Langenbeck's Archives of Surgery (2023) 408:66
https://doi.org/10.1007/s00423-023-02817-4

RESEARCH

Re-evaluation of the prognosis of alpha-fetoprotein-producing gastric cancer from a single center: a case series study

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Received: 5 November 2022 / Accepted: 18 January 2023 / Published online: 25 January 2023

Abstract

Background Alpha-fetoprotein (AFP)-producing gastric cancer (AFPGC) is reported to have biologically aggressive features and poor prognosis. A relatively large number of patients with AFPGC have achieved a long-term prognosis after surgery in our institution. This study aimed to clarify the clinical features of and re-evaluate the long-term outcomes of AFPGC.

Methods This analysis involved 465 patients who underwent surgery for gastric cancer (GC) at our institute between 1996 and 2020. The clinical features and long-term outcomes of the 24 patients with AFPGC were assessed. The differences in clinicopathological characteristics between AFPGC and non-AFPGC patients were statistically analyzed.

Results In patients with AFPGC, the median preoperative serum AFP level was 232 ng/mL. Tumor invasion of AFPGC was classified and clinical characteristics of AFPGC patients were as follows: nodal metastasis, simultaneous liver metastasis, with malignant cells in ascites, lymphatic, and venous involvement. Postoperative surveillance revealed adjuvant therapy in fourteen, recurrence in eight, and four patients died of GC. The 3- and 5-year overall survival (OS) rates were 85.2% and 75.7% in AFPGC patients and 79.6% and 77.7% in non-AFPGC patients, respectively. The log-rank test identified no significant difference in OS between AFPGC and non-AFPGC patients. Tumor depth, nodal, and venous involvement showed significant differences between AFPGC and non-AFPGC patients.

Conclusions AFPGC has aggressive biological features, but long-term prognosis after surgery does not seem to be as poor as claimed in previous studies. Therefore, it may be important to detect and start treatment early when surgery is feasible.

Keywords Alpha-fetoprotein-producing gastric cancer (AFPGC) · Prognosis · Surgery · Recurrence

Introduction

Gastric cancer (GC) is the fifth most common malignancy in the world [1]. The mortality rate of GC accounts for one-fifth of all tumors [2]. Alpha-fetoprotein-producing gastric cancer (AFPGC) was first reported in 1970 by Bourrille et al. [3] as a rare type of gastric cancer (GC) and is more common in Asian countries, such as Japan and China [4, 5]. Alpha-fetoprotein (AFP) is a glycoprotein that is normally synthesized in the fetal liver and yolk sac during gestation [6]. While AFP is a useful tumor marker of hepatocellular carcinomas or yolk sac tumors, several studies have shown the existence of other types of malignant tumors that produce AFP, including GC [7, 8].

Generally, AFPGC is considered to have poor prognosis. However, a relatively large number of patients with AFPGC have achieved long-term prognosis at our institution. Therefore, we were interested in determining further on the prognosis of patients with AFPGC. In this study, we aimed to primarily understand the clinical characteristics and prognosis of AFPGC using a case series study and then to re-evaluate the long-term prognosis of AFPGC using a retrospective cohort study.

Material and methods

Study population

From a prospectively collected database maintained at the Department of Gastroenterological Surgery, Toranomon

