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Alpha-fetoprotein is a significant prognostic factor for gastric cancer: Results from a propensity score matching analysis after curative resection

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Abstract

Background: Prognosis of alpha-fetoprotein positive gastric cancer (AFPP-GC) remains elusive so far due to disparities in cohort size and baseline characteristics in previous studies. A propensity score matching (PSM) analysis as well as multivariable model was performed for unbiased evaluation of the outcome in AFPGC.

Methods: Among 3034 gastric cancer patients who underwent curative gastric cancer surgery (R0, M0) at the National Cancer Center, Korea between 2002 and 2007, we identified 97 patients being positive for AFP either by elevation of serum-AFP levels >10 μg/L or by immunohistochemical staining. Due to marked disparities in baseline characteristics and cohort size, propensity-score-matching was performed which matched 87 AFPP-GC patients to the same number of AFP-negative gastric cancer (AFPN-GC) patients. Baseline characteristics were compared using χ^2-test. Survival curves were compared using the Kaplan-Meier-method and multivariable regression analysis was performed to evaluate the effect of AFP-positivity while adjusting the effects of confounding variables.

Results: AFPP-GC and AFPN-GC patients revealed marked disparities in patient cohorts. After PSM, groups were balanced for age, sex, tumor size, BMI, tumor location, grade of differentiation, presence of lymphatic vessel infiltration (LVI), Lauren histologic type and stage distribution. In multivariable regression analysis of the PSM-groups, only AFP-positivity and pathologic stage were predictive for overall survival (HR 2.98, CI 95% {1.7–5.1}, $p < 0.0001$). Five-year-survival rates were significantly worse for AFPP-GC patients (57.9% vs. 76.1%, $p = 0.014$). Recurrence was significantly more frequent in AFPP-GC patients ($p = 0.003$).

Conclusion: AFP can be considered as an independent negative predictor of overall and recurrence-free survival in patients with gastric cancer.

Keywords: Gastric cancer; AFP; Surgery

Introduction

Several case series and retrospective analyses on alpha-fetoprotein (AFP)-positive gastric cancer were published over the recent years.[1–4] AFP-positive gastric cancer (AFPP-GC) appears to be a rare entity compared to common gastric cancer. The incidence is reported to be 1–15% among gastric cancer patients. AFPP-GCs combined with liver metastasis were first reported in 1970.[5] Further reports concluded that AFPP-GC revealed poor prognosis, high recurrence rates and high potential to metastasize to the liver and lymph nodes.[1–5] This appears to be related to a histologically more aggressive tumor phenotype. AFPP-GCs tend to show higher rates of

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lymphatic and blood vessel infiltration,[1] which may lead to higher recurrence rates and shorter postoperative survival.

Most of the previous reports could not provide data for direct comparisons between AFPP-GC and AFP-negative gastric cancer (AFPN-GC) due to small and heterogeneous cohort sizes and marked differences in baseline characteristics.[2] Only one Chinese analysis reported a matched cohort result.[3] However, the matching algorithm was not reported which leads to the notion that selection bias may not be completely excluded. Therefore the purpose of this analysis was to examine prognosis of AFPP-GC from a large patient population after propensity score matching (PSM) which attempts to eliminate the disparities in cohort size and baseline characteristics.

Patients and methods

The screening of the prospectively documented database for gastric cancer at the National Cancer Center Korea (NCCK) revealed 3034 patients who were subjected to primary curative oncologic resection (R0) for gastric cancer between January 2002 and August 2007 without undergoing preoperative chemo- or radiochemotherapy. All patients in whom metastatic disease was ruled out, received oncologic resection according to Japanese guidelines including D2 lymph node dissection.[6] All specimens were examined postoperatively by specialized pathologists and staged according to the 6th UICC edition TNM staging system.[7] Serum AFP was tested in all patients preoperatively and were considered as AFP-positive when elevated preoperative serum AFP levels (>10 μg/L) were detected. IHC was only done in those patients with preoperatively elevated AFP-levels and hepatoid features in the preoperative biopsy. Finally, 97 patients were identified as AFP-positive. Patients received adjuvant chemotherapy in case of metastatic lymph nodes and/or from pathologic stages II-IV. Patients were followed postoperatively via the outpatient clinic in regular intervals (every 6 months for the first 24 months and then every 12 months until at least 60 months postoperatively for early gastric cancer patients and every 3 months until 3 years postoperatively and then every 6 months until the sixth postoperative year for advanced gastric cancer patients). The follow-up period was calculated from the day of surgery to the last follow-up date. During this five year period 187 patients were diagnosed with gastric cancer but didn't receive curative resections. Among them, 174 patients were tested for AFP and ten of them were AFP-positive (AFP>10 μg/L).

Overall survival (OS) was defined as the time from surgery to death and otherwise the patients were censored. Recurrence-free survival (RFS) was defined as the time from surgery to recurrence evaluation.

Statistical analysis

Intergroup comparisons were analyzed by χ^2-testing for categorical, t-test or Wilcoxon-test for continuous variables as appropriate. Categorical variables were presented as proportions and continuous variables as mean ± standard deviation. Survival curves were estimated by the Kaplan–Meier method and differences were evaluated by the log-rank test. Univariable and multivariable regression analysis for overall survival were performed by using the Cox proportional hazards model.

Propensity score matching (PSM) for reduction of intergroup disparities was performed by logistic regression analysis on all variables with possible influence on the outcome variable (i.e. OS and RFS).Variable with the greatest estimated influence were selected using backward variable selection with an elimination criterion of p-value >0.2, and the propensity score computed.[8,9] Shortly, multivariable logistic regression was performed on AFP-positivity (positive vs. negative) using all variables with possible influence on the patients' survival. Variables finally included in the multivariable logistic regression after backward variable selection were sex, histology, Lauren's classification, and UICC stages. Due to some missing data in these variables, only 2838 patients were used to generate the propensity score. A propensity score was then estimated for all subjects using this logistic regression, and AFP-positive patients (n = 87) were matched to AFP-negative patients (n = 87) using the nearest neighbor matching within a caliper of 0.20 times the standard deviation of the propensity score. Matching was performed without replacement. P-values of <0.05 were considered as statistically significant. All data were analyzed using SAS version 9 (SAS Institute Inc., Cary, NC, USA).

This retrospective analysis was approved by the local institutional review board (IRB-Nr: NCC2014-0036).

Results

Baseline characteristics

Direct comparison between AFPP-GC (n = 97) and AFPN-GC (n = 2937) patients revealed significant differences in preoperative AFP-levels ($p < 0.0001$), gender distribution ($p = 0.0013$), tumor size ($p = 0.04$), Lauren classification ($p = 0.0006$), presence of lymphatic vessel infiltration (LVI) ($p = 0.0003$), pT/pN/UICC-stage distribution ($p < 0.0001$ respectively) and recurrence rates ($p < 0.0001$). For AFP-positive patients no statistical difference in OS between patients with positive IHC or just AFP elevation over 10 μg/L ($p = 0.79$) was found. There were no differences for age, location, histology (differentiation according to Japanese guidelines) and the number of retrieved lymph nodes. There was no statistically

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