Patients with normal-range CA19-9 levels represent a distinct subgroup of pancreatic cancer patients

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Abstract. Pancreatic cancer remains a lethal disease that responds poorly to multiple types of treatment. Therefore, the identification of distinct subgroups that exhibit unique therapeutic responses is an urgent requirement. In the present multicenter study (1,912 cases), the differences between the therapeutic responses and clinical characteristics of two subgroups of pancreatic cancer, carbohydrate antigen 19-9 (CA19-9)-normal (baseline serum level, ≤37 U/ml) and CA19-9-elevated (baseline serum level, >37 U/ml), were analyzed. CA19-9-normal expression was identified to be an independent prognostic factor for patients with stage I-II [hazard ratio (HR)=0.77; P=0.037] and stage III-IV (HR=0.68; P<0.001) pancreatic cancer. The 5-year survival rate of the stage III-IV CA19-9-normal subgroup was increased compared with the stage I-II CA19-9-elevated subgroup (15.4 vs. 13.8%). In the stage I-II CA19-9-normal and CA19-9-elevated subgroups, gemcitabine-based chemotherapy was a significant positive prognostic factor for survival (CA19-9-normal, HR=0.54, P=0.013; CA19-9-elevated, HR=0.55, P<0.001). However, among stage III-IV patients, the CA19-9-normal subgroup exhibited a poor response to gemcitabine-based chemotherapy (HR=0.77; P=0.165), while the CA19-9-elevated subgroup exhibited a favorable response, resulting in a lower rate of mortality (HR=0.70; P<0.001) compared with no chemotherapy. It was concluded that CA19-9-normal pancreatic cancer is a less aggressive subgroup; however, advanced CA19-9-normal pancreatic cancer exhibits a poorer response to gemcitabine-based chemotherapy.

Introduction

Although marked progress in recent decades has been made in the treatment of cancer, pancreatic cancer remains a lethal disease, with a 5-year survival rate of <6% (1,2). Personalized medicine and surgery is tailored to the individual patient, and has the potential to improve the management of pancreatic cancer (3,4). As pancreatic cancer is a malignant tumor that exhibits heterogeneous biological characteristics, it may be susceptible to treatment with personalized medicine (5). Global genomic analyses have revealed various core signaling pathways in pancreatic cancer that may represent ideal targets for personalized treatment, including K-Ras, transforming growth factor β, c-Jun N-terminal kinases, integrin, Wnt/Notch, Hedgehog, control of G1/S phase, apoptosis, DNA damage control, small GTPases, invasion and homophilic cell adhesion (4). It is necessary to identify distinct pancreatic cancer subgroups with unique characteristics in order to allow the selection of personalized treatments.

Carbohydrate antigen 19-9 (CA19-9) is a tumor-associated biomarker and its expression requires the presence of sialylated Lewis antigen (6-10). It has been extensively used as a pancreatic cancer biomarker at various phases of pancreatic cancer management (6,8,9,11-13). The recommended upper limit for normal serum CA19-9 expression is 37 U/ml, as determined by the standard deviation of CA19-9 expression in the normal population (11,12,14). Several studies have demonstrated that early- and advanced-stage pancreatic cancer patients with normal serum CA19-9 expression (≤37 U/ml) had a significant survival advantage compared with patients with elevated serum CA19-9 expression (>37 U/ml) (11,14,15). However, the clinical features of pancreatic cancer occurring with normal CA19-9 levels remain unknown.

In the present multicenter study, an extensive analysis of the clinical, pathological and biological features of patients with various stages of pancreatic cancer, who were stratified by normal and elevated baseline serum CA19-9 levels, was performed.

