ORIGINAL ARTICLE

Retrospective Study

Preoperative defining system for pancreatic head cancer considering surgical resection

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Abstract

AIM: To provide appropriate treatment, it is crucial to share the clinical status of pancreas head cancer among multidisciplinary treatment members.

METHODS: A retrospective analysis of the medical records of 113 patients who underwent surgery for pancreas head cancer from January 2008 to December 2012 was performed. We developed preoperative defining system of pancreatic head cancer by describing "resectability - tumor location - vascular relationship - adjacent organ involvement - preoperative CA19-9 (initial bilirubin level) - vascular anomaly". The oncologic correlations with this reporting system were evaluated.

RESULTS: Among 113 patients, there were 75 patients (66.4%) with resectable, 34 patients (30.1%) with borderline resectable, and 4 patients (3.5%) with locally advanced pancreatic cancer. Mean disease-free survival was 24.8 mo (95%CI: 19.6-30.1) with a 5-year disease-free survival rate of 13.5%. Pretreatment tumor size ≥ 2.4 cm [Exp(B) = 3.608, 95%CI: 1.512-8.609, *P* = 0.044] and radiologic vascular invasion [Exp(B) = 5.553, 95%CI: 2.269-14.589, *P* = 0.002] were independent predictive factors for neoadjuvant treatment. Borderline resectability [Exp(B) = 0.222, *P* = 0.008], pancreatic

head cancer involving the pancreatic neck [Exp(B) = 9.461, *P* = 0.001] and arterial invasion [Exp(B) = 6.208, *P* = 0.010], and adjusted CA19-9 $\geq$ 50 [Exp(B) = 1.972 *P* = 0.019] were identified as prognostic clinical factors to predict tumor recurrence.

CONCLUSION: The suggested preoperative defining system can help with designing treatment plans and also predict oncologic outcomes.

Key words: Preoperative defining system; Pancreas head cancer; Borderline resectable; Adjusted CA19-9; Neoadjuvant therapy

Core tip: Owing to the anatomical complexity of the pancreas head cancer, it is not always easy to share the exact disease status among multidisciplinary treatment members. So, we made a preoperative defining system, which contained the important clinical variables (resectability, tumor location, vascular relationship, adjacent organ involvement, preoperative CA19-9, vascular anomaly) to decide the treatment plan for pancreas head cancer. Through internal validation, we proved that this system could be useful not only to clarify the disease characteristics but also to predict oncologic outcomes of pancreas head cancer.

INTRODUCTION

Pancreatic cancer is one of the lethal malignant diseases arising from the gastrointestinal tract. It is well-known that only margin-negative resection of the tumor can lead to long-term survival[1]. However, most patients treated with curative pancreatectomy develop tumor recurrences, especially in the liver. Therefore, effective adjuvant systemic chemotherapy should be mandatory[2].

In general, resectable pancreatic cancer is defined as a clinical tumor condition confined to the pancreas without radiologic evidence suggesting invasion of the major vascular system or systemic metastases. However, there is some controversy about the definition of borderline resectable pancreatic cancer[3]. Currently, there are two systems for defining borderline resectable pancreatic cