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Original Article

Prognosis of Alpha-Fetoprotein-Produced Gastric Cancer in the Japanese Population: A Systematic Review of Case Reports

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ABSTRACT

Introduction: Alpha-fetoprotein (AFP)-produced gastric cancer has a poor prognosis because of frequent hepatic metastases. Most reports of AFP-produced gastric cancer are single case reports from Japan. Therefore, we systematically reviewed Japanese reports on AFP-produced gastric cancer to evaluate the clinical significance of the AFP values.

Methods: We reviewed the clinical characteristics and prognostic significance of AFP-produced gastric cancer from reports in the Japan Medical Abstracts Society databases from 1987 to 2019. We evaluated the association between the prognosis of patients and AFP values.

Results: One hundred and eleven papers showed AFP-produced gastric cancer cases (n = 304). Among the 304 cases, 102 cases included the AFP value (>20 mg/dL), prognosis, histology, and distant metastasis. AFP values were significantly higher in patients with hepatic metastases, but there were no differences in AFP values based on gender, age, tumor depth, and metastatic factors. The median overall survival was 16 months. Univariate analysis showed that tumor depth ($p = 0.021$) and distant and hepatic metastases ($p < 0.001$) were associated with poor prognosis. Multivariate analysis showed that tumor depth was an independent risk factor for reduced overall survival. The AFP value itself was not associated with poor prognosis.

Conclusions: Although tumor depth was independently associated with poor prognosis, the AFP value itself was not independently associated with poor prognosis. Tumor depth and distant metastasis are useful in predicting the survival of patients with AFP-produced gastric cancer.

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KEYWORDS: alpha-fetoprotein, gastric cancer, prognosis

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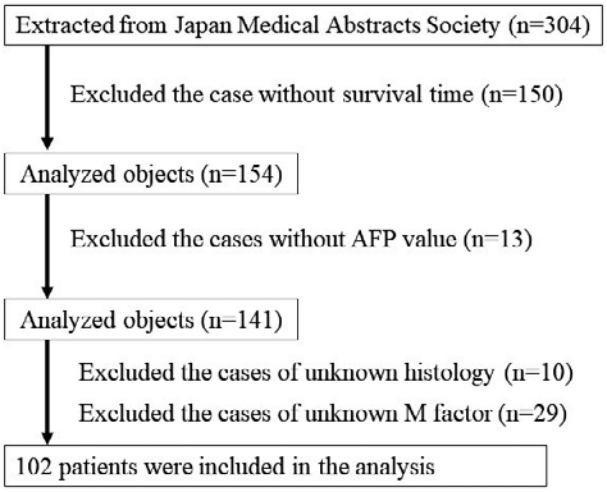

Fig. 1 Flowchart showing articles about AFP-produced gastric cancer selected in this study.
Abbreviations: AFP, alpha-fetoprotein; M, distant metastasis

Introduction

Alpha-fetoprotein (AFP)-producing gastric cancer is rare, accounting for only 1%-5% of all gastric cancers.[1–4] In addition, its rate of liver and lymph node metastases is high.[5–7] Most previous reports in the PUBMED database analyzed Chinese or Japanese populations, and no large-scale reports from other countries have been published. Moreover, the prognostic impact of AFP values themselves is controversial.[8–11]

The Japan Medical Abstracts Society database, which includes all Japanese publications, contains more than 13 million articles and is one of the biggest databases of medical research reports apart from PUBMED. As the Japan Medical Abstracts Society database includes only articles written in Japanese, systematic reviews and meta-analyses published in PUBMED usually do not include the data of the Japan Medical Abstracts Society database. Most papers in the Japan Medical Abstracts Society database related to AFP-produced gastric cancer were case reports, and as of October 2021, there is no meta-analysis regarding the pathological features and prognosis of AFP-produced gastric cancer in this database.

Therefore, we systematically reviewed and evaluated the clinical characteristics and prognosis of AFP-produced gastric cancer by meta-analysis of Japanese literature published between 1987 and 2019 obtained from the Japan Medical Abstracts Society database.

Methods

Japanese reports published between 1987 and 2019 in the Japan Medical Abstracts Society database were comprehensively searched using "AFP-produced gastric cancer" as a keyword. A total of 304 cases in 111 reports on AFP-produced gastric cancer (Fig. 1) were identified. Among the 304 cases, 150 did not have data on the survival time of patients, 13 either did not show the AFP value or it was less than 20 mg/dL, 10 did not have histological results, and 29 did not show whether distant metastasis occurred. This left 102 cases available for the final analysis, of which 38 did not have information regarding the tumor depth.

Statistical analyses

The AFP values were compared among the clinicopathological characteristics of patients using the Mann-Whitney U test for two groups. The Kaplan-Meier method was used to estimate the survival rate, and the log-rank test was used to compare the survival time among the groups. Cox proportional hazards regression was used for the hazard ratio (HR) and multivariate analysis of survival times. All statistical analyses were performed using the EZR software.[12] A p value of <0.05 was considered statistically significant.

Results

Clinical characteristics of AFP-producing gastric cancer

The clinicopathological characteristics of AFP-produced gastric cancer are shown in Table 1. One hundred and two patients were divided into two groups, namely, low AFP and high AFP, based on the median AFP value of 1167.5 ng/ml. Patients with H factor positive (hepatic metastasis) had significantly higher AFP values than other patients ($p = 0.005$). However, there were no differences in AFP values based on gender ($p = 0.934$), age ($p = 0.790$), T factor (tumor depth) ($p = 0.500$), and M factor (distant metastasis) ($p = 0.243$).

Overall survival according to AFP values, tumor depth, distant metastasis, and hepatic metastasis in AFP-produced gastric cancer

The median survival time of the 102 patients was 16 months, with a 5-year survival rate of 34.3% (Fig. 2). The overall survival according to the AFP values, tumor depth, distant metastasis, and hepatic metastasis are shown in Fig. 3. High AFP values showed slightly worse prognosis

Table 1 Clinical characteristics of AFP-produced gastric cancers

Variables		Number of Patients	median AFP (ng/ml)	P-value
All patients		102	1167.5 (23-340000)	
Gender	Male	81	1531 (23-144510)	0.934 †
	Female	21	1097 (23.4-340000)	
Age	under 65	41	1466 (23-100314)	0.790 †
	65 and over	61	1097 (24-340000)	
AFP values	Low AFP	51	168 (23-1100)	＜0.001 †
	High AFP	51	5715 (1235-340000)	
T factor ‡	T 1/2	23	801.4 (41-26500)	0.500 †
	T 3/4	56	986.5 (23-340000)	
M factor	M0	25	737 (28-36800)	0.243 †
	M1	77	1466 (23-340000)	
H factor	H0	38	471 (28-36800)	0.005 †
	H1	64	2457.5 (23-340000)	

†: Mann-Whitney U test; ‡: include missing values
Abbreviations: M, metastasis; H, hepatic metastasis

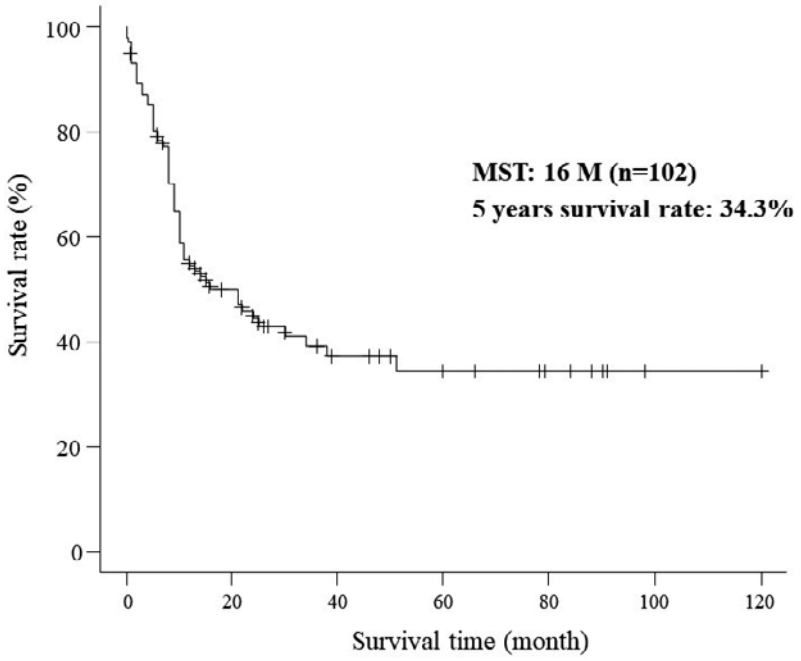

Fig. 2 Overall survival curve in all 102 cases.
Abbreviation: MST, median survival time

than low AFP values; however, the difference was not significant (p = 0.235, Fig. 3a). Patients with tumor depth stage T 3/4 had a significantly worse prognosis than those with tumor depth stage T1/2 (p = 0.021/HR: 2.661, Fig. 3b). Patients with distant and hepatic metastases (M1/H1) showed a significantly worse prognosis than the other patients (p < 0.001, HR: 3.459, 2.620, Fig. 3c, d).

Multivariate analysis of risk factors for overall survival in AFP-produced gastric cancer

Multivariate analysis of overall survival using AFP values, T factor, M factor, and H factor as covariates are shown in Fig. 4. Tumor depth was an independent risk factor for poor overall survival (p = 0.041, HR: 2.55). Although the M and H factors seemed to be independent risk factors, the difference was not statistically significant. On the

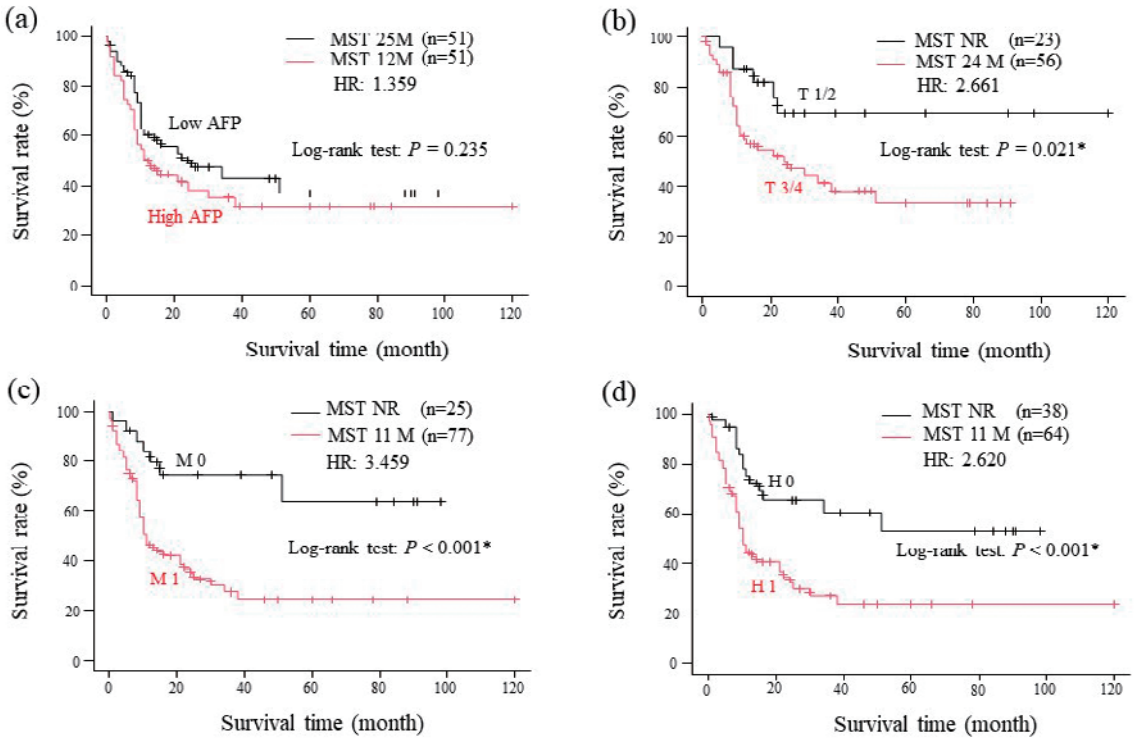

Fig. 3 Overall survival according to the tumor depth, distant metastasis, AFP values, and histology in AFP-produced gastric cancer. (a) AFP values, (b) tumor depth, (c) distant metastasis, and (d) hepatic metastasis. Abbreviations: NR, not reached; HR, hazard ratio; MST, median survival time

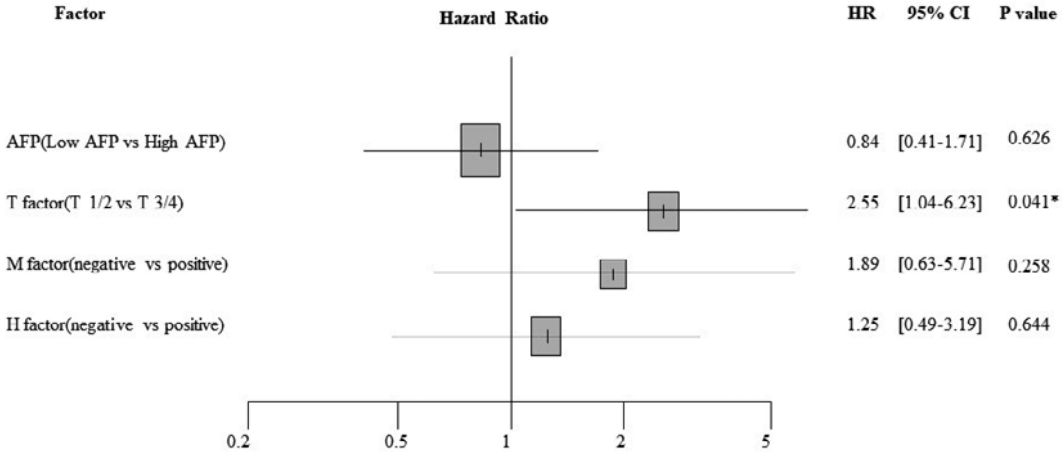

Fig. 4 Multivariate analysis of risk factors for overall survivals in AFP-produced gastric cancer. Abbreviations: AFP, alpha-fetoprotein; M, distant metastasis; HR, hazard ratio; OS, overall survival

other hand, a high AFP value was not an independent risk factor for poor overall survival.

Discussion

Based on the Japan Medical Abstracts Society database, there were 314 cases of AFP-produced gastric cancer. Among the 314 cases, 102 were selected to evaluate the clinicopathological significance of the AFP values. The AFP values were higher in patients with hepatic metastases (H1) than those in other groups. Tumor depth and distant and hepatic metastases resulted in significantly poorer survival, but only tumor depth was an independent risk factor for survival. The AFP values themselves were not associated with poor prognosis. Compared with the 5-

year survival rate of typical gastric cancer (61.6%-70.9%),[13, 14] the 5-year survival rate of AFP-produced gastric cancer was poorer (34.3%) in this study. Similarly, a study on Chinese gastric cancer reported that even at the same T stage, the hepatic metastasis status of AFP-positive gastric cancer was higher than that of the negative group, and the AFP-positive group had a worse prognosis than the negative group.[15] AFP is generally not measured in gastric cancer because it is covered by insurance for hepatic cell carcinoma or ovarian carcinoma. Although carcinoembryonic antigen and carbohydrate antigen 19-9 values are associated with gastric cancer prognosis, AFP is not.[16, 17] Further, in early-stage gastric cancer, the positive rate of AFP was as low as 1.5%, and AFP was not a prognostic factor.[18] Therefore, it is difficult to detect AFP-produced gastric cancer at an early stage, and the cancer is considered to be unresectable and advanced at the time of diagnosis. It is known that AFP-producing gastric carcinomas frequently develop hepatic metastasis.[5–7] Shimizu et al. reported that CCAAT/enhancer-binding protein-β, a transcription factor involved in AFP transcription, enhances liver metastasis in a rat study.[19] In this study, the high AFP group was predominantly high in hepatic metastasis cases, suggesting that AFP is associated with hepatic metastasis.

Tumor depth, distant metastasis, and hepatic metastasis significantly worsened overall survival. However, multivariate analysis showed that tumor depth was the only independent prognostic factor. However, there was no significant difference in survival between the low AFP and high AFP groups. In the high AFP group, six patients survived for 5 years. These six patients had no specific tendency in common in the number of liver metastases or postoperative chemotherapy. Despite the AFP value not being an independent poor prognostic factor, it is worth screening in advanced gastric cancer because the prognosis of AFP-produced gastric cancer is poor. Adachi et al. reported that the AFP value was not a prognostic factor in unresected cases, although it was affected by AFP in resected cases.[20] Of the 102 cases in this report, 25 were surgical cases and 77 were unresected cases, suggesting that the tendency of unresected cases was strongly reflected.

Despite the significant difference in survival of factors M and H in this study, multivariate analysis showed no significant difference. As tumor depth is an independent factor, distant metastasis (peritoneal or other organs), excluding hepatic metastasis, is expected to be a prognostic factor.

There were some limitations in this study. The epidemiological data analyzed in this study were limited to the Japanese population. Even though we selected the papers, some reports lacked a description of the TNM stages, surgical procedures, and chemotherapy regimens. Thus, the results of this study may include bias. The other limitation was that our meta-analysis included the various chemotherapy regimens. Although the combination of paclitaxel and cisplatin (CDDP) seemed to prolong survival, 5-fluorouracil + cisplatin combination regimens did not show any tendency (data not shown). A prospective study should be conducted to explore adequate chemotherapy regimens for AFP-produced gastric cancer.

In conclusion, a high AFP value is not an independent risk factor for poor prognosis. However, this study suggests that AFP is a factor in hepatic metastasis and tumor depth is a prognostic factor.

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Authors' contribution: H.S. designed the study. N.N. analyzed the data. H.S., Y.K., and M.O. supervised the study. N.N. and H.S. wrote the manuscript.

Ethics statement: This article does not contain any study with humans or animals as participants that was performed by any of the authors.

Conflicts of interest: M.O. received lecture fees less than 500,000 yen.

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