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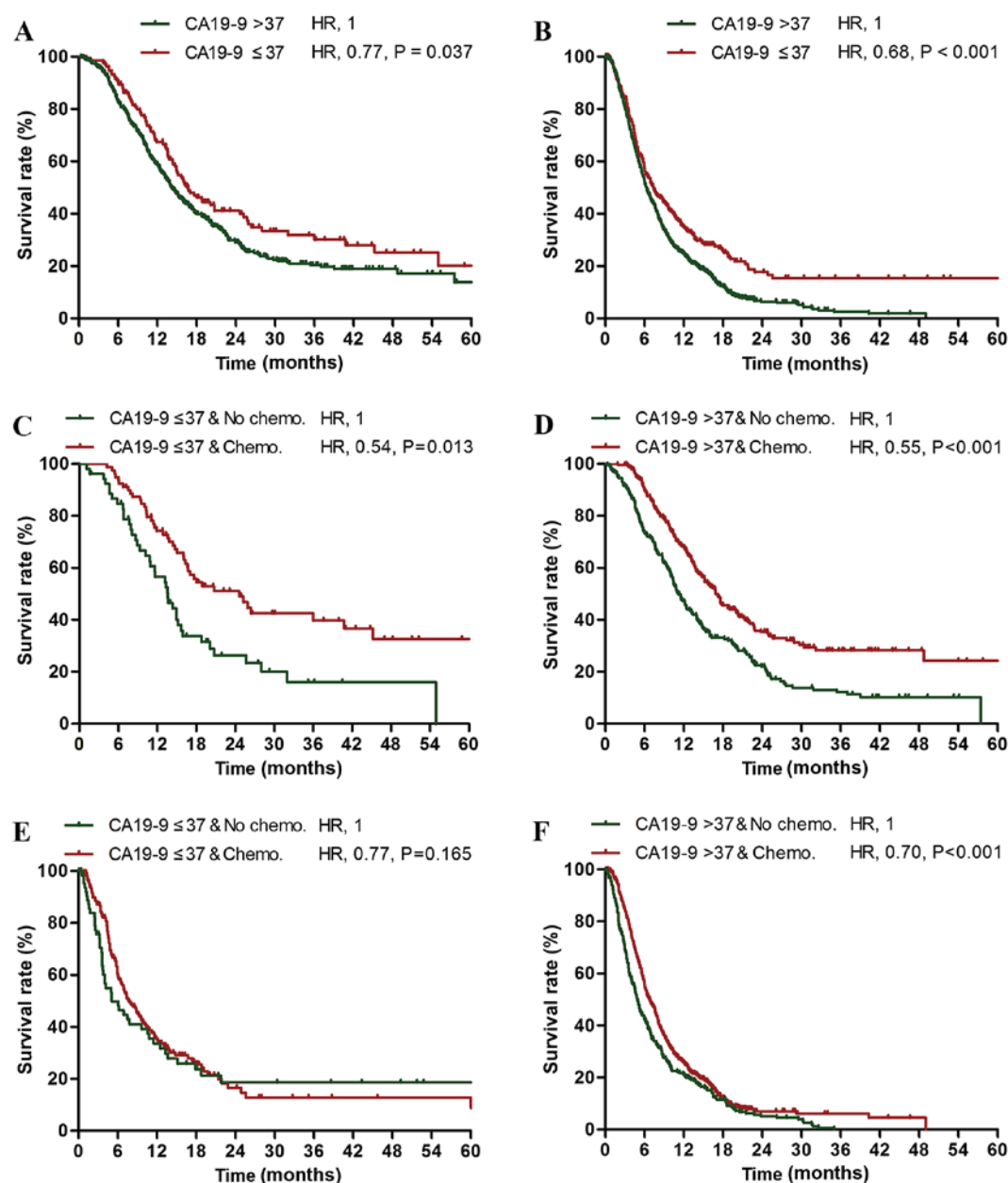E-mail: yuxianjun@fudanpci.org

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Figure 1. Kaplan-Meier estimators for patients with pancreatic cancer subdivided by baseline serum CA19-9 levels (CA19-9-normal, ≤37 U/ml; CA19-9-elevated, >37 U/ml), tumor stage and chemotherapy. Survival rates for patients with (A) stage I-II and (B) stage III-IV pancreatic cancer were significantly improved in the CA19-9-normal subgroups compared with the CA19-9-elevated subgroups. Among stage I-II patients, survival rates were significantly improved by treatment with gemcitabine in (C) CA19-9-normal and (D) CA19-9-elevated subgroups. Among stage III-IV patients, survival rates were not significantly improved by gemcitabine treatment in (E) the CA19-9-normal subgroup, but were in (F) the CA19-9-elevated subgroup. CA19-9, carbohydrate antigen 19-9; HR, hazard ratio; chemo., chemotherapy.