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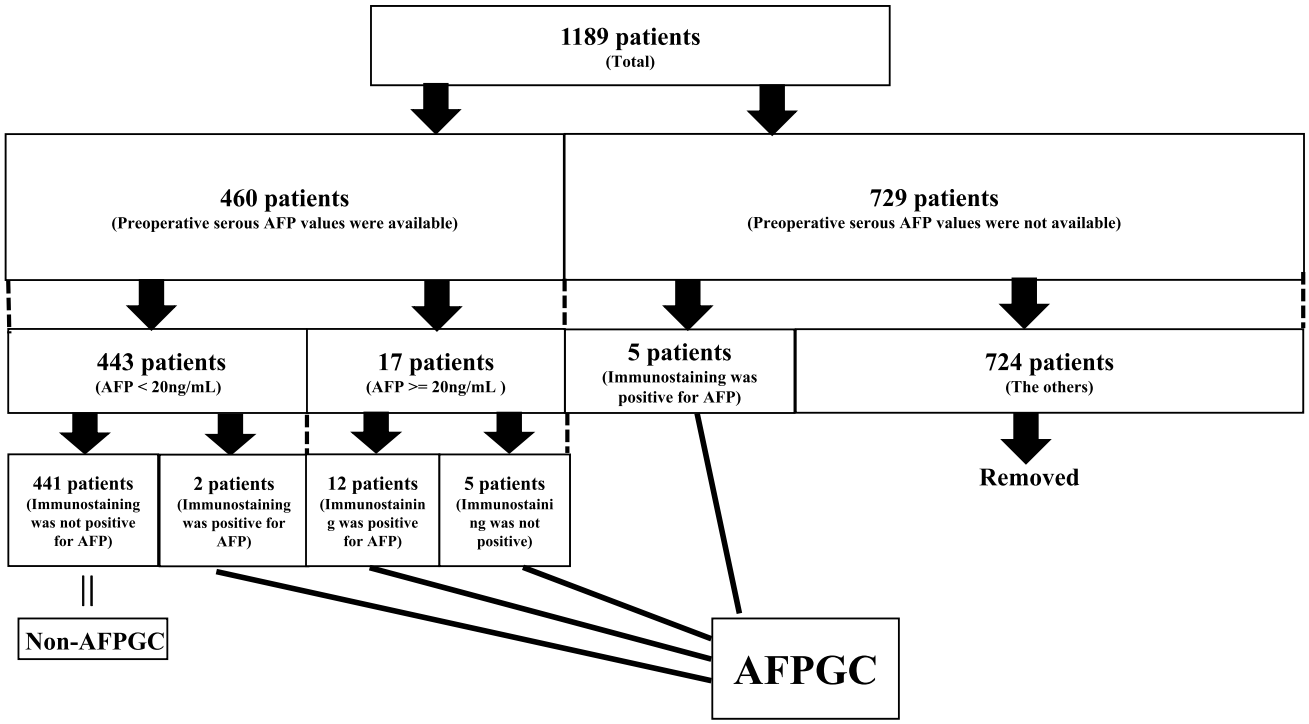

Fig. 1 Study population workflow. The number of patients for each cohort, AFPGC, non-AFPGC, and removed group are provided. The study population was categorized based on the availability of serous AFP values and immunostaining findings

Hospital, Tokyo, Japan, 1189 patients who underwent surgery for GC between 1996 and 2020 and whose pathological data were available were identified. Of them, 465 patients (460 patients whose preoperative serous AFP values were available and 5 patients whose immunostaining showed positivity) were enrolled in this study. The remaining 724 patients were removed from this study because the unavailability of their preoperative AFP values could cause statistical bias (Fig. 1). Although the definition of AFPGC has not been clearly established, AFPGC was defined, in the present study, as gastric cancers whose preoperative AFP values were above the threshold (20.0 ng/mL) or whose immunohistochemistry showed positivity for AFP (Fig. 1). This study was performed in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan with the approval of the Institutional Review Board (No. 2349).

Clinicopathological factors

Detailed clinicopathological factors were retrieved from hospital records. Tumor staging was determined according to the TNM classification of the Union for International Cancer Control [9]. Macroscopic classification was based on the Borrmann classification (types I–V) [10]. Early stage superficial GC is categorized as type 0. The tumor infiltrative pattern (INF) was defined in the Japanese Classification of Gastric Carcinoma, which categorizes GC as expansive growth type (INFa), intermediate growth type (INFb), and infiltrative type (INFc) [11]. In our institute, patients are regularly screened for recurrence with esophagogastroduodenoscopy, computed tomography, ultrasonography, and tumor markers for at least 5 years after surgery, when possible. Relapse-free survival (RFS) was calculated from the day of surgery to the day of relapse or most recent follow-up. Overall survival (OS) was calculated from the day of surgery to the day of death or last follow-up.

Statistical analyses

Statistical analysis was performed using the JMP software (ver. 12.2.0; SAS Institute, Inc., Cary, NC, USA) and R 4.2.1 (https://cran.r-project.org/). Continuous values are expressed as median (range). Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. The propensity score weighting approach, inverse probability of treatment weighting (IPTW), was also utilized to reduce potential bias between AFPGC and non-AFPGC. This process created a weighted cohort of patients that was well balanced and appropriate for direct comparison. As our data contained several missing values, the final IPTW was calculated as an average of that generated in each imputed dataset. The propensity score model included the following covariates: patient age, sex, maximum tumor diameter,

Table 1 The clinicopathological characteristics of 24 patients with AFPGC

General	
N	24
Age, y	85.5 (59-86)
Male sex	21 (87.5)
Chief complaint	
A.Abdominal pain/anemia/weight loss/melena/none	2 (8.3)/6 (25.0)/3 (12.5)/1 (4.2)/12 (50.0)
Serum CEA, ng/mL	2.9 (1.0-78.2)
Serum CA19-9, U/mL	12.0 (0.0-141)
Serum AFP, ng/mL	232 (3.0-2640)
Preoperative treatment	
Present/absent	2 (8.3)/22 (91.7)
Surgical procedure	
DG/PG/TG/others	12 (50.0)/4 (16.7)/7 (29.2)/1 (4.2)
Lymphadenectomy	
D0/D1/D2	3 (12.5)/3 (12.5)/18 (75.0)
Tumor location	
Upper/middle/lower	7 (29.2)/9 (37.5)/8 (33.3)
Anterior/posterior/greater/lesser/circular	3 (12.5)/3 (12.5)/5 (20.8)/12 (50.0)/1 (4.2)
Maximum tumor diameter, mm	45 (18–127)
Macroscopic classification	
0/I/II/III/IV/V	3 (12.5)/4 (16.7)/11 (45.8)/5 (20.8)/1 (4.2)/0 (0.0)
Lymphatic involvement	
Positive/negative	14 (58.3)/10 (41.7)
Venous involvement	
Positive/negative	19 (79.1)/5(20.8)
Infiltrative growth pattern	
INFa/INFb/INFc/unknown	5 (20.8)/15 (62.5)/1 (4.2)/3 (12.5)

Figures represent median (range) or number (percentage)

"Anterior and posterior" mean anterior wall and posterior wall, respectively. "Greater and lesser" mean greater curvature and lesser curvature. "Circular" means circular lesion

Abbreviations: *CEA*, carcinoembryonic antigen; *CA19-9*, carbohydrate antigen 19-9; *AFP*, alpha-fetoprotein; *DG*, distal gastrectomy; *TG*, total gastrectomy; *PG*, proximal gastrectomy

nodal involvement, lymphatic involvement, venous involvement, simultaneous liver metastasis, simultaneous peritoneal metastasis, T classification, and final tumor stage. Survival analysis using the Kaplan-Meier method and the log-rank test was also conducted in the IPTW sample. Categorical variables are expressed as percentages (%) and were compared using Fisher's exact test. Statistical significance was set at $p < 0.05$.

Results

Case series study of patients with AFPGC

The clinicopathological characteristics of the 24 AFPGC patients are presented in Table 1. The median age was 85.5 years. The median serum AFP level was 232 ng/mL. The main tumors were located in the upper (7/24), middle (9/24), and lower parts (8/24) of the stomach. The tumors were found mainly at the anterior wall (3/24), posterior wall (3/24), lesser curvature (12/24), and greater curvature (5/19) in three, three, 12, and five patients. One patient had a circular lesion. Only two patients (Patients 22 and 24) had received neoadjuvant therapies. Lymphatic and venous involvement were found in 14 (58.3%) and 19 (79.1%) patients, respectively. The median tumor size was 45 mm.

Table 2 shows the postoperative therapies and long-term outcomes of the involved patients. Tumor invasion was classified as the following: T1b (4/24, 16.7%), T2 (5/24, 20.8%), T3 (10/24, 41.7%), T4a (4/24, 16.7%), and T4b (1/24, 4.2%). Seventeen patients (70.8%) had nodal metastasis (N1 in seven patients and N2 in ten patients). The final tumor staging was classified into IA in two (8.3%), IIA in eight (33.3%), IIB in five (20.8%), IIIA in five (20.8%), IIIB in one (4.2%), and IV in three (12.5%) patients. One patient with simultaneous liver metastasis, one with simultaneous peritoneal metastasis and one with malignant cells for

