Biological risk based on preoperative serum CA19-9 and histology grade predicts prognosis in patients with pancreatic cancer

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Abstract

Background: Preoperative serum CA19-9 and histology grade could reflect the biological characteristics of pancreatic ductal adenocarcinoma (PDAC). This study aims to explore the combined effect of preoperative CA19-9 and histology grade on the prognosis of patients with PDAC. **Methods:** A total of 612 patients with PDAC undergoing curative pancreatectomy were retrospectively enrolled. A biological risk model was established based on preoperative CA19-9 and histology grade. Prognostic significance of the biological risk was evaluated. **Results:** 360 (58.8%) patients had preoperative CA19-9>112 U/ml and 348 (56.9%) patients had high histology grade. Biological risk based on preoperative CA19-9 and histology grade was independently associated with survival of PDAC patients. The biological risk was incorporated into the eighth edition of the TNM staging system and a modified TNM (mTNM) staging system was developed. The ROC curves showed that the area under curve(AUC) of the mTNM staging system was significantly greater than that of the TNM staging system. **Conclusion**: Biological risk based on preoperative CA19-9 and histology grade was an independent prognostic factors for patients with PDAC. Incorporating the biological risk into the TNM staging system could improve the the accuracy of the TNM staging system in predicting prognosis of PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal malignancies. According to the World Health Organization, the estimated number of new cases of pancreatic cancer ranked 12th among all malignant tumors in 2020[1]. The 5-year survival rate was approximately 11.5%[2]. Multiple disciplinary therapy based on the tumor stage and biological characteristics of primary lesion is highlighted in improving the survival of patients with PDAC. Therefore, it is vital to classify PDAC more accurately.

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system is the most commonly used classification for the prognostic evaluation and treatment decision of PDAC[3]. The TNM classification has undergone continuous improvement to reflect the current understanding of the extent of disease[4]. Several studies have clarified the accuracy of the TNM staging of Pancreatic Cancer (8th ed., 2017) [5,6,7], in contrast, several other studies demonstrated no survival differences between stages of TNM classification and proposed modified TNM or newly staging system[8,9].

Tumor biology shows significant impact on the prognosis of patients with malignancy and has been incorporated into the staging system to improve the accuracy of prognostic prediction[10,11]. Since both tumor burden and malignant degree could reflect the characteristics of tumor biology[12,13], we supposed that combination of the factors which represent tumor burden and malignant degree would provide a full understanding of tumor biology on prognosis of cancer, and incorporating factors associated with tumor biology into staging system could improve the accuracy of the TNM staging system in predicting prognosis. Carbohydrate

antigen 19-9 (CA19-9) is associated with the tumor burden [14]and histology grade is associated with the degree of malignancy[15,16]. Therefore, the combination of preoperative serum CA19-9 and histology grade could reflect the tumor biology of PDAC. In the present study, we retrospectively analysed the data of 612 patients with PDAC who underwent curative resections. The aim of this study was to explore the combined effect of preoperative serum CA19-9 and histology grade on the prognosis of patients with PDAC.

Materials and methods

This study was approved by the Ethical Review Committees of Tianjin Medical University Cancer Institute and Hospital, and conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Informed consent was waived due to retrospective nature of the study.

Patients

A total of 692 patients with PDAC who underwent curative resection in the Department of Pancreatic Cancer, Tianjin Medical University Cancer Institute and Hospital between January 2011 and December 2018 were eligible for this study. Eligibility criteria included: (I) patients with PDAC; (II) patients with R0 resection; (III) patients who were completely followed up. Exclusion criteria included: (I) patients with history of pancreatectomy or other malignancy; (II) patients with arterial tumor contact (celiac axis, superior mesenteric artery, or common hepatic artery); (III) patients with distant metastasis; (V) patients who accepted neoadjuvant chemotherapy; (VI) patients who died during the initial hospital stay or 1 month after surgery. After excluding 10 patients with pancreatic mucinous carcinoma, 9 patients with pancreatic adenosquamous carcinoma, 1 patient with lung cancer, 1 patient with gastric cancer, 3 patients with breast cancer, 10 patients with R1 resection, 1 patient with R2 resection, 14 patients confirmed with distant metastasis during laparotomy, 22 patients lost, 4 patients accepted neoadjuvant chemotherapy, 2 patients died during the initial hospital stay and 3 patients died within 1 month after surgery, ultimately, 612 patients were included in this study.

