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Original Article

Recurrent metastatic patterns and prognosis after radical surgery in patients with alpha-fetoprotein-producing gastric cancer: a retrospective cohort study

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Abstract: Alpha-fetoprotein-producing gastric cancer (AFPGC) is a rare and aggressive subtype of gastric cancer associated with poor prognosis. This study aimed to investigate the recurrent metastatic patterns and prognostic factors in AFPGC patients undergoing radical surgical resection. Data from 241 AFPGC patients diagnosed between January 2017 and January 2020 who underwent surgical resection were analyzed across multiple centers. Recurrence patterns, metastatic sites, and survival outcomes were evaluated. Univariate and multivariate analyses were performed to identify risk factors for recurrent metastasis, overall survival (OS), and disease-free survival (DFS). There is an annual increase in the proportion of AFPGC cases, rising from 3.45% in 2017 to 7.88% in 2023. Higher serum AFP level was associated with increased likelihood of lymph node metastasis (P=0.006), deeper invasion depth (P=0.000) and greater tumor diameter (P=0.036). Independent predictors of recurrent metastasis included T4 infiltration, lymph node metastasis, tumor diameter >5 cm, poorly differentiated-undifferentiated pathology, preoperative AFP>1000 ng/mL, and postoperative increasing trend in AFP levels. The 5-year OS and DFS rates were 36.5% and 34.2%, respectively, with poorer survival linked to higher preoperative AFP levels and postoperative increasing trend in AFP level. Independent risk factors for poor OS and DFS included T4 infiltration, lymph node metastasis, poorly differentiated-undifferentiated pathology, preoperative AFP>1000 ng/mL, and postoperative increasing trend in AFP. Serum AFP level can serve as a potential predictive and prognostic biomarker. Identifying independent risk factors informs risk stratification and personalized treatment for AFPGC patients.

Keywords: Alpha-fetoprotein-producing gastric cancer, recurrent metastasis patterns, prognostic factors, radical surgery, serum alpha-fetoprotein levels

Introduction

Gastric cancer remains one of the most prevalent and lethal malignancies worldwide, accounting for a significant burden on global health [1, 2]. Among the various subtypes, alpha-fetoprotein-producing gastric cancer (AFPGC) is a rare and distinct entity characterized by the production of alpha-fetoprotein (AFP), a glycoprotein typically associated with fetal development and certain malignancies [3-6]. Despite its rarity, AFPGC has garnered considerable attention due to its aggressive clinical behavior and poor prognosis compared to conventional gastric adenocarcinoma [7].

Radical surgery, often involving gastrectomy with lymph node dissection, has been the main-

stay treatment for resectable AFPGC cases [8, 9]. However, the high propensity for metastasis and recurrence remains a significant challenge, leading to dismal long-term outcomes [10, 11]. Understanding the recurrent metastatic patterns and identifying prognostic factors are crucial for optimizing treatment strategies, surveillance protocols, and improving patient outcomes.

Numerous single-center studies have investigated the clinicopathological features, treatment modalities, and survival outcomes of AFPGC patients [12-14]. However, these studies have been limited by small sample sizes and potential institutional biases. For instance, Zuo et al. included 106 AFPGC patients in a retrospective study [13], and the findings may not accurately reflect the true patterns and prognostic factors associated with this rare malignancy. In this context, the present multicenter retrospective cohort study aims to comprehensively investigate the recurrent metastatic patterns and prognostic factors in AFPGC patients undergoing radical surgery. By leveraging data from multiple institutions, this study seeks to overcome the limitations of previous single-center studies and provide a more robust and generalizable understanding of this unique disease entity.

Methods and materials

Patient selection

This retrospective cohort study utilized data from the Hebei Gastric Cancer Collaborative Network Database (http://hbss.suvalue.com/), which collects data from the Fourth Hospital of Hebei Medical University, a large cancer center in Hebei Province, China, and three other research centers (Shijiazhuang People's Hospital, Baoding Central Hospital, and Hengshui People's Hospital). Patients with AFPGC who underwent radical surgical resection between January 2017 and January 2023 were retrospectively analyzed.

Inclusion criteria: 1) Peripheral blood serum alpha-fetoprotein (AFP) level ≥20 ng/mL; 2) No prior history of anti-tumor treatment; 3) Receipt of radical surgical resection. Exclusion criteria: 1) Incomplete clinical information; 2) Concurrent presence of other malignancies; 3) R1/R2 surgical resection; 4) Loss to follow-up or non-compliance during follow-up. Incomplete clinical information refers to any missing or insufficient data regarding a patient's medical history, diagnostic tests, treatments, or outcomes, which impedes a comprehensive understanding of the clinical scenario. Loss to follow-up or non-compliance during follow-up refers to situations where patients cannot be contacted or fail to adhere to the prescribed follow-up protocols, resulting in incomplete data collection during the follow-up period.

The final cohort consisted of 241 AFPGC patients who underwent curative resection. The study was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University (approval number: 2023KY139) and complied with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments. Informed consent was waived due to the retrospective study design.

Detection of serum AFP level

The serum AFP level was measured using an enhanced chemiluminescence immunoassay with Cobas E601 chemiluminescence analyzer [Roche Diagnostic Products (Shanghai) Co., Ltd.] and associated kits, adhering to the manufacturer's standard operating procedures and instructions. This method involves binding the specimen's AFP antigen to a monoclonal AFP antibody fixed in the solid phase, followed by linkage to a polyclonal AFP antibody tagged with acridinium ester in the liquid phase. Gastric cancer is classified as AFP-positive when serum AFP levels exceed 20 ng/mL and AFP-negative when levels are 20 ng/mL or below [15].

Collection of clinical variables

In this study, we collected demographic data (gender and age), performance status (ECOG score), comorbidity data (Charlson Comorbidity Index), and preoperative serum tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigens 19-9 (CA19-9) and CA72-4 from patients upon admission. Furthermore, we evaluated postoperative pathological features, such as tumor size, location, differentiation, invasion depth, lymph node involvement, vascular and neural invasion, and Lauren classification. The study also included pTNM stag-

ing and the expression of molecular markers like HER2, PD-L1, and MMR. Crucially, we systematically tracked longitudinal changes in peripheral blood serum AFP levels across all AFPGC patients to assess their potential correlation with prognosis.

Postoperative treatment

All the enrolled AFPGC patients underwent radical gastrectomy, achieving R0 resections. Following the 2021 Chinese Society of Clinical Oncology (CSCO) clinical diagnosis and treatment guidelines for gastric cancer, postoperative adjuvant therapy was determined by TNM staging [16, 17]. This included high-risk patients at T1 stage and all patients with T2 stage or higher, who were administered 5-FU-based adjuvant chemotherapy. The chemotherapy regimens comprised Tegafur (S-1) or single-agent capecitabine [18].

Postoperative follow-up

Overall survival (OS) was determined from the date of surgery to tumor-related death or last follow-up, and disease-free survival (DFS) was measured from surgery to death due to recurrence [19, 20]. The follow-up protocol conformed to the Chinese Society of Clinical Oncology guidelines, with evaluations conducted quarterly for the first two years and then biannually or annually. Follow-up assessments comprised telephone consultations, clinical visits, imaging studies, endoscopic examinations, and tumor marker tests. The follow-up period concluded on March 1, 2024.