Table 2 Postoperative therapy and long-term outcomes of our 24 cases of AFPGC

Patient (No.)	T classification	N classification	M classification	Final stage	Postoperative therapy		Initial relapse site	Outcome	RFS (months)	OS (months)
					Pre-relapse	Post-relapse				
1	T2	N2	M0	IIB	None	Methotrexate/5-fluorouracil	Liver	Alive	6	276
2	T1b	N2	M0	IIA	None		None	Died of the other causes	12	12
3	T3	N1	M0	IIB	None		None	Died of the other causes	57	57
4	T3	N2	M1 (CY1)	IV	Performed (details unknown)		Unknown	Died of the disease	Unknown	95
5	T4a	N1	M0	IIIA	S-1		None	Alive	44	44
6	T4a	N2	M0	IIIA	S-1	Participation in clinical trials (details unknown)	Lymph node	Died of the other causes	31	61
7	T2	N1	M0	IIA	None		None	Died of the other causes	24	24
8	T3	N0	M0	IIA	S-1	Radiofrequency ablation for liver metastasis	Liver	Alive	16	119
9	T1b	N2	M0	IIA	S-1		None	Alive	107	107
10	T1b	N0	M0	IA	None		None	Alive	90	90
11	T4a	N2	M0	IIIA	None	Trastuzumab + Cisplatin/Capecitabine	Liver	Alive	7	27
12	T4a	N2	M0	IIIA	None	S-1	Liver	Died of the disease	4	7
13	T3	N0	M1 (H1)	IV	None		None	Alive	68	68
14	T3	N1	M0	IIB	Capecitabine/Oxaliplatin	Trastuzumab + Cisplatin/Capecitabine	Liver	Died of the disease	2	9
15	T4b	N1	M0	IIIB	S-1		None	Alive	55	55
16	T2	N2	M0	IIB	Etoposide/Carboplatin	Amrubicin	Bone	Alive	10	11
17	T1b	N0	M0	IA	None		None	Alive	9	9
18	T3	N0	M0	IIA	None		None	Alive	20	20
19	T3	N0	M0	IIA	None		None	Alive	13	13
20	T2	N1	M0	IIA	S-1		None	Alive	137	137
21	T4a	N0	M0	IIB	None		None	Died of the other causes	93	93
22	T4a	N2	M0	IIIA	Trastuzumab + S-1	Paclitaxel + Ramucirumab	Lymph node	Alive	9	48
23	T2	N1	M0	IIA	None		None	Alive	6	6
24	T4a	N2	M1 (P1)	IV	Cisplatin/Capecitabine		Unknown	Died of the disease	Unknown	5

"CY1" means the existence of malignant cells for cytodiagnosis of ascites. "H1" means simultaneous liver metastasis. "P1" means simultaneous peritoneal metastasis

Abbreviations: *RFS*, relapse-free survival; *OS*, overall survival

Table 3 Baseline characteristics of the entire cohort of 465 GC patients

General	
N	465
Age, y	85.5 (23–93)
Male sex	313 (67.3)
Tumor location	
Upper/middle/lower/unknown	94 (20.2)/134 (28.8)/163 (35.1)/74(15.9)
Anterior/posterior/greater/lesser/circular	49 (10.5)/70 (15.1)/75 (16.1)/151 (32.5)/40 (8.6)/80 (17.2)
Maximum tumor diameter, mm	47.0 (1.4–210)
Macroscopic classification	
0/I/II/III/IV/V/unknown	195 (41.8)/13 (2.6)/68 (14.6)/78 (16.7)/25 (5.4)/8 (1.7)/77 (16.6)
T classification	
T1a/T1b/T2/T3/T4a/T4b/Unknown	116 (24.9)/80 (17.2)/41 (8.8)/59 (12.7)/66 (14.2)/20 (4.3)/83 (17.8)
Nodal involvement	
Present/absent/unknown	127 (27.3)/237 (51.0)/101 (21.7)
Simultaneous liver metastasis	
Present/unknown	7 (1.5)/17 (3.7)
Simultaneous peritoneal metastasis	
Present/unknown	27 (5.8)/5 (1.1)
Final stage	
I/IIA/IIB/III/IV/unknown	190 (40.8)/48 (10.3)/42 (9.0)/54 (11.6)/51 (11.0)/80 (17.2)
AFPGC	24(5.2)
Lymphatic involvement	
Positive/negative/unknown	177 (38.1)/184 (39.6)/104 (22.4)
Venous involvement	
Positive/negative/unknown	185 (39.8)/176 (37.8)/104 (22.4)
Postoperative observation term, m	25.8 (0–276)
Death due to postoperative tumor progression	56(16.0)
Death due to postoperative liver recurrence	6 (1.7)

Figures represent median (range) or number (percentage)

cytodiagnosis of ascites were identified. Postoperative adjuvant chemotherapy was administered in 14 patients.