Evaluation of clinicopathological variables and survival

Clinicopathological variables studied included 14 factors: sex, age at surgery, preoperative serum CA19-9, preoperative serum carcinoembryonic antigen(CEA), preoperative serum CA242, tumor location, type of surgery, TNM stage,T stage, N stage, histology grade, lymphovascular invasion, perineural invasion and postoperative adjuvant chemotherapy.

The levels of preoperative serum tumor markers (CA19-9, CEA and CA242) were detected within 1 week before surgery. The normal upper limits of serum tumor markers were adopted as follows: CA19-9 (37.0 U/ml), CEA (5.0 ng/ml) and CA242 (20 U/ml). In this study, all patients with total bilirubin [?] 250mmol/L were treated with percutaneous transhepatic biliary drainage or endoscopic retrograde biliary drainage. After biliary darinage, the level of preoperative serum CA19-9 was detected again.

The pathological diagnosis was established by two professional pathologists. Tumors were staged according to the 8^{th}edition of AJCC TNM staging of pancreatic cancer. The histology grade were classified into two groups based on the degree of tumor differentiation: low grade, including well or moderately differentiated adenocarcinoma; and high grade, including poorly differentiated or undifferentiated adenocarcinoma. Lymphovascular infiltration (LVI) was referred to as blood vessel and lymphatic invasion. Perineural invasion is an infiltrative process of peripheral nerves by the primary neoplasm within the immediate vicinity. Patients who received more than three cycles of postoperative adjuvant chemotherapy were defined as chemotherapy group.

Follow-up

Patients were reviewed monthly for 6 months after surgery. Then they were followed up every 3 moths for up to 2 years after surgery, then every 6 moths for up to 5 years, and then every year or until death. A physical examination, laboratory tests including serum CA19-9 and CEA levels, and abdominal ultrasound were performed at each visit, whereas chest and abdominal computed tomography or abdominal magnetic

resonance imaging were routinely obtained every 6 moths. For patients with suspected recurrence or metastasis, imaging examinations were performed at any time. The OS was calculated from the day of surgery until time of death or final follow-up. The RFS was defined as the interval from the surgical time until tumor recurrence or the last follow-up. The median follow-up were 51 months (range: 1-126) for OS and 49 months (range: 1-126) for RFS, respectively. The date of the final follow-up was March 30, 2022.

Statistical analysis

The receiver operating characteristic (ROC) curves were used to identify the potential cut-off values of preoperative serum CA19-9 in predicting survival. The ROC curves were also used to compare the area under curves (AUC) of the modified TNM(mTNM) staging system and the eighth edition of the TNM staging system to show the advantage of each in predicting survival. The OS curves were calculated using the Kaplan-Meier method based on the length of time between the primary surgical treatment and final follow up or death.The log-rank test was used to assess significant differences between curves. Independent prognostic factors were identified by the COX proportional hazard regression model which were used to measure homogeneity and discriminatory ability. P<0.050 (bilateral) was considered statistically significant. The statistical analysis was performed using the statistical analysis program package IBM SPSS 23.0 and MedCalc v.19.6.1.

Results

Clinicopathological characteristics of the whole cohort

The baseline characteristics of the whole cohort is listed in**Table I** . The 612 patients included 352 males (57.5) and 260 females (42.5). The age ranged from 31 to 82 years, and the media age was 61 years. The median levels of preoperative CA19-9, CEA and CA242 were 156.25 U/ml, 3.3550 ng/ml and 19.64 U/ml, respectively. There were 416 patients with PDAC located at the head of pancreas and 196 patients at body and tail. A total of 414 patients accepted pancreaticoduodenectomy, 195 patients accepted distal pancreatectomy and 3 patients accepted total pancreatectomy. Of the 264 patients with low histology grade, 23 patients were well differentiated and 241 patients were moderate differentiated. The remaining 348 patients who were poorly differentiated were classified into high histology grade. The median OS of the entire cohort was 18 months (6-126 months), with survival rates of 71.3, 43.3, 31.3 and 19.1% after 1, 2, 3 and 5 years of follow-up, respectively.

Survival analysis of patients with PDAC

The ROC curves showed that preoperative serum CA19-9 could predict the prognosis of patients with PDAC (AUC=0.576, 95%CI:0.535-0.615, P=0.003)(**Figure 1**). The optimal cutoff point of preoperative serum CA19-9 to predict survival was 112 U/ml. Then, the patients were categorized into two groups according to the optimal cutoff value of preoperative serum CA19-9: group 1, in which the level of peroperative serum CA19-9 was [?]112 U/ml; and group 2, in which the level of preoperative serum CA19-9 was >112 U/ml.

The results of the univariate and multivariate survival analyses were presented in **Table II** . In the univariate analysis, the following 8 factors evaluated had a significant effect on survival: age at surgery (<70 years vs [?]70 years), preoperative CA19-9 ([?]112 U/ml vs >112 U/ml), preoperative serum CEA ([?]5 ng/ml vs >5 ng/ml), postoperative adjuvant chemotherapy, TNM stage, histology grade (low grade vs high grade), perineural invasion and lymphovascular invasion.

PDAC patients with CA19-9 >112U/ml had a significantly less 5-year OS than those with CA19-9 [?]112U/ml (5-year OS: 15.9% vs 22.6%, P<0.001, **Figure 2, A**), and patients with high grade also had a significant less 5-year OS than those with low grade (5-year OS: 15.7% vs 23.5%, P<0.001, **Figure 2, B**).

In the multivariate analysis, preoperative serum CA19-9 (HR was 1.355 for CA19-9>112 U/ml, P=0.005) and histology grade (HR was 1.545 for high grade, P<0.001) were found to be independent prognostic factors for OS, as were age at surgery ([?]70 years), TNM stage and postoperative adjuvant chemotherapy.

Development of biological risk model

Initially, all patients were categorized into four groups according to the levels of preoperative serum CA19-9 and histology grade: group 1, CA19-9[?]112 U/ml and low grade; group 2, CA19-9[?]112 U/ml and high grade; group 3, CA19-9>112 U/ml and low grade; group 4, CA19-9>112 U/ml and high grade. The 5-year OS rates were 28.5, 23.0, 18.6 and 11.9% in group 1, 2, 3 and 4, respectively. There was no survival difference between group 2 and group 3 (5-year OS: 23.0% vs 18.6%, P=0.805) (**Figure 3, A**).

Peroperative serum CA19-9 and histology grade were used to build a biological risk (BR) score taking into account of their hazard ratios in the multivariate analysis. Patients with preoperative serum CA19-9 [?]112 U/ml and low grade were given a BR score of 0. Patients with preoperative CA19-9>112U/ml and low grade as well as those with preoperative serum CA19-9 [?]112 U/ml and high grade were given a BR score of 1. Patients with preoperative CA19-9>112U/ml and high grade were given a BR score of 2. The BR score was 0 for 129 patients, 1 for 267 patients and 2 for 216 patients, respectively. Patients were divided into three groups according to the BR score: low risk group (BR=0), middle risk group (BR=1) and high risk group (BR=2). The 5-year OS rates were 28.5%, 14.9% and 7.7% for patients in the low-risk group, middle-risk group and high-risk group, respectively (χ^2=92.762, P<0.001)(**Figure 3, B**). In the multivariate analysis, the BR score was an independent prognosis factor for OS (HR was 1.342, P=0.047). Preoperative serum CA19-9 and histology grade were not significant if the BR score was included in the multivariate analysis (**Table III**).

Incorporation of biological risk into the eighth edition of AJCC TNM staging system

With the TNM-stratified analysis, there was no significant survival difference between low-risk group and middle-risk group in stage I, while the OS of the two groups was significantly better than that of high-risk group in stage I (**Figure 4,A**). Of the patients in stage II, the survival differences were significant between each two groups (**Figure 4,B**). Of the pateints in stage III, there was no significant survival difference among the three groups (**Figure 4,C**). The OS of patients in low-risk and middle-risk group, who were at stage I was similar to that of patients in low-risk group who were at stage II. The OS of patients in high-risk group who were at stage I was similar to that of patients in middle-risk group who were at stage II. The OS of patients in high-risk group who were at stage II was similar to that of patients in stage III(**Figure 4,D**).

According to the results of the strata analysis, we incorporated the biological risk into the eighth edition of the TNM staging system and introduced our modified TNM (mTNM) staging system (**TableIV**). In the mTNM staging system, the 5-year OS rates of stage mI, mII and mIII were 31.5%, 17.2% and 7.2%, respectively (χ^2=78.603, P <0.001). In the TNM staging system, the 5-year OS rates of stage I, II and III were 28.2%, 14.9% and 7.7%, respectively (χ^2=37.794, P <0.001) (**Table V, Figure 5 A,B**). Then, the mTNM stage and the factors associated with OS in the univariate analysis were included in the multivariate analysis again. This time, age at surgery, postoperative adjuvant chemotherapy and mTNM stage were found to be independent prognostic factors for OS. The, biological risk and TNM stage were not significant in the multivariate analysis (**Table III**).

Predictive performance of m TNM staging system

The differences in prognostic prediction between the eighth edition of the TNM staging system and the mTNM classification system were compared directly. The -2 log likelihood of the mTNM stage was 4688.361, which was less than the value of the TNM staging system (4694.876), which indicates a better performance in predicting survival (**Table V**). The ROC curves showed that the AUC of the mTNM stage was significantly greater than that of the TNM stage (AUC: 0.646 vs 0.587%, P=0.0007) (**Figure 6**).

Discussion

Both tumor burden and malignant degree can reflect biological characteristics of tumor, and they are also associated with the survival of patients with malignancy. The AJCC TNM classification which reflects tumor burden was the most widely used staging system for malignancy, however, it was a macroscopic classification mainly based on anatomy and did not incorporate the factors reflecting microscopic tumor burden which could not be detected by imageology[14], neither the factors reflecting malignant degree of tumor. As a result,

there were always biases of accuracy when the TNM stage was used to predict prognosis[8,9]. In the present study, we supposed to incorporate preoperative serum CA19-9, which could compensate the deficiency of TNM stage in evaluating microscopical tumor burden, and histology grate, which could make up for the defect of TNM stage in reflecting malignant degree, into the TNM staging system to reduce the biases.

In this study, patients with preopertive serum CA19-9 level >112 U/ml demonstrated a significantly lower OS rate than those with CA19-9 [?]112U/ml (5-year OS: 15.9% vs. 22.6%, P<0.001). Patients with high grade also had a significant decreased OS than those with low grade (5-year OS: 15.7% vs. 23.5%, P<0.001). In the multivariate analysis, both preoperative serum CA19-9 and histology grade were identified as independent prognostic factors for OS. Our proposed biological risk of PDAC was established according to the preoperative serum CA19-9 and histology grade. All patients were categorized into three groups according to the biological risk of PDAC: low-risk, middle-risk and high-risk group. Significant differences in OS were observed among the three groups. After incorporating the biological risk into the eighth edition of TNM staging system, mTNM staging was established. It was confirmed that the mTNM staging system was more accurate in predicting postoperative prognosis of PDAC patients than the eighth edition of the AJCC TNM staging system.

CA19-9 was the most widely used serum tumor marker. Kang et al reported that both pretreatment and posttreatment CA19-9 levels or their changes after treatment had good prognostic value in determining the survival of pancreatic cancer patients[17]. At present, there was no recognized cut-off value of CA19-9 to predict the prognosis of PDAC [18,19,20,21], as the level of CA19-9 fluctuated very widely, in our study, the CA19-9 level ranged from 0.6 to 178850 U/ml, besides, the proportion of negative Lewis-antigen patients varied across countries, ethnicities and studies (6% in white population, 22% in black population, 5-10% in yellow population)[22,23,24,25]. Even so, multiple researches have confirmed the advantage of CA19-9 over other serum tumor markers in predicting prognosis of PDAC[26,27,28], which was consistent with our results.

Histology grade was defined as the degree of differentiation of the tumor. Differentiation refers to the morphologic and functional resemblance between a tumor cell and a normal cell of the same tissue. Malignant neoplasms usually evolve from low grade to high grade. In the process of malignancy, the higher the tumor grade, the more aggressive, and the greater the tumor burden[29,30]. Many studies have demonstrated that histology grade was significantly associated with survival of patients with PDAC and could be used to modify the TNM staging system[31,32], so was the case in our study.

To the best of our knowledge, this study is the first to categorize patients with PDAC according to the biological risk based on preoperative CA19-9 and histology grade, and assess the impact of tumor biology on the survival. Our results reveled that patients with low risk had a significant higher OS than those with middle risk, and patients with middle risk also demonstrated a better prognosis than those with high risk. The biological risk was confirmed to be an independent prognostic factor in the multivariate analysis. In our opinion, the combination of preoperative serum CA19-9 and histology grade contains unique prognostic information which represents the microscopic tumor burden and malignant degree, which is not included in the TNM staging system.

There are several limitations to the study. First, it was a retrospective study conducted at a single center. Second, patients were included from 2011 to 2020, therefore, current neoadjuvant therapy were not used routinely. In addition, we could not exclude patients with negative Lewis antigen, which may have an uncertain impact on accuracy. As the constraints listed above may cause bias in the results, data from other centers is required for further validation of our findings.

Conclusion

All in all, preoperative serum CA19-9 and histology grade were independent prognostic factors for patients with PDAC. Biological risk which consists of preoperative serum CA19-9 and histology grade could predict survival of patients with PDAC. Incorporating the biological risk could improve the the accuracy of the TNM staging system in predicting prognosis of PDAC.

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Figure legends:

Figure 1 Receiver operating characteristic curve for predicting survival of pancreatic cancer by various cut-off values of CA19-9(AUC=0.576, 95%CI:0.535-0.615, P=0.003). Cut-off value of CA19-9 with the maximum sensitivity + specificity for predicting survival of pancreatic cancer was 112 U/mL.

Figure 2 Overall survival curves after curative resection. (A) Patients grouped according to CA19-9 level (P <0.001, log-rank test). (B) Patients grouped according to histology grade (P <0.001). Low grade: well and moderate differentiation, high grade: poor differentiation and undifferentiation.

Figure 3 Overall survival curves after curative resection. (A) 4 groups according to the status of CA19-9 and histology grade: group 1, CA19-9[?]112 U/ml and low grade; group 2, CA19-9[?]112 U/ml and high grade; group 3, CA19-9>112 U/ml and low grade; group 4, CA19-9>112 U/ml and high grade. (B) 3 groups according to the biological risk score: low risk group: CA19-9[?]112 U/ml and low grade; middle risk group: CA19-9[?]112 U/ml+high grade or CA19-9>112 U/ml+low grade; high risk group: CA19-9>112 U/ml+high grade.

Figure 4 Overall survival curves stratified by TNM stage.The survival differences were only observed in pancreatic cancer patients with stage I and stage II disease.(A) Stage I.(B) Stage II.(C) Stage III.(D) Overall survival curves of pancreatic cancer patients according to the TNM stage and biological risk.

Figure 5 Overall survival curves of all pancreatic cancer patients. There were significant differences in OS with mTNM or TNM stage. (A) mTNM stage. (B) TNM stage.

Figure 6 Receiver operating characteristic curve for comparing the area under curves between mTNM and TNM. AUC(mTNM)=0.646, AUC(TNM) =0.587,P=0.0007.

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