9, 14, 15, 18]. Our results were consistent with those of these studies. In our study, the primary cancer was above the antrum in 15 patients with AFPGC (50%) and in 590 patients with normal serum AFP levels (47.8%). Regarding clinical staging, studies have reported varying observations. In a large series (270 patients), Adachi et al. [17] reported that most patients with AFPGC had serosal invasion and lymph node and liver metastases, and that three-quarters of the patients had stage III or IV AFPGC. Moreover, they reported that the 5-year survival rate after gastrectomy was only 22%. The poor prognosis was attributable mostly to simultaneous metastases or early recurrence. However, Chun et al. [9] reported that 74% (n = 26) of their patients with AFPGC were in stage I or II. In our study, the patients with normal serum AFP were observed to have more stage I disease (25.2% vs. 0% in patients with AFPGC) and less stage IV disease (26.3% vs. 66.7%, *p* < 0.001).

More patients died of gastric cancer in the AFPGC group than in the AFP ≤ 20 group (66.7% vs. 27.1%, p < 0.001), This observation might be explained by a low rate of curative surgery and a high rate of recurrent gastric cancer and liver metastasis in patients with high serum AFP levels. In patients with AFPGC, the rate of early gastric cancer (EGC) has been reported to be 0%–42.9% [3, 6, 9, 14-16, 18, 20, 21], with most studies reporting a rate of < 10% [6, 15, 16]. However, different observations have also been reported. Chun et al. [9] reported that 42.9% of their patients with AFPGC (n = 15) had early-stage disease. In our study, EGC was not observed in any patient with a high serum AFP level (*p* < 0.001). Our findings are compatible with those of most other studies (0%–19.4%) [6, 14, 16] that reported that advanced gastric cancer was present in most patients with AFPGC [3, 6, 15, 16]. In our study, compared with patients with normal serum AFP levels, more patients with AFPGC had advanced gastric cancer (100% vs. 69.9%, *p* < 0.0001). Surgery is currently the main therapy for gastric cancer. However, radical surgery was successful in only two patients with AFPGC (6.7%). By contrast, radical surgery was much more successful in patients with normal serum AFP levels (n = 468, 37.9%, *p* < 0.001). That difference might explain why the AFPGC group had more liver metastasis and a poorer prognosis than did the normal serum AFP group.

**CONCLUSIONS**

In this study, the patients with AFPGC had a low rate of successful surgery, high rate of liver and lymph node metastases, and extremely poor prognosis.

**Table 1. Serum alpha-fetoprotein (AFP) and clinicopathologic features in patients with gastric cancer**

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**Variable afp concentration p Value**

 **≤20 ng/ mL(%) >100 ng/ mL(%)**

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**Patients (n) 1236 30**

**Sex [n (%) men] 976 (78.2) 26 (86.7) >0.1**

**Mean age (years) 66.2±11.7 68.3±9.8 >0.1**

**Mean tumour size (cm) 5.7±4.1 6.4±2.7 >0.1**

**Peritoneal seeding 179 (14.5) 7 (23.3) >0.1**

**Metastasis [n (%) yes]**

**Liver 53 (4.4) 13 (43.3) <0.001a**

**Lymph nodes 750 (60.7) 28 (93.3) <0.001b**

**Location of main tumour >0.1**

 **Cardia 195 (15.8) 5 (16.7)**

**Body 395 (32.0) 10 (33.3)**

**Antrum 646 (52.3) 15 (50.0)**

**Invasion [n (%) yes]**

**Lymphatic 738 (59.7) 26 (86.7) <0.01b**

**Vascular 47 (3.8) 11 (36.7) <0.001a**

**Stage <0.001a**

 **Ia 319 (25.2)**

**Ib 114 (9.0) 1 (3.3)**

**II 158 (12.5) 2 (6.7)**

**IIIa 190 (15.0) 2(6.7)**

**IIIb 153 (12.1)**

**IV 333 (26.3) 20 (66.7)**

 **Curative surgery [n (%)] 468 (37.9) 2 (6.7) <0.001b**

 **Cause of death [n (%) cancer] 330 (27.1) 20 (66.7) <0.001a**

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**a By chi-square test. b By Fisher exact test.**

**Table 2. Serum alpha-fetoprotein (**AFP) **and clinicopathologic features in patients with gastric cancer with serum AFP between 20 and 100 ng/mL versus >100 ng/mL**

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**Variable AFP concentration p Value**

 **20 -100 ng/ mL (%) >100 ng/ mL(%)**

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**Patients (n) 32 30**

**Sex [n (%) men] 28 (87.5) 26 (86.7) >0.1**

**Mean age (years) 68.2±10.1 68.3±9.8 >0.1**

**Mean tumour size (cm) 6.2±2.9 6.4±2.7 >0.1**

**Peritoneal seeding 6 (14.5) 7 (23.3) >0.1**

**Metastasis [n (%) yes]**

**Liver 5 (15.6) 13 (43.3) 0.0247**

**Lymph nodes 31(96.8) 28 (93.3) >0.1**

**Location of main tumour >0.1**

 **Cardia 4(12.5) 5 (16.7)**

**Body 12(37.5) 10 (33.3)**

**Antrum 14 (43.7) 15 (50.0)**

**Invasion [n (%) yes]**

**Lymphatic 24 (75) 26 (86.7) >0.1**

**Vascular 12(37.5) 11 (36.7) >0.1**

**Stage >0.1**

**II 6 (21.8) 2 (6.7)**

**III 6 (15.0) 2(6.7)**

**IV 20 (50) 20 (66.7)**

 **Curative surgery [n (%)] 5(15.6) 2 (6.7) >0.1**

 **Cause of death [n (%) cancer] 25 (78.1) 20 (66.7) >0.1**

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