Patients with stage IA (Patients 10 and 17) showed no recurrence without any additional treatment. Of the eight patients with stage IIA disease (Patients 2, 7, 8, 9, 18, 19, 20, and 23), five patients (Patients 2, 7, 18, 19, and 23) showed no recurrence without additional treatment. Two patients with stage IIA (Patients 9 and 20) achieved relatively long survivals (107 and 137 months, respectively) after the administration of S-1. The other patient with stage IIA (Patient 8) attained 119-month survival regardless of the existence of liver recurrence, which was treated with radiofrequency ablation. Of the five patients with stage IIB (Patients 1, 3, 14, 16, and 21), two patients (Patients 1 and 16) were alive with the change in chemotherapy regimen, although two patients (Patients 3 and 21) died of liver recurrence. Of the five patients with stage IIIA (Patients 5, 6, 11, 12, and 22), two patients (Patients 6 and 12) died of tumor recurrence. Nonetheless, one patient with stage IIIB (Patient 15) achieved a 55-month RFS with the administration of S-1.

Study population with GC

Clinicopathological features of the global population in which surgery for GC was performed are shown in Table 3. The median observation term was 25.8 (0.0–276) months. Tumor invasion was categorized as T1a in 116 (24.9%) patients, T1b in 80 (17.2 %), T2 in 41 (8.8 %), T3 in 59 (12.7 %), T4a in 66 (14.2 %), T4b in 20 (4.3 %), and unknown in 83 (17.8 %) patients. Nodal involvement was observed in 127 (27.3%) patients. The final tumor staging was classified as I in 190 (0.8%), IIA in 48 (10.3%), IIB in 42 (9.0%), III in 54 (11.6%), IV in 51 (11.0%), and unknown in 80 (17.2%) patients. Lymphatic and venous involvement were found in 177 (38.1%) and 185 (39.8%) patients, respectively. Twenty-four patients (5.2%) were diagnosed with AFPGC. Simultaneous liver and peritoneal metastases were found in 7 (1.5%) and 27 (5.8%) patients, respectively. Among the total population, 56 (16.0%) patients died of tumor recurrence. Of these, 6 (1.7%) died of liver recurrence.

Table 4 The differences of OS according to each clinicopathological factor in the entire cohort of 465 GC patients

	P
Age ≧ 65 (vs. < 65)	<0.001
T3-4 (vs. T1-2)	<0.001
Maximum tumor diameter >40 mm (vs.≦ 40mm)	<0.001
Nodal involvement	<0.001
Lymphatic involvement	<0.001
Venous involvement	<0.001
AFPGC (vs. non-AFPGC)	0.600
Simultaneous liver metastasis	<0.001
Simultaneous peritoneal metastasis	<0.001
Final stage III–IV (vs. I–II)	<0.001

Comparison of clinicopathological features between AFPGC and non-AFPGC

Table 5 shows the results of the comparison of clinicopathological factors between the 24 patients with AFPGC and 441 with non-AFPGC. In summary, tumor depth (P =0.019), nodal ($P < 0.001$), and venous involvement ($P < 0.001$) were significantly different between AFPGC and non-AFPGC patients.

Discussion

In the present study, we successfully summarized the clinicopathological characteristics and long-term postoperative outcomes of 24 patients who underwent surgery for AFPGC.