Statistical analyses

Statistical analyses were conducted using SPSS software version 21.0 (SPSS Inc., USA). Normally distributed continuous variables were presented as mean ± standard deviation (SD), and non-normally distributed variables as median and interquartile range (IQR). Categorical variables were summarized using counts (n) and percentages (%). Continuous variables were compared using the independent t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data, whereas categorical variables were analyzed using the chi-square test or Fisher's exact test as appropriate. To identify risk factors for postoperative recurrence and metastasis in AFPGC patients, both univariate and multivariate logistic regression analyses were conducted, with results reported as odds ratios (OR) and 95% confidence intervals (CI). Similarly, Cox regression models were used for univariate and multivariate analyses of overall survival (OS) and disease-free survival (DFS), with findings presented as hazard ratios (HR) and 95% confidence intervals (CI). Graphical visualizations were generated with GraphPad Prism version 8.01 (GraphPad Inc., USA), and *P* values <0.05 were deemed statistically significant.

Results

Diagnosis and treatment of early gastric cancer

From January 2017 to January 2023, all patients who underwent radical surgical resection for gastric cancer were retrieved. **Figure 1A** illustrates an annual increase in the proportion of AFPGC cases, rising from 3.45% in 2017 to 7.88% in 2023. Moreover, the proportion of AFPGC patients with stage III-IV consistently exceeded that of stage I-II patients (**Figure 1B**). Additionally, the distribution of treatment modalities for AFPGC underwent a dynamic shift, transitioning from predominantly surgical resection to a comprehensive regimen of preoperative neoadjuvant chemotherapy/conversion therapy followed by surgical resection, with a progressive increase in the proportion of preoperative treatment (**Figure 1C**). Concurrently, with the advancement of molecular marker detection technologies for HER2 and PD-L1, an increasing number of patients received targeted therapy and immunotherapy in addition to chemotherapy (**Figure 1C**).

Patients' characteristics

To further analyze the recurrence, metastasis patterns, and prognostic risk factors of AFPGC patients after radical resection, we selected cases diagnosed between January 2017 and January 2020 from the database. After applying the inclusion and exclusion criteria, a total of 241 AFPGC patients who underwent surgical resection were identified, with 165 cases (68.5%) from the Fourth Hospital of Hebei Medical University, 35 cases (14.5%) from Shijiazhuang People's Hospital, 23 cases (9.5%) from Hengshui People's Hospital, and

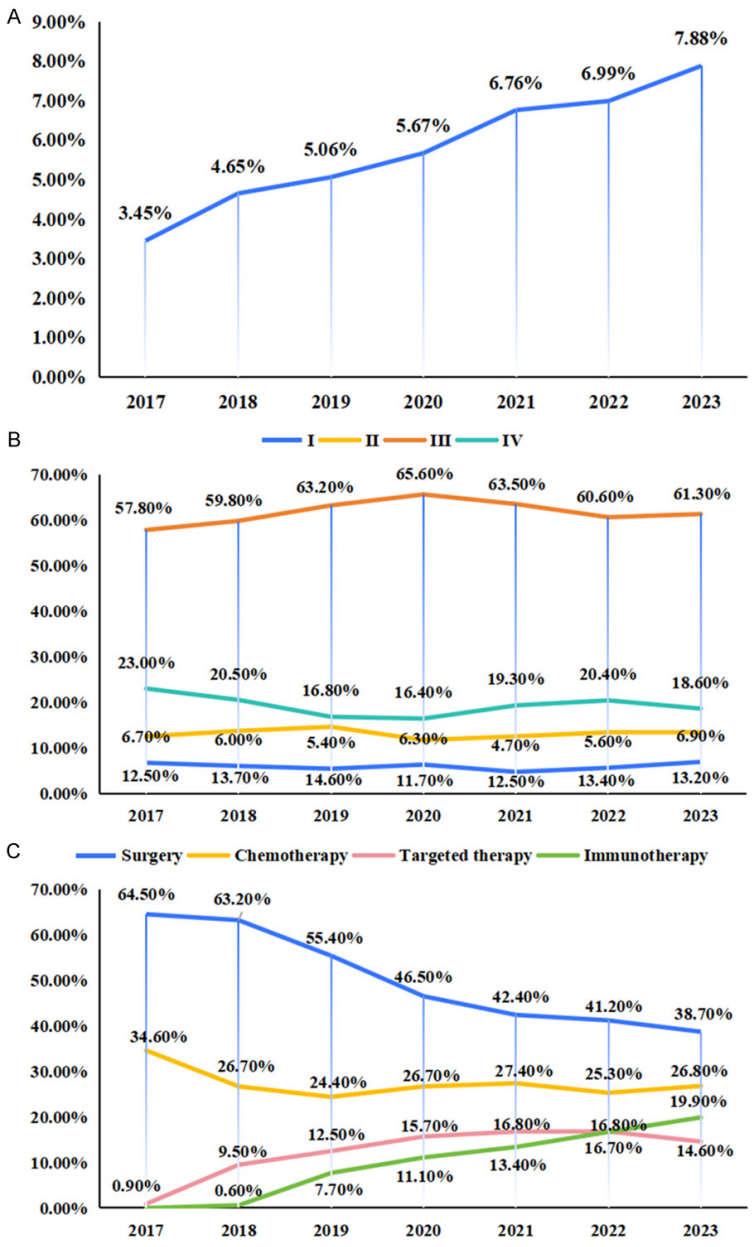

Figure 1. Dynamics of admission rates and treatment options for AFGC patients. A. Changes in the proportion of AFPGC admissions from 2017 to 2023; B. Distribution of TNM stages of AFPGC patients from 2017 to 2023; C. Changes in the proportion of treatment methods for AFPGC patients from 2017 to 2023.

18 cases (7.5%) from Baoding Central Hospital (**Figure 2**).

The median age of the AFPGC patients was 59.8 years, and 147 (61.0%) were male. As depicted in the clinical characteristics heatmap (**Figure 3A**), the primary tumor location was the upper stomach in 82 cases (34.0%), middle stomach in 54 cases (22.4%), and lower stomach in 105 cases (43.6%). The proportion of T4 stage at diagnosis and treatment was significantly higher than T2-T3 stage (66.4% vs. 33.6%), and 193 patients (80.1%) had lymph node metastasis (**Figure 3B**, **3C**). Additionally, we analyzed the expression of HER2 and PD-L1 molecular markers in postoperative specimens, revealing that 8.7% (21/241) of AFPGC patients had HER2 (3+), while 12.2% (29/241) exhibited strong PD-L1 positivity (CPS>10) (**Figure 3D**, **3E**).

Based on preoperative serum AFP levels, the cohort was divided into four subgroups: 148 cases (61.4%) with 20-200 ng/mL, 54 cases (22.4%) with 200-500 ng/mL, 27 cases (11.2%) with 500-1000 ng/mL, and 12 cases (5.0%) with >1000 ng/mL. Compared to patients with 20-200 ng/mL, higher serum AFP values were associated with increased likelihood of lymph node metastasis (P=0.006), deeper invasion depth (P=0.000), and larger tumor diameter (P=0.036) (**Table 1**).

Postoperative recurrence patterns of AFPGC patients

All AFPGC patients in this study underwent open or laparoscopic D2 radical gastrectomy. During regular postoperative follow-up, we found that a total of 132 patients (54.7%) developed recurrent metastases, with the liver being the most common site, followed by retroperitoneal lymph nodes, supraclavicular lymph nodes, and rarely brain metastases (**Figure 4A**, **4F**). As of the last follow-up date, AFPGC patients who developed recurrent metastases had the earliest median time to liver metastasis (9.8 months, 95% CI: 5.7-13.6 months) and the longest median time to bone metastasis (31.5 months, 95% CI: 24.7-43.6 months) (**Figure 4K**). Furthermore,

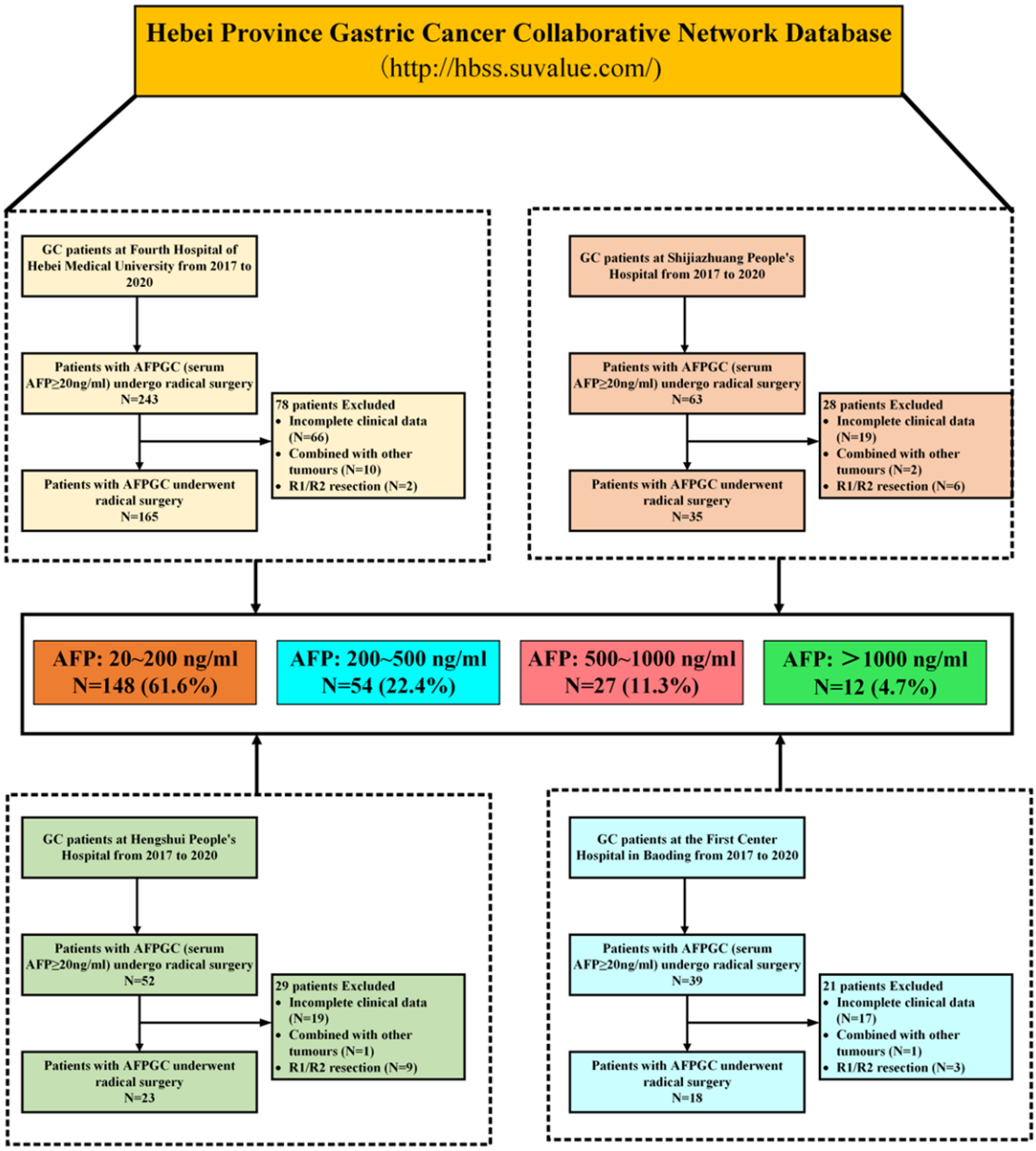

Figure 2. Flow chart of AFPGC patient screening and enrollment.

our subgroup analysis based on serum AFP levels revealed that liver metastasis remained the most frequent site of recurrent metastasis, and the proportion of liver metastasis increased with higher AFP values, while the median time to liver metastasis exhibited a decreasing trend (**Figure 4B-E**, **4G-J**, **4L-O**).

Subsequently, we analyzed the longitudinal dynamic changes of serum AFP in all patients after surgery and found that the 241 AFPGC patients could be divided into four subgroups: 132 cases (54.8%) with a continuous decreasing trend in postoperative AFP level, 23 cases (9.5%) with a continuous increasing trend, 55 cases (22.8%) with a flat change, and 31 cases (12.9%) with an increasing and then decreasing trend (**Figure 5A-D**). Interestingly, patients with a persistent increase in AFP changes developed liver metastasis in a shorter period after

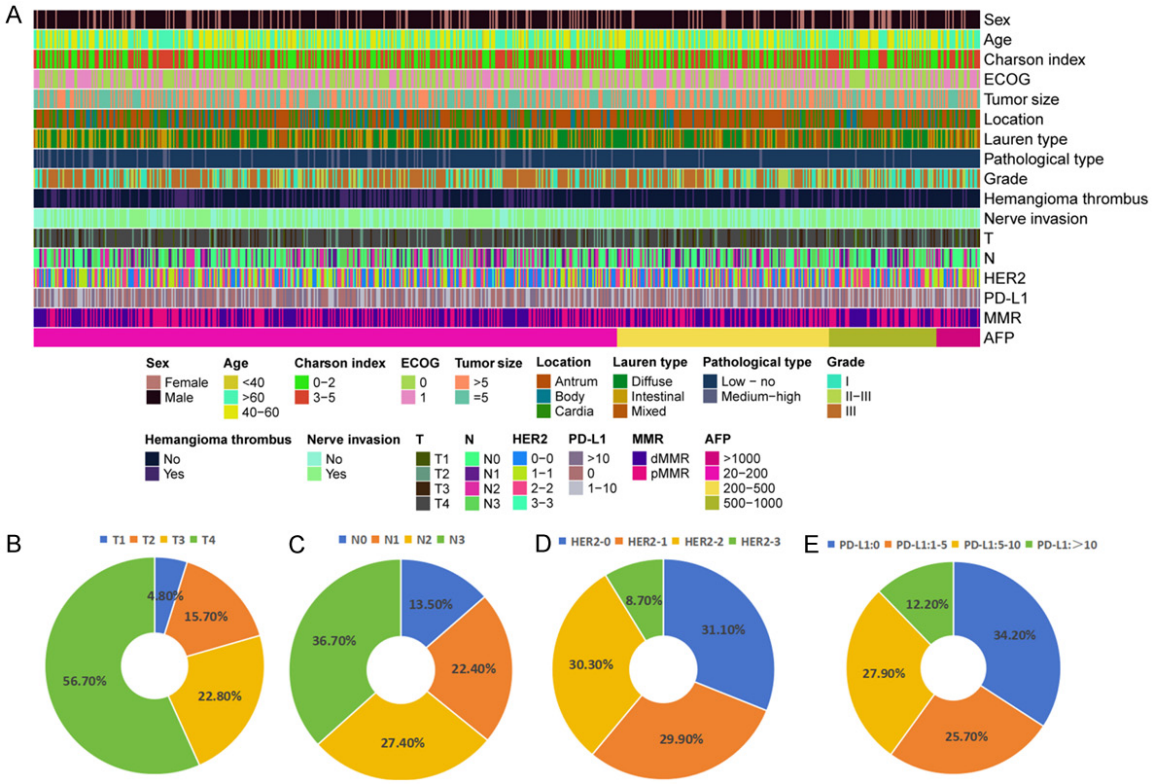

Figure 3. Heat map of clinical characteristics analysis of AFPGC patients. A. Heatmap of the distribution of clinical characteristics of AFPGC patients; B. Distribution of T-stages of AFPGC patients; C. N-stages of AFPGC patients; D. Distribution of different states of the molecular marker HER2 in AFPGC patients; E. Distribution of different states of the molecular marker PD-L1 in AFPGC patients.

surgery and had the highest percentage of liver metastasis compared to the other subgroups (**Figure 5E-P**).

Risk factors for the development of recurrent metastases after radical surgery in patients with AFPGC

Univariate analysis revealed that the depth of tumor infiltration, lymph node metastasis status, tumor diameter, pathology type, Lauren classification, preoperative peripheral blood AFP expression level, and postoperative longitudinal dynamic changes in AFP were significantly associated with the emergence of recurrence after radical surgery in AFPGC patients (all P<0.05). In contrast, gender, age, ECOG score, CCI index, tumor site, pathological grade, and molecular markers HER2 and PD-L1 were not significantly associated with postoperative recurrence in these patients (all P>0.05) (**Table 2**).

Multivariate logistic regression identified the following as independent predictors for the development of postoperative recurrent metastasis in AFPGC patients: T4 infiltration (OR=3.781, 95% CI: 1.852-7.893; P=0.005), presence of lymph node metastasis (OR=4.427, 95% CI: 1.666-9.467; P=0.001), tumor diameter >5 cm (OR=1.765, 95% CI: 1.124-3.346; P=0.025), poorly differentiated-undifferentiated pathological type (OR=2.428, 95% CI: 1.364-6.708; P=0.009), preoperative AFP>1000 ng/mL (OR=5.672, 95% CI: 2.670-13.642; P=0.001), and postoperative increasing trend in AFP levels (OR=7.409, 95% CI: 2.567-16.788; P=0.001) (**Table 2**).

Risk factors for prognosis in patients with AFPGC

After a median follow-up of 57.8 months (range 24.6-70.7 months) in the entire AFPGC patient cohort, the 5-year OS and DFS rates were 36.5% and 34.2%, respectively. Firstly, stratified analysis based on preoperative peripheral serum AFP levels revealed that the 5-year OS and DFS rates were 63.5% and 52.7% for

Table 1. Clinicopathological characterization of patients with AFPGC [n (%)]

Clinical variables	All (n=241)	Stratification of serum AFP				*P* value
		AFP: 20-200 (n=148)	AFP: 200-500 (n=54)	AFP: 500-1000 (n=27)	AFP: >1000 (n=12)	
Gender						0.885
Male	147 (61.0%)	92 (62.2%)	32 (59.3%)	15 (55.6%)	8 (66.7%)	
Female	94 (39.0%)	56 (37.8%)	22 (40.7%)	12 (44.4%)	4 (33.3%)	
Age (years)						0.844
≤65	154 (63.9%)	93 (62.8%)	34 (63.0%)	18 (66.7%)	9 (75.0%)	
>65	87 (36.1%)	55 (37.2%)	20 (37.0%)	9 (33.3%)	3 (25.0%)	
ECOG						0.950
0-1	218 (90.5%)	135 (91.2%)	48 (88.9%)	24 (88.9%)	11 (91.7%)	
2	23 (9.5%)	13 (8.8%)	6 (11.1%)	3 (11.1%)	1 (8.3%)	
Charlson Comorbidity Index						0.875
≤3	199 (82.6%)	122 (82.4%)	46 (85.2%)	21 (77.8%)	10 (83.3%)	
>3	42 (17.4%)	26 (17.6%)	8 (14.8%)	6 (22.2%)	2 (16.7%)	
T stage						0.006
T2/T3	81 (33.6%)	61 (41.2%)	15 (27.8%)	4 (14.8%)	1 (8.3%)	
T4	160 (66.4%)	87 (58.8%)	39 (72.2%)	23 (85.2%)	11 (91.7%)	
N stage						0.000
N0	48 (19.9%)	13 (8.8%)	15 (27.8%)	12 (44.4%)	8 (66.7%)	
N+	193 (80.1%)	135 (91.2%)	39 (72.2%)	15 (55.6%)	4 (33.3%)	
Primary site						0.999
Up 1/3	82 (34.0%)	50 (33.8%)	18 (33.4%)	10 (37.1%)	4 (33.3%)	
Middle 1/3	54 (22.4%)	34 (23.0%)	12 (22.2%)	5 (18.5%)	3 (25%)	
Lower 1/3	105 (43.6%)	64 (43.2%)	24 (44.4%)	12 (44.4%)	5 (41.7%)	
Tumor size (cm)						0.036
≤5	89 (36.9%)	65 (43.9%)	15 (27.8%)	7 (25.9%)	2 (16.7%)	
>5	152 (63.1%)	83 (56.1%)	39 (72.2%)	20 (74.1%)	10 (83.3%)	
Histology						0.06
None/Low	202 (83.8%)	131 (88.5%)	43 (79.6%)	19 (70.4%)	9 (75%)	
High/Median	39 (16.2%)	17 (11.5%)	11 (20.4%)	8 (29.6%)	3 (25%)	
Grade						0.139
I	58 (24.1%)	27 (18.2%)	18 (33.3%)	10 (37.0%)	3 (25%)	
II	89 (36.9%)	55 (37.2%)	21 (38.9%)	8 (29.6%)	5 (41.7%)	
III	94 (39.0%)	66 (44.6%)	15 (27.8%)	9 (33.4%)	4 (33.3%)	
Lauren						0.394
Diffuse/Mix type	143 (59.3%)	82 (55.4%)	37 (68.5%)	17 (63.0%)	7 (58.3%)	
Intestinal type	98 (40.7%)	66 (44.6%)	17 (31.5%)	10 (37.0%)	5 (41.7%)	
Vascular invasion						0.700
Yes	88 (36.5%)	51 (34.5%)	20 (37.0%)	11 (40.7%)	6 (50.0%)	
No	153 (63.5%)	97 (65.5%)	34 (63.0%)	16 (59.3%)	6 (50.0%)	
Nerve invasion						0.172
Yes	98 (40.7%)	59 (39.9%)	24 (44.4%)	15 (55.6%)	8 (66.7%)	
No	143 (59.3%)	89 (60.1%)	30 (55.6%)	12 (44.4%)	4 (33.3%)	
HER2						0.127
Positive	22 (9.1%)	10 (6.8%)	5 (9.3%)	4 (14.8%)	3 (25%)	
Negative	219 (90.9%)	138 (93.2%)	49 (90.7%)	23 (85.2%)	9 (75%)	
PD-L1						0.021
0	67 (27.8%)	33 (22.3%)	18 (33.3%)	12 (44.5%)	4 (33.3%)	
1-10	106 (44.0%)	78 (52.7%)	15 (27.8%)	8 (29.6%)	5 (41.7%)	
>10	68 (28.2%)	37 (25%)	21 (38.9%)	7 (25.9%)	3 (25%)	

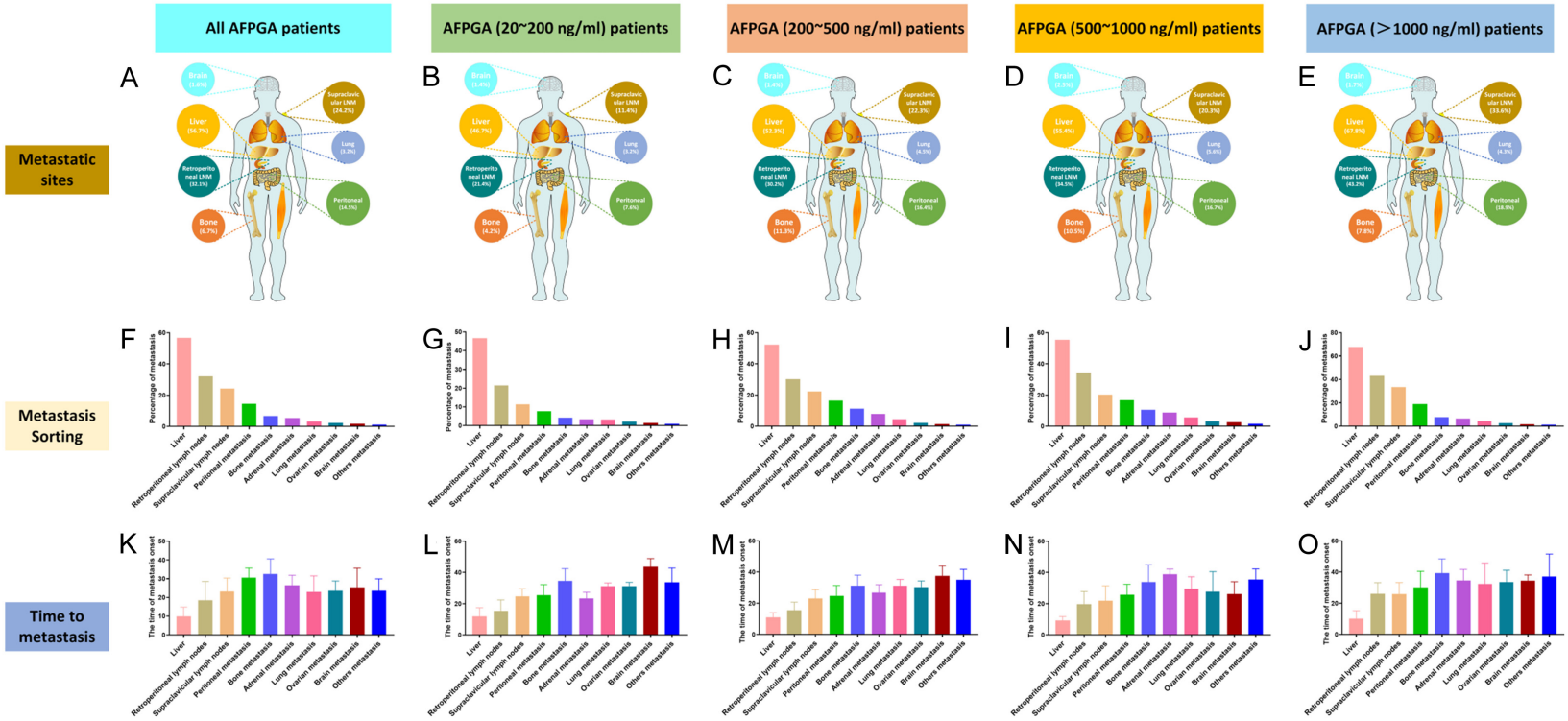

Figure 4. Recurrent metastasis patterns based on stratified analysis of serum AFP expression values. A. Distribution of recurrent metastatic sites in all enrolled AFPGC patients; B. Distribution of recurrent metastatic sites in AFPGC patients with AFP expression values of 20-200 ng/mL; C. Distribution of recurrent metastatic sites in AFPGC patients with AFP expression values of 200-500 ng/mL; D. Distribution of recurrent metastatic sites in AFP expression values of 500-1000 ng/mL AFPGC patients with AFP expression values of 500-1000 ng/mL; E. Distribution of recurrent metastatic sites in AFPGC patients with AFP expression values of >1000 ng/mL; F. Distribution of the most frequent recurrent metastatic sites in all enrolled AFPGC patients; G. Distribution of the most frequent recurrent metastatic sites in AFPGC patients with AFP expression values of 20-200 ng/mL; H. Distribution of the most frequent recurrent metastatic sites in AFPGC patients with AFP expression values of 200-500 ng/mL; I. Distribution of the most frequent recurrent metastatic sites in AFPGC patients with AFP expression values of 500-1000 ng/mL; J. Distribution of the most frequent recurrent metastatic sites in AFPGC patients with AFP expression values >1000 ng/mL; K. Median time to recurrent metastasis in all enrolled AFPGC patients; L. Median time to recurrent metastasis in AFPGC patients with AFP expression values of 20-200 ng/mL; M. Median time to recurrent metastasis in AFPGC patients with AFP expression values of 200-500 ng/mL; N. Median time to recurrent metastasis in AFPGC patients with AFP expression values of 500-1000 ng/mL; O. Median time to recurrent metastasis in AFPGC patients with AFP expression values of >1000 ng/mL.

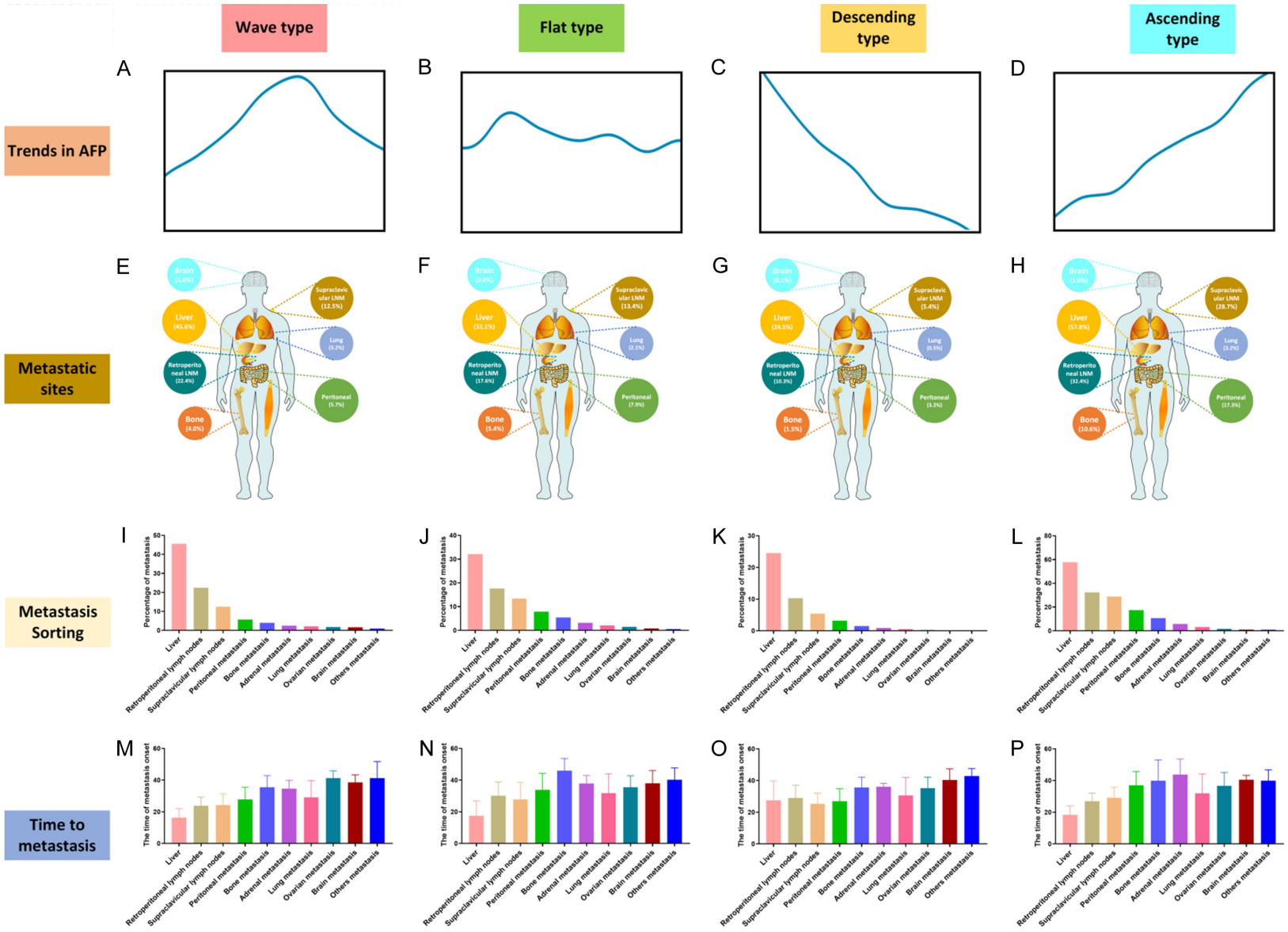

Figure 5. Patterns of recurrent metastasis based on stratified analysis of serum AFP trends. A. Peaked trend in the longitudinal dynamics of AFP; B. Flat trend in the longitudinal dynamics of AFP; C. Declining trend in the longitudinal dynamics of AFP; D. Ascending trend in the longitudinal dynamics of AFP; E. Distribution

of recurrent metastatic sites in the population with peaked trends; F. Distribution of recurrent metastatic sites in the population with flat trends; G. Distribution of recurrent metastatic sites in the population with declining trends situation; H. Distribution of recurrent metastatic sites in the ascending trend population; I. Distribution of the most frequently occurring recurrent metastatic sites in the cresting trend population; J. Distribution of the most frequently occurring recurrent metastatic sites in the flat trend population; K. Distribution of the most frequently occurring recurrent metastatic sites in the descending trend population; L. Distribution of the most frequently occurring recurrent metastatic sites in the ascending trend population; M. Median time to recurrent metastasis in the crested trend population; N. Median time to recurrent metastasis in the flat trend population; O. Median time to recurrent metastasis in the descending trend population; P. Median time to recurrent metastasis in the ascending trend population.

Table 2. Univariate and multifactorial analysis of risk factors affecting recurrence in patients with AFPGC

Variable	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Gender				
Male	Reference			
Female	0.561 (0.212-1.422)	0.571		
Age (years)				
≤65	Reference			
>65	0.802 (0.410-2.651)	0.326		
ECOG				
0-1	Reference			
2	0.486 (0.146-1.208)	0.422		
Charlson Comorbidity Index				
≤3	Reference			
>3	0.771 (0.457-2.133)	0.634		
T stage				
T2/T3	Reference		Reference	
T4	4.632 (2.187-10.672)	0.008	3.781 (1.852-7.893)	0.005
N stage				
N0	Reference		Reference	
N+	6.704 (2.783-15.369)	0.013	4.427 (1.666-9.467)	0.001
Primary site				
Up 1/3	Reference			
Middle 1/3	1.454 (0.783-2.332)	0.533		
Lower 1/3	1.123 (0.635-1.997)	0.762		
Tumor size (cm)				
≤5	Reference		Reference	
>5	2.508 (1.234-5.538)	0.003	1.765 (1.124-3.346)	0.025
Histology				
High/Median	Reference		Reference	
None/Low	3.554 (1.552-8.529)	0.011	2.428 (1.364-6.708)	0.009
Grade				
I	Reference			
II	1.642 (0.646-2.563)	0.673		
III	2.309 (0.784-1.997)	0.310		
Lauren				
Intestinal type	Reference		Reference	
Diffuse/Mix type	1.709 (1.122-4.653)	0.027	1.234 (0.787-3.345)	0.078
Vascular invasion				
No	Reference			
Yes	1.326 (0.652-2.264)	0.074		

Nerve invasion				
No	Reference			
Yes	1.671 (0.786-2.887)	0.091		
HER2				
Positive	Reference			
Negative	1.542 (0.667-2.347)	0.524		
PD-L1				
0	Reference			
1-10	1.673 (0.782-2.806)	0.061		
>10	2.309 (0.988-3.570)	0.056		
Serum AFP expression (ng/ml)				
20-200	Reference		Reference	
200-500	1.543 (1.212-5.646)	0.031	1.353 (1.143-2.312)	0.025
500-1000	2.686 (1.663-4.874)	0.018	3.128 (1.795-6.645)	0.007
>1000	4.794 (2.542-9.769)	0.001	5.672 (2.670-13.642)	0.001
Trends in serum AFP				
Descending type	Reference		Reference	
Ascending type	6.623 (2.892-14.532)	0.001	7.409 (2.567-16.788)	0.001
Flat type	3.452 (1.762-7.894)	0.008	3.267 (1.673-8.785)	0.019
Wave type	2.567 (1.116-6.724)	0.041	1.765 (1.098-5.643)	0.038

patients with AFP 20-200 ng/mL, 50.0% and 42.5% for 200-500 ng/mL, 33.3% for both in the 500-1000 ng/mL group, and 33.3% and 25.9% for >1000 ng/mL, respectively. Notably, the 5-year OS and DFS rates were 33.3% and 25.9% for patients with AFP>1000 ng/mL, indicating a worsening prognosis with increasing AFP levels (**Figure 6A**, **6B**). Moreover, our analysis of postoperative longitudinal AFP dynamics yielded similar results, with patients exhibiting an increasing trend having the worst 5-year OS and DFS compared to those with other trend changes (**Figure 6C**, **6D**).