Materials and methods

Patients. All patients (1,912 cases) were selected from a multicenter database constructed by the Shanghai Cancer Center of Fudan University and the Shanghai Cancer Institute (Shanghai, China); patients treated between December 2006 and March 2016 were included. The protocol used in the present study conformed to the ethical guidelines of The Declaration of Helsinki and was approved by the Ethics Boards of the Shanghai Cancer Institute and Shanghai Cancer Center. Written informed consent was obtained from all patients participating in the study. Patients were stratified according to their baseline serum CA19-9 level and type of

treatment received (surgery, chemotherapy, radiotherapy or best supportive care). Survival time was calculated as the time between the date of diagnosis and the date of the latest follow-up or mortality (14). Follow-up information was updated in April 2016.

The included patients were those who had histological or cytological evidence of pancreatic adenocarcinoma. Exclusion criteria included endocrine or acinar pancreatic carcinoma, or intraductal papillary mucinous neoplasm associated pancreatic adenocarcinoma. Patients lacking detailed information for serum CA19-9 levels were also excluded. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer (Chicago, IL, USA) classification (16). All patients

Table I. Multivariate analysis (Cox proportional hazards model) of the association between mortality and the clinical characteristics of patients with stage I-II and stage III-IV pancreatic cancer.

Clinical characteristics	Stage I-II[a]		Stage III-IV[b]	
	HR	P-value	HR	P-value
Age (>60 vs. ≤60 years)	1.14	0.217	1.15	0.037
Gender (female vs. male)	0.94	0.548	0.93	0.270
Tumor location (pancreatic head vs. all others)	1.13	0.255	1.09	0.194
ECOG performance status (2-3 vs. 0-1)	/	/	1.65	<0.001
Tumor size (>4 vs. ≤4 cm)	1.79	<0.001	1.15	0.042
Nerve invasion status (positive vs. negative)	1.89	0.001	/	/
Vessel invasion status (positive vs. negative)	1.59	0.002	/	/
Lymph node metastasis status (positive vs. negative)	1.67	<0.001	/	/
Tumor grade (high vs. low)	1.32	0.012	/	/
Distant metastasis status (positive vs. negative)	/	/	1.93	<0.001
Chemotherapy (administered vs. not administered)	0.58	0.001	0.71	<0.001
CA19-9 level (≤37 vs. >37 U/ml)	0.77	0.037	0.68	<0.001

[a]All patients with stage I-II disease had ECOG performance status 0-1 and no distant metastasis. [b]Patients with stage III-IV had no curative resection and no information regarding nerve and vessel invasion, lymph node metastasis or tumor grade. HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; CA19-9, carbohydrate antigen 19-9; /, not evaluated.

with stage I or II pancreatic cancer received curative-intent resection. Although serum CA19-9 levels have been documented to be affected by altered biliary excretion, such as with biliary tract obstruction (9), this effect was ignored as the subjects in this study were subdivided into subgroups with CA19-9 levels ≤37 U/ml (CA19-9-normal) and ≥37 U/ml (CA19-9-elevated).

Statistical analysis. Continuous variables are presented as the mean ± standard deviation. Time-to-event variables and the 2- and 5-year survival rates were examined using the Kaplan-Meier estimator. The treatment arms were compared using log-rank tests, and stratified by serum CA19-9 levels and type of treatment received. Multivariate analysis of the association between mortality and the clinical characteristics of patients was performed by Cox proportional hazards model. Continuous variables were compared using the Student's t-test or the Wilcoxon rank-sum test, where appropriate. Dichotomous variables were compared using the χ^2 test. STATA statistical software package (version 12.0; StataCorp LP, College Station, TX, USA) was used for all analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. The present study analyzed a total of 1,912 cases (588 of stage I-II and 1,324 of stage III-IV), of which the median survival time was 8.7 months and the 5-year survival rate was 8.0%. A total of 80.4% of patients exhibited baseline serum CA19-9 levels of >37 U/ml. No statistically significant differences in patient age (P=0.495), gender (P=0.670), tumor location (P=0.215), tumor size (P=0.352), tumor grade (P=0.947), lymph node metastasis

(P=0.166), nerve invasion status (P=0.656) or vessel invasion status (P=0.863) were observed between the CA19-9-normal and CA19-9-elevated subgroups in patients of stage I-II. In addition, no statistically significant differences in patient age (P=0.077), gender (P=0.489), Eastern Cooperative Oncology Group (ECOG) performance status (P=0.762), tumor location (P=0.487), tumor size (P=0.119) or distant metastasis status (P=0.939) were observed between the CA19-9-normal and CA19-9-elevated subgroups in patients of stage III-IV.

Improved prognosis in the CA19-9-normal subgroup. Among the patients with stage I-II cancer, the CA19-9-normal subgroup exhibited an increased survival rate compared with the CA19-9-elevated subgroup (median survival times, 16.6 vs. 14.2 months; 2-year survival rates, 39.9 vs. 29.1%; Fig. 1A). In addition, among the stage III-IV patients, the CA19-9-normal subgroup exhibited an increased survival rate compared with the CA19-9-elevated subgroup (median survival times, 7.4 vs. 6.3 months; 2-year survival rates, 17.6 vs. 6.3%; Fig. 1B). The 5-year survival rate of the stage III-IV CA19-9-normal subgroup was increased compared with the stage I-II CA19-9-elevated subgroup (15.4 vs. 13.8%; Fig. 1A and B). Normal serum CA19-9 level was identified to be an independent prognostic factor for mortality in patients with stage I-II and stage III-IV pancreatic cancer [stage I-II, hazard ratio (HR)=0.77, P=0.037; stage III-IV, HR=0.68, P<0.001; Table I].

Efficacy of gemcitabine-based chemotherapy. Patients with stage I-II pancreatic cancer who underwent neoadjuvant therapy, adjuvant radiotherapy or non-gemcitabine-based adjuvant chemotherapy were excluded from the evaluation of the response to gemcitabine-based chemotherapy.

Table II. Association between mortality and the clinical characteristics of patients with stage I-II pancreatic cancer stratified by baseline CA19-9 levels according to Cox proportional hazards model.

Clinical characteristics	CA19-9 ≤37 U/ml		CA19-9 >37 U/ml	
	HR	P-value	HR	P-value
Age (>60 vs. ≤60 years)	1.37	0.198	1.08	0.528
Gender (female vs. male)	0.66	0.103	1.00	0.983
Tumor location (pancreatic head vs. all others)	1.25	0.396	1.10	0.439
Tumor size (>4 vs. ≤4 cm)	2.13	0.046	1.75	0.001
Nerve invasion status (positive vs. negative)	2.50	0.052	1.83	0.004
Vessel invasion status (positive vs. negative)	2.55	0.019	1.56	0.007
Lymph metastasis status (positive vs. negative)	0.66	0.234	1.97	<0.001
Tumor grade (high vs. low)	1.39	0.202	1.33	0.024
Chemotherapy (administered vs. not administered)	0.54	0.013	0.55	<0.001

HR, hazard ratio; CA19-9, carbohydrate antigen 19-9.

Table III. Association between the mortality rate and clinical characteristics of patients with stage III-IV pancreatic cancer according to Cox proportional hazards model.

Clinical characteristics	CA19-9 ≤37 U/ml		CA19-9 >37 U/ml	
	HR	P-value	HR	P-value
Age (>60 vs. ≤60 years)	1.44	0.028	1.10	0.173
Gender (female vs. male)	1.01	0.954	0.92	0.245
Tumor location (pancreatic head vs. all others)	0.93	0.687	1.13	0.093
ECOG performance status (0-1 vs. 2-3)	0.54	0.005	0.68	<0.001
Tumor size (>4 vs. ≤4 cm)	1.17	0.377	1.18	0.035
Distant metastasis status (positive vs. negative)	1.88	0.001	1.96	<0.001
Chemotherapy (administered vs. not administered)	0.77	0.165	0.70	<0.001

HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; CA19-9, carbohydrate antigen 19-9.

In addition, patients with stage III-IV pancreatic cancer who underwent radiotherapy or non-gemcitabine based chemotherapy were excluded from the evaluation of response to gemcitabine-based chemotherapy. No statistically significant differences were observed in the proportion of gemcitabine-based chemotherapy administered in the stage I-II CA19-9-normal subgroup compared with the stage I-II CA19-9-elevated subgroup (59.8 vs. 55.7%; P=0.397), or in the stage III-IV CA19-9-normal subgroup compared with the stage III-IV CA19-9-elevated subgroup (71.9 vs. 72.0%; P=0.976). The stage I-II CA19-9-normal (HR=0.54; P=0.013) and CA19-9-elevated (HR=0.55; P<0.001) subgroups exhibited significantly increased survival rates following treatment with gemcitabine compared with the untreated subgroups (Table II; Fig. 1C and D). However, the stage III-IV CA19-9-normal subgroup exhibited no significant change in survival rate following treatment with gemcitabine compared with the untreated subgroup (HR=0.77; P=0.165; Table III; Fig. 1E), while the stage III-IV CA19-9-elevated subgroup exhibited a significant increase in the 2-year and 5-year survival rates following treatment with gemcitabine compared with the untreated subgroup (HR=0.70; P<0.001; Table III; Fig. 1F) sp16.

Discussion

CA19-9 is the most important tumor marker in pancreatic cancer and is aberrantly secreted by the majority of pancreatic tumors (6,9,11-15,17,18). However, a distinct subset of patients with pancreatic cancer present with normal serum CA19-9 levels and are occasionally Lewis antigen-positive. These patients exhibit decreased or no CA19-9 secretion, independent of Lewis antigen genotype (18). In the present study, patients with CA19-9-normal pancreatic cancer were demonstrated to be a distinct subgroup that has a more favorable prognosis and unique therapeutic response.

The improved prognosis and distinct therapeutic response of the CA19-9-normal subgroup cannot be attributed to tumor burden or stage, but to its biological behavior. CA19-9, also known as sialylated Lewis a antigen, has been reported to

promote metastasis by binding E-selectin, which is expressed on the surface of endothelial cells (7,19). Several studies have demonstrated that CA19-9 promotes pancreatic cancer cell metastasis (20-22), suggesting that CA19-9 is a therapeutic target in the treatment of pancreatic cancer. However, further studies are required to confirm this hypothesis.

Chemotherapy is frequently utilized in the treatment of pancreatic cancer. In the present study, it was observed that patients with stage I-II pancreatic cancer exhibited a significantly increased survival rate following gemcitabine-based adjuvant chemotherapy, compared with the untreated patients. In addition, gemcitabine-based chemotherapy was effective against stage III-IV pancreatic tumors with elevated CA19-9 expression. However, patients with stage III-IV CA19-9-normal pancreatic cancer exhibited a poor response to gemcitabine-based chemotherapy. Novel chemotherapeutic agents and regimens are required for the treatment of advanced stage pancreatic cancer with normal CA19-9 expression.

The present study did not determine the clinical and pathological characteristics of Lewis antigen-negative patients with pancreatic cancer. However, several studies have observed similar survival rates in patients with resectable pancreatic adenocarcinoma with undetectable and normal CA19-9 levels (14,15,23). Furthermore, abnormal Lewis antigens (including types a and b) and the Lewis enzyme have been detected in normal and neoplastic tissue samples from patients typed as Lewis antigen a-b- on red blood cells (18,24-27). For example, Orntoft *et al* (27) detected Lewis antigens in 3/6 cancer-bearing patients using immunohistology and immunochemistry; however all 6 patients were typed as Lewis antigen a-b- according to hemagglutination assays. These observations further support that normal serum CA19-9 expression should be viewed as a distinct subgroup of pancreatic cancer, independently of Lewis antigen status.

In conclusion, CA19-9-normal pancreatic cancer is a less aggressive subgroup of pancreatic cancer that has distinct clinical, pathological and biological characteristics. The characterization of this subgroup may have a great impact on the overall management of pancreatic cancer. Clinical trials should be separately conducted on patients with pancreatic cancer who are subdivided by baseline serum CA19-9 levels. Despite its large sample size, the present study is limited by its retrospective nature; therefore prospective randomized clinical studies are required to confirm the results.

Acknowledgements

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