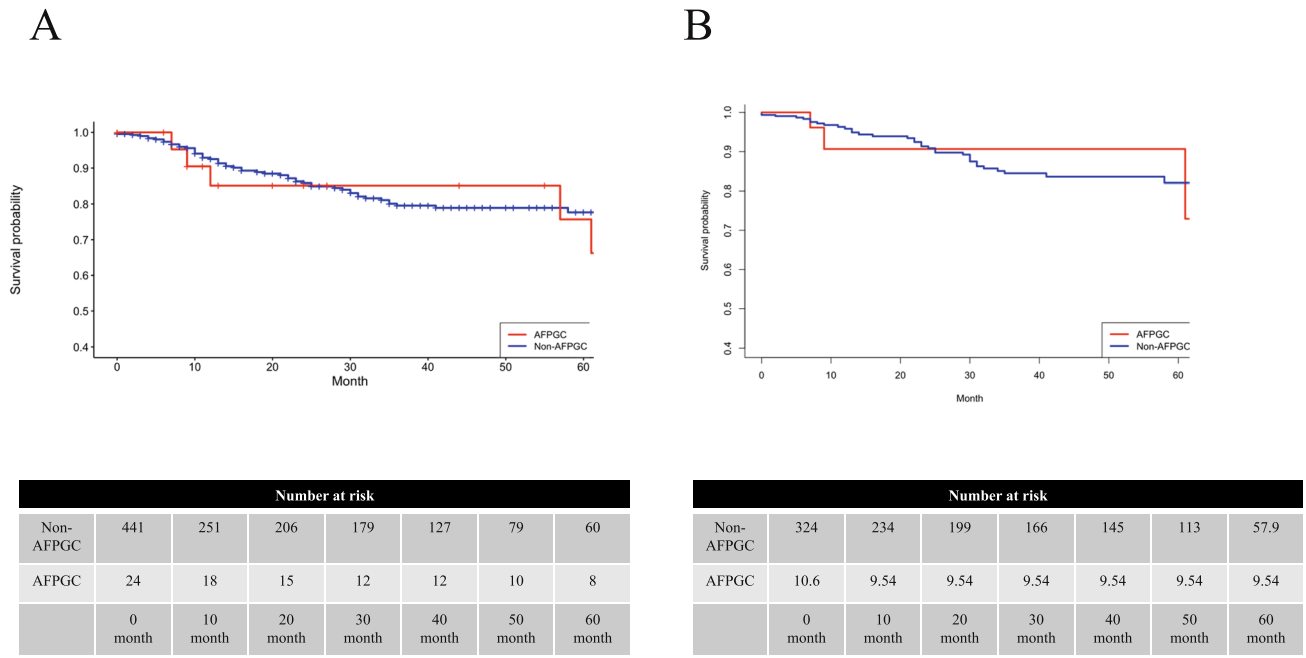

Fig. 2 Survival curves and number at risk between patients with AFPGC and non-AFPGC before and after IPTW adjustment. No significant difference in OS between AFPGC and non-AFPGC was found (P= 0.600 before IPTW adjustment (**A**) and 0.844 after IPTW adjustment (**B**))

Comparison of long-term survival between AFPGC and non-AFPGC

The prognostic determinants of GC were investigated using the log-rank test for the entire cohort of 465 patients (Table 4). The results showed no significant difference in OS between AFPGC and without AFPGC (P = 0.600) (Figs. 1A and 2A). The 3- and 5-year survival rates were 85.2% and 75.7% in AFPGC patients and 79.6% and 77.7% in non-AFPGC patients, respectively. Even after IPTW adjustment, no statistically significance was identified in OS between AFPGC and without AFPGC (P = 0.844) (Fig. 2B).

This case series included a variety of information on each patient's preoperative and postoperative follow-up periods would be extremely rare and valuable. Our analysis suggests that the long-term prognosis of AFPGC patients might not be as poor as that of non-AFPGC patients, as reported by recent researches. Furthermore, AFPGC tended to be associated with more lymphovascular invasion than non-AFPGC, and recurrence of AFPGC was characterized by a higher frequency of liver metastases, which is similar to the results of previous reports.

AFPGC has been reported to be associated with aggressive biological characteristics and poor prognosis compared

Table 5 Clinicopathological characteristics between AFPGC and non-AFPGC

	AFPGC	Non-AFPGC	*P*
N	24 (5.2)	441 (94.8)	
Serous AFP value (ng/mL)	232 (3.0–2640)	3.0 (1.0–9.0)	<0.001
Tumor deepness (T3–T4)	15 (62.5)	130 (29.5)	0.019
Maximum tumor diameter (>40 mm)	13 (54.2)	165 (37.4)	0.392
Nodal involvement	17 (70.8)	110 (24.9)	<0.001
Lymphatic involvement	14 (58.3)	163 (37.0)	0.150
Venous involvement	19 (79.2)	166 (37.6)	<0.001
Final stage (III–IV)	9 (37.5)	96 (21.8)	0.355
Simultaneous liver metastasis	1 (4.2)	6 (1.4)	0.671
Simultaneous peritoneal metastasis	1 (4.2)	26 (5.9)	1.000
Death due to tumor progression	4 (16.7)	52 (11.8)	1.000
Death due to postoperative liver recurrence	2 (8.3)	4 (0.91)	0.056