Multivariate Cox regression identified the following as independent risk factors affecting OS and DFS in AFPGC patients: T4 infiltration (OS: HR=4.341, 95% CI: 2.135-12.673, P=0.001; DFS: HR=4.733, 95% CI: 1.998-12.780, P=0.001), lymph node metastasis (OS: HR=5.553, 95% CI: 2.675-11.093, P=0.001; DFS: HR=6.543, 95% CI: 2.788-15.098, P=0.001), poorly differentiated-undifferentiated pathology (OS: HR=2.655, 95% CI: 1.318-15.780, P=0.001; DFS: HR=3.352, 95% CI: 1.312-5.711, P=0.026), preoperative AFP>1000 ng/mL (OS: HR=7.137, 95% CI: 2.770-13.542, P=0.001; DFS: HR=11.562, 95% CI: 4.232-27.809, P=0.001), and postoperative increasing trend in AFP dynamics (OS: HR=7.485, 95% CI: 3.651-16.334, P=0.001; DFS: HR=9.876, 95% CI: 3.708-20.768, P=0.001) (**Tables 3**, **4**).

Discussion

The present multicenter retrospective cohort study provides a comprehensive analysis of the recurrent metastatic patterns and prognostic factors in patients with alpha-fetoprotein-producing gastric cancer (AFPGC) who underwent radical surgical resection. AFPGC represents a rare and aggressive subtype of gastric cancer, characterized by elevated serum AFP levels and dismal outcomes compared to conventional gastric adenocarcinoma [21]. By leveraging data from multiple institutions, this study overcomes the limitations of small sample sizes and potential biases associated with single-center investigations, thereby enhancing the generalizability and robustness of the findings.

A notable observation from our study is the increasing proportion of AFPGC cases among gastric cancer patients over the years, rising from 3.45% in 2017 to 7.88% in 2023. This trend may be attributed to improved diagnostic techniques and heightened awareness of this unique entity. Additionally, our data revealed a consistent predominance of advanced-stage (III-IV) AFPGC cases, underscoring the aggres-

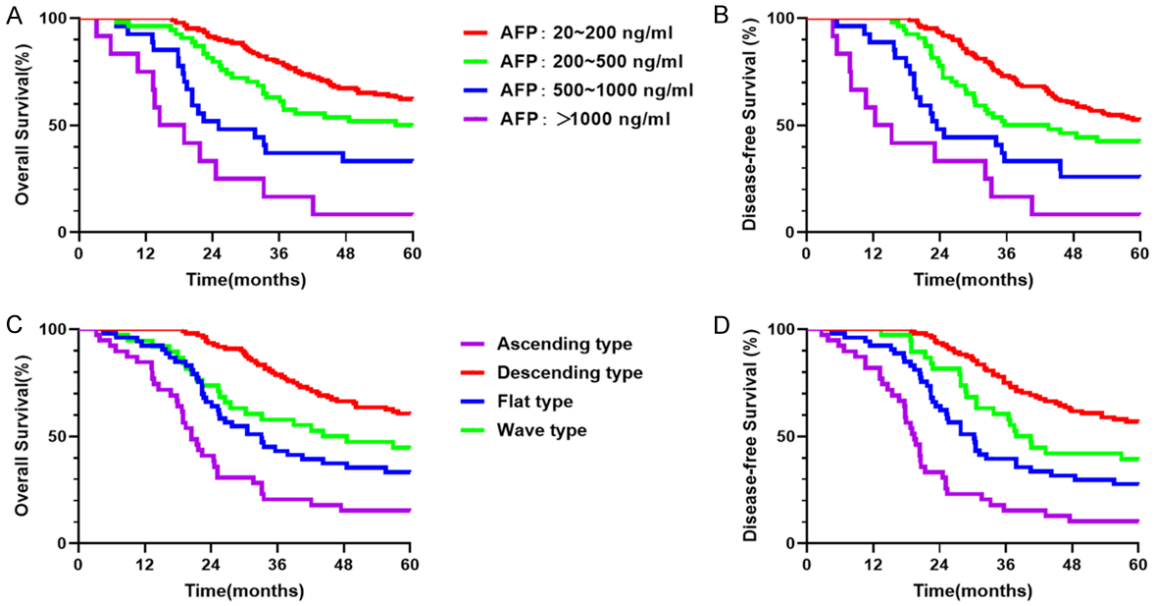

Figure 6. Analysis of OS and DFS in patients with AFPGC based on differences and changing trends in serum AFP expression values. A. OS survival curves of a stratified cohort of patients based on different values of peripheral blood serum AFP expression at the time of initial diagnosis; B. DFS survival curves of a stratified cohort of patients based on different values of peripheral blood serum AFP expression at the time of initial diagnosis; C. OS survival curves of a stratified cohort of patients based on longitudinal dynamic changes in the expression value of peripheral blood serum AFP at the time of surgery; D. DFS survival curves of a stratified DFS survival curves of cohort patients.

Table 3. Univariable and multifactorial analysis for overall survival

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Male	Reference			
Female	0.651 (0.322-1.687)	0.762		
Age(years)				
≤65	Reference			
>65	0.828 (0.467-1.469)	0.665		
ECOG				
0-1	Reference			
2	1.098 (0.573-2.148)	0.548		
Charlson Comorbidity Index				
≤3	Reference			
>3	1.476 (0.874-2.655)	0.473		
T stage				
T2/T3	Reference		Reference	
T4	3.988 (1.996-9.786)	0.001	4.341 (2.135-12.673)	0.001
N stage				
N0	Reference		Reference	
N+	4.674 (2.311-10.541)	0.001	5.553 (2.675-11.093)	0.001
Primary site				
Up 1/3	Reference			
Middle 1/3	1.542 (0.781-2.321)	0.761		
Lower 1/3	1.134 (0.895-2.004)	0.667		

