ORIGINAL ARTICLE

Accuracy of preoperative serum CA19-9 levels in predicting the resectability of patients with pancreatic adenocarcinoma

Ying Li[1], Xiaojuan Yang[2], Zhanzhan Zhang[3], Xiaoning Kang[2], Shanglong Liu[4] (✉)

[1] Department of Blood Transfusion, Affiliated Hospital of Medical College, Qingdao University, Qingdao 266003, China
[2] Department of Operating Room, Affiliated Hospital of Medical College, Qingdao University, Qingdao 266003, China
[3] Department of Nephropathy, Tengzhou Hospital of Traditional Chinese Medicine, China
[4] Department of General Surgery, Affiliated Hospital of Medical College, Qingdao University, Qingdao 266003, China

Abstract

Objective   To assess the accuracy of preoperative serum CA19-9 levels in predicting the resectability of pancreatic adenocarcinoma.

Methods   Patients with biopsy-proven pancreatic adenocarcinoma who had preoperative serum CA19-9 level data were enrolled in the present retrospective analysis. Receiver operating characteristics (ROC) curve analysis was used to determine the optimal cut-off value of CA19-9. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated at this cut-off point.

Results   Seventy-six patients with pancreatic adenocarcinoma that was considered potentially resectable according to radiological imaging were included. Of all 76 patients, 44 received complete resection of the pancreatic adenocarcinoma. The preoperative serum CA19-9 level was significantly higher in the unresectable tumor group than in the resectable tumor group ($P = 0.0036$). The area under the ROC curve was 0.749 (95% confidence interval [CI]: 0.637–0.842). When the cut-off value of CA19-9 was set to 359.1 U/mL, the sensitivity, specificity, positive and negative predictive values were 71.9% (95% CI: 53.3%–86.3%), 70.5% (95% CI: 54.8%–83.2%), 63.9% (95% CI: 46.0%–79.4%), and 77.5% (95% CI: 61.5%–89.2%), respectively.

Conclusion   The preoperative serum CA19-9 level is useful for predicting the resectability of pancreatic adenocarcinoma.

Key word: pancreatic adenocarcinoma; CA19-9; resectability

Pancreatic adenocarcinoma is a major cause of cancer mortality worldwide. It is an aggressive tumor that frequently presents with dissemination to the regional lymph nodes or distant metastatic sites at the early phase. With the developments of surgical techniques and adjuvant treatment, the survival of patients has improved drastically. However, the outcome is still unsatisfactory. Patients with pancreatic adenocarcinoma have an overall cumulative 5-year survival rate of <1% [1], the lowest for any cancer, with a median survival of only 5-6 months [2–3]. The optimal treatment for pancreatic adenocarcinoma involves resecting the entire tumor with microscopically negative margins. However, as many patients with pancreatic adenocarcinoma already have metastases or invasion at the time of the initial diagnosis, curative surgery can be performed in less than 20% of patients

[4–5]. Accordingly, a precise estimation of the possible resectability of pancreatic adenocarcinoma is necessary. Preoperative evaluation of pancreatic adenocarcinoma can identify patients in whom surgical intervention may result in survival benefit, and some patients could thus avoid unnecessary laparotomy and undergo a more appropriate therapy. However, there is currently no effective method for predicting the appropriateness of complete resection of pancreatic adenocarcinoma.

As a major tumor marker for pancreatic adenocarcinoma, CA19-9 has many important clinical implications. CA19-9 has a sensitivity of 68%–94% and specificity of 76%–100% for the diagnosis of pancreatic cancer [6]. Moreover, CA19-9 is associated with the clinical course and prognosis of pancreatic adenocarcinoma [7]. However, the correlation between the levels of CA19-9 and the existence of metastasis or invasion in this disease remain largely unknown. The CA19-9 level could be elevated due to tumor burden and spread of disease [8]. The present study was conducted to determine the ability of CA19-9 in evaluating the resectability among patients with pancreatic adenocarcinoma, with the aim to improve the selection of surgical candidates.

Materials and methods

The medical records of patients treated between July 2014 and July 2016 at the Hospital Affiliated Qingdao University were reviewed. Patients with biopsy-proven pancreatic adenocarcinoma who had preoperative serum CA19-9 level data were eligible for this retrospective analysis. The study consisted of 76 patients who had undergone surgery for potentially resectable primary pancreatic adenocarcinoma. All patients were preoperatively assessed by using contrast-enhanced computed tomography. The exclusion criteria were as follows: (1) Evidence of distant metastasis; (2) Invasion or extension of the tumor to the superior mesenteric artery or celiac axis; and (3) Inability to undergo major surgery. Moreover, patients were excluded from our study if they (1) had a history of another malignant tumor in the previous 5 years or (2) had any other histological type, such as mucinous adenocarcinoma or endocrine tumors. After reviewing the medical records, the following information was collected to constitute our database: sex, age, tumor location, date of operation, surgical exploration and operative records, pathology and cytology reports, and preoperative serum CA19-9 levels. Resectability was defined as complete removal of the tumor, with negative margins.

A CA19-9 radioimmunoassay kit (Abbott Laboratory, Chicago, IL) was employed to evaluate the CA19-9 levels. The recommended normal range by the manufacturer is 0–37 U/mL. Receiver operating characteristics (ROC) curve analysis was used to determine the optimal cut-off value of CA19-9. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A P value of less than 0.05 was considered as statistical significance. Statistical analysis was performed with SPSS version 16.0 and GraphPad Prism version 4.0. Our study was approved by the Institutional Ethical Committee of Peiking Union Hospital.

Results

The patients' age ranged from 37 to 89 years. There were 41 male and 35 female patients (n = 76), with median ages of 59.1 and 62.0 years, respectively. The characteristics of the patients are shown in Table 1. The pancreatic adenocarcinoma involved the head (n = 52), body (n = 9), and tail (n = 15) of the pancreas. A total of 44 patients received complete resection of the pancreatic adenocarcinoma, although all 76 patients were considered to have potentially resectable disease on the preoperative examination (pylorus-preserving pancreaticoduodenectomy, n = 21; Whipple's operation, n = 19; distal pancreatectomy, n = 4). Regional lymph node dissection was also performed on the basis of tumor location. The other 32 patients did not receive complete resection due to unexpected metastasis or local invasion. Of all unresectable tumors, 13 cases had distant metastasis (peritoneal metastasis, n = 8; liver metastasis, n = 5), while 15 cases showed local invasion (superior mesenteric artery invasion, n = 12; celiac axis, n = 3). Positive margins were found in 2 cases on postoperative pathological examination.

In the resectable tumor group, the CA19-9 values ranged from 8.3 to 2104.8 U/mL, with a median value of 392.4 ± 70.71 U/mL. In the unresectable tumor group, the CA19-9 values ranged from 97.1 to 3101.2 U/mL, with a median value of 814.6 ± 133.4 U/mL. The preoperative

Table 1   Characteristics of patients with pancreatic adenocarcinoma

Characteristics	n (%)
Patients (n)	76
Sex	
Male	41 (53.9)
Female	35 (46.1)
Tumor location	
Head	52 (68.5)
Body	9 (11.8)
Tail	15 (19.7)
Type of operation	
Pylorus-preserving pancreaticoduodenectomy pancreaticoduodenectomy	21 (27.6)
Whipple's operation	19 (25)
Distal pancreatectomy	4 (5.3)
Exploratory laparotomy and biopsy	32 (42.1)

serum CA19-9 levels was significantly higher in the unresectable tumor group than in the resectable tumor group (P = 0.0036; Fig. 1).

The ROC curve analysis predicting the value of CA19-9 for resectability is illustrated in Fig. 2. ROC curve analysis showed that the area under the curve of preoperative serum CA19-9 levels was 0.749 in predicting the resectability of pancreatic adenocarcinoma (95% confidence interval [CI]: 0.637–0.842). The standard error was 0.0563, with P < 0.001. The best cut-off value for CA19-9 to predict resectability was 359.1 U/mL. When the preoperative serum CA19-9 level was adopted as 359.1 U/mL, the sensitivity was 71.9% (95% CI: 53.3%–86.3%) and the specificity was 70.5% (95% CI: 54.8%–83.2%). Moreover, by using this cut-off value, the positive predictive value was 63.9% (95% CI: 46.0%–79.4%) and the negative predictive value was 77.5% (95% CI: 61.5%–89.2%).

Discussion

The poor survival of patients with pancreatic adenocarcinoma is generally attributed to its chemo-resistance and undetected metastases or invasion at the time of initial diagnosis. Determining resectability preoperatively is the principle goal for the treatment of patients with pancreatic adenocarcinoma. Improvement in radiological imaging has increased the accuracy of preoperative diagnosis. Contrast-enhanced computed tomography plays an important role in predicting unresectable lesions. At present, computed tomography has become the principle preoperative staging modality [9]. However, it overestimates resectability by up to 48% [10–11]. Thus, it is imperative to explore additional modalities.

CA19-9 was first described as a colorectal carcinoma antigen by Koprowski *et al* [12]. At present, it has become the most important tumor marker for pancreatic cancer. CA19-9 is useful for the diagnosis, prognosis, and monitoring of patients with pancreatic adenocarcinoma [13]. For diagnosing pancreatic adenocarcinoma, the
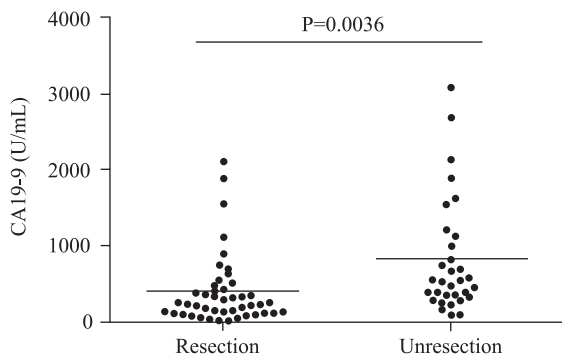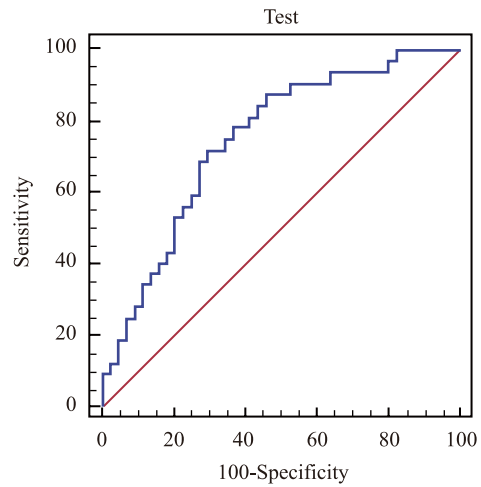
Fig. 2 Receiver operating characteristics curve analysis for the optimal value of CA19-9 for predicting resectability

sensitivity and specificity of CA19-9 are higher than those of other tumor markers such as carcinoembryonic antigen and cancer antigen-242 [14]. Based on the finding that the CA19-9 level could be elevated due to tumor burden and spread of disease [8], we hypothesized that the preoperative serum CA19-9 level is indicative of the pancreatic adenocarcinoma stage and could predict the resectability of the tumor to some extent. ROC curve analysis is an effective way to evaluate the predictive value of a certain cut-off point, and has been widely used as a standard model for describing the accuracy of medical diagnostic tests [15].

The results of this study showed that there was a significant difference in the CA19-9 levels between the resectable and unresectable groups (P = 0.0036). The preoperative CA19-9 level was lower in the resectable tumor group than in the unresectable tumor group, indicating that the preoperative serum CA19-9 levels may be associated with pancreatic adenocarcinoma staging. The area under the curve of the preoperative serum CA19-9 levels was 0.749 (95% CI: 0.637–0.842), indicating that CA19-9 is a useful tumor marker for assessing the resectability of pancreatic adenocarcinoma. When the cut-off value was set to 359.1 U/mL, the best cut-off value for CA19-9 to predict resectability, the sensitivity, specificity, and positive and negative predictive values were 71.9% (95% CI: 53.3%–86.3%), 70.5% (95% CI: 54.8%–83.2%), 63.9% (95% CI: 46.0%–79.4%), and 77.5% (95% CI: 61.5%–89.2%), respectively. This result suggests that a high preoperative serum CA19-9 level can be regarded as a parameter associated with unresectable pancreatic adenocarcinoma, consistent with other reports [16–17]. In the resectable tumor group, 13 patients had preoperative CA19-9 higher than 359.1 U/ml (29.5%), while in the unresectable group, 9 patients

Fig. 1 CA19-9 levels in the resectable and unresectable tumor groups of pancreatic adenocarcinoma

had preoperative CA19-9 less than 359.1 U/mL (28.1%).

There are several limitations of our study. Because of the retrospective design, there might be unmeasured clinical factors that influence the accuracy of preoperative CA19-9 levels in predicting the resectability of pancreatic adenocarcinoma, such as the sample size and the unadjusted CA19-9 level according to the bilirubin level. In addition, resectability of pancreatic adenocarcinoma is also associated with the surgeon training and experience, so operations performed by different surgeons at various facilities would influence the accuracy. Despite these limitations, our study provides some information about the accuracy of preoperative CA19-9 in predicting the resectability of pancreatic adenocarcinoma.

In conclusion, the preoperative serum CA19-9 level may be useful for predicting the resectability of pancreatic adenocarcinoma. A combination of radiological imaging and CA19-9 may increase the positive predictive value of preoperative staging in pancreatic adenocarcinoma, and thus, many patients could potentially avoid unnecessary laparoscopy.

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