Figures represent median (range) or number (percentage)

with non-AFPGC [12] [13]. High proliferative activity, weak apoptosis, and rich neovascularization are currently reported to be at the root of the aggressive features of AFPGC [14]. Liu et al. reported a 5-year OS rate of only 28.0%, while that of non-AFPGC patients was 38.0% [12]. Previous studies focusing on the long-term outcomes of AFPGC have identified vascular invasiveness, liver metastasis, and nodal involvement as evidence of the aggressive nature of AFPGC [4] [15]. An interesting recent study also supported the idea of aggressiveness of AFPGC from a molecular biological point of view [16]. The present study is consistent with previous studies in that we also observed significant differences in tumor depth, nodal involvement, and lymphovascular involvement between AFPGC and non-AFPGC. An important result of this study is that AFPGC patients presented a satisfactory prognosis, with no significant difference compared to non-AFPGC patients. This indicates that the factors proving the aggressiveness of AFPGC (tumor depth, nodal involvement, and lymphovascular involvement) may not have negative effects on the long-term outcomes of AFPGC. Moreover, the favorable prognosis of AFPGC might be due, in part, to the fact that some cases of liver metastasis of AFPGC are relatively controllable by surgical resection [17]. Therefore, it is necessary to investigate the differences between the present and previous studies on the poor prognosis of AFPGC. According to Hirajima et al., multivariate analysis revealed that AFP positivity was not an independent prognostic factor [18]. The previous study also showed that the prognosis of AFPGC was similar to that of non-AFPGC without simultaneous liver metastasis and that liver metastasis was the only prognostic factor in AFPGC [18]. In our cohort, there was no significant difference in the incidence of simultaneous liver metastasis between AFPGC and non-AFPGC ($P = 0.671$), indicating that our study population was analyzed in a situation where the impact of simultaneous liver metastasis was statistically negligible. Thus, our study may indicate the validity of the study conducted by Hirajima et al. [18].

This study population was limited to patients whose preoperative blood AFP values were available. Thus, it can be noticed that high preoperative blood AFP levels would not necessarily mean positive immunostaining for AFP or that pathological study may later identify AFPGC even if preoperative blood AFP values are within the normal range (Fig. 1). Considering the characteristics of heterogeneity within a tumor, AFP-producing cells can sometimes form nodules and be hidden in some parts of the tumor. Therefore, the positivity for AFP could be partly influenced by how to cut the specimen. This may indicate that the definition of AFPGC in possible multicenter studies should be based not only on pathological findings, but also on the trends of blood AFP levels and clinical background.

Our study has some limitations. First, because this study was designed retrospectively, there was no unified follow-up strategy. It should be noted that some of the enrolled patients were followed-up for a relatively small observation period, while others were meticulously followed-up for a long period. Second, due to the single institutional analysis, this study included a relatively small number of patients mainly due to the low frequency of AFPGC (with approximately 1.2–15% of GC) [9]. A different result might be obtained if a larger sample size is involved. Third, there may have been a selection bias, since this study was limited to operable patients. In addition, not all gastric specimens have been routinely immunostained for AFP at our institution, since it was performed only when AFPGC was suspected by pathologists based on preoperative serum AFP levels and pathological findings. Therefore, the possibility of AFPGC misdiagnosis should be considered. Further multicenter studies with larger sample sizes are needed before definitive conclusions can be drawn, providing guidelines for optimizing therapeutic strategies for AFPGC.

In conclusion, although AFPGC may have aggressive features, such as tumor depth, nodal involvement, and lymphovascular involvement, the long-term prognosis of patients who underwent surgery does not seem to be as poor as previously reported. In AFPGC, early detection and initiation of therapeutic intervention at the stage when surgery is feasible may be important.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00423-023-02817-4.

Authors' contributions All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by Miho Akabane. The first draft of the manuscript was written by Miho Akabane, and all the authors commented on the previous versions of the manuscript. Akikazu Yago helped to draft the manuscript. All authors have read and approved the final manuscript.

Funding Miho Akabane received a research grant from the Okinaka Memorial Institute for Medical Diseases.

Data availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable

Declarations

Ethics approval Approval was obtained from the ethics committee of the Toranomon Hospital. The study procedures adhered to the tenets of the Declaration of Helsinki.

Consent to participate The requirement for individual informed consent was waived due to the retrospective nature of the study.

Conflict of interest The authors declare no competing interests.

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