Tumor size (cm)				
≤5	Reference		Reference	
>5	2.552 (1.435-5.673)	0.021	1.676 (0.964-3.534)	0.068
Histology				
High/Median	Reference		Reference	
None/Low	3.346 (1.755-7.662)	0.019	2.655 (1.312-5.711)	0.026
Grade				
I	Reference			
II	1.333 (0.752-2.163)	0.067		
III	1.542 (0.863-2.672)	0.088		
Lauren				
Intestinal type	Reference		Reference	
Diffuse/Mix type	2.356 (1.422-6.672)	0.023	1.4636 (0.982-2.435)	0.067
Vascular invasion				
No	Reference		Reference	
Yes	3.231 (1.674-7.863)	0.003	1.761 (0.994-3.762)	0.053
Nerve invasion				
No	Reference			
Yes	1.542 (0.891-3.671)	0.186		
HER2				
Negative	Reference		Reference	
Positive	2.009 (1.151-5.342)	0.021	1.432 (0.781-3.131)	0.061
PD-L1				
0	Reference			
1-10	1.569 (0.671-2.173)	0.057		
>10	2.119 (0.873-4.042)	0.061		
Serum AFP expression (ng/ml)				
20-200	Reference		Reference	
200-500	1.569 (1.121-3.531)	0.037	1.892 (1.321-3.421)	0.021
500-1000	3.132 (1.754-6.092)	0.011	3.565 (1.754-7.322)	0.008
>1000	5.672 (2.121-10.534)	0.001	7.137 (2.770-13.542)	0.001
Trends in serum AFP				
Descending type	Reference		Reference	
Ascending type	6.323 (3.431-14.542)	0.001	7.485 (3.651-16.334)	0.001
Flat type	3.571 (1.437-7.542)	0.010	2.645 (1.231-5.467)	0.032
Wave type	3.623 (1.762-8.904)	0.023	3.170 (1.430-6.212)	0.017

sive nature of this malignancy and the need for early detection and prompt intervention.

Regarding treatment modalities, a dynamic shift was observed, transitioning from predominantly surgical resection to a comprehensive regimen incorporating preoperative neoadjuvant or conversion therapy followed by surgical resection. This evolution aligns with the growing recognition of the benefits of multimodal treatment approaches in managing aggressive malignancies and reflects the commitment to improving outcomes for AFPGC patients.

Our analysis of recurrent metastatic patterns unveiled the liver as the most common site of metastasis, followed by retroperitoneal and supraclavicular lymph nodes, with brain metastases being relatively rare. This finding is consistent with previous reports and emphasizes the need for vigilant surveillance and tailored follow-up strategies, particularly for the early detection of liver metastases [22-25]. Interestingly, patients with higher preoperative serum AFP levels exhibited an increased propensity for liver metastasis and a shorter median time

Table 4. Univariable and multifactorial analysis for disease-free survival

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Male	Reference			
Female	0.642 (0.232-1.451)	0.432		
Age (years)				
≤65	Reference			
>65	0.932 (0.422-1.776)	0.884		
ECOG				
0-1	Reference			
2	0.750 (0.412-1.731)	0.131		
Charlson Comorbidity Index				
≤3	Reference			
>3	1.472 (0.878-2.071)	0.672		
T stage				
T2/T3	Reference		Reference	
T4	3.683 (1.438-6.762)	0.002	4.733 (1.998-12.780)	0.001
N stage				
N0	Reference		Reference	
N+	4.708 (2.548-13.506)	0.001	6.543 (2.788-15.098)	0.001
Primary site				
Up 1/3	Reference			
Middle 1/3	1.523 (0.678-2.452)	0.271		
Lower 1/3	0.737 (0.422-1.806)	0.071		
Tumor size (cm)				
≤5	Reference		Reference	
>5	2.652 (1.538-5.532)	0.021	2.023 (0.983-4.340)	0.054
Histology				
High/Median	Reference		Reference	
None/Low	4.565 (2.168-9.672)	0.001	3.532 (1.521-6.541)	0.010
Grade				
I	Reference			
II	1.567 (0.788-2.603)	0.065		
III	1.805 (0.890-2.891)	0.043		
Lauren				
Intestinal type	Reference		Reference	
Diffuse/Mix type	2.672 (1.322-4.430)	0.025	1.622 (0.782-2.672)	0.176
Vascular invasion				
No	Reference		Reference	
Yes	1.796 (1.272-3.672)	0.031	1.106 (0.874-1.482)	0.161
Nerve invasion				
No	Reference			
Yes	1.009 (0.541-2.313)	0.071		
HER2				
Positive	Reference		Reference	
Negative	2.649 (1.432-5.570)	0.032	1.565 (0.8921-2.894)	0.072
PD-L1				
0	Reference			
1-10	1.729 (0.872-2.733)	0.073		
>10	2.272 (0.902-3.138)	0.061		

Serum AFP expression (ng/ml)				
20-200	Reference		Reference	
200-500	2.493 (1.2451-4.621)	0.031	2.782 (1.356-5.092)	0.022
500-1000	4.762 (2.082-8.995)	0.007	4.095 (1.347-7.873)	0.010
>1000	10.892 (3.709-25.784)	0.001	11.562 (4.232-27.809)	0.001
Trends in serum AFP				
Descending type	Reference		Reference	
Ascending type	8.824 (2.562-15.342)	0.001	9.876 (3.708-20.768)	0.001
Flat type	4.342 (1.642-8.092)	0.010	4.897 (2.334-12.589)	0.012
Wave type	5.806 (2.903-13.867)	0.021	3.965 (1.697-10.987)	0.031

to liver metastasis development, suggesting a potential role for serum AFP as a predictive biomarker for metastatic risk stratification [26].

Furthermore, our study identified several independent risk factors associated with the development of recurrent metastasis after radical surgery in AFPGC patients. These factors include T4 infiltration, presence of lymph node metastasis, tumor diameter greater than 5 cm, poorly differentiated-undifferentiated pathological type, preoperative AFP levels exceeding 1000 ng/mL, and a postoperative increasing trend in AFP dynamics. These findings underscore the importance of comprehensive clinicopathological evaluation and close monitoring of serum AFP levels in the postoperative period, as they may aid in identifying high-risk patients who could potentially benefit from adjuvant therapies or intensified surveillance protocols.

Notably, our survival analysis revealed a dismal prognosis for AFPGC patients, with a 5-year overall survival rate of 36.5% and a disease-free survival rate of 34.2%. Stratified analyses based on preoperative serum AFP levels and postoperative AFP dynamics consistently demonstrated a poorer prognosis associated with higher AFP values and an increasing trend in AFP levels, respectively. These observations further reinforce the potential prognostic utility of serum AFP levels in AFPGC and underscore the need for tailored management strategies based on this biomarker.

Multivariate analyses identified several independent risk factors significantly impacting overall survival and disease-free survival in AFPGC patients. These factors included T4 infiltration, lymph node metastasis, poorly differentiated-undifferentiated pathology, preoperative AFP levels greater than 1000 ng/mL, and a postoperative increasing trend in AFP dynamics. These findings align with the risk factors identified for recurrent metastasis and highlight the interconnected nature of these adverse prognostic indicators.

In summary, this multicenter retrospective cohort study provides valuable insights into the recurrent metastatic patterns and prognostic factors in AFPGC patients undergoing radical surgery. The identification of the liver as the predominant metastatic site, coupled with the association between serum AFP levels and metastatic risk, emphasizes the importance of tailored surveillance strategies and the potential utility of AFP as a predictive and prognostic biomarker.

The elucidation of independent risk factors for recurrent metastasis and poor survival outcomes lays the foundation for risk stratification and personalized treatment approaches. As this study is retrospective, it inevitably suffers from biases such as selection bias and information bias. Additionally, we aim to expand the sample size in future studies to improve the reliability and validity of the results. Besides, further prospective studies are warranted to validate these findings and explore novel therapeutic strategies aimed at improving outcomes for AFPGC patients.

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Informed consent was performed for all the study subjects.

Disclosure of conflict of interest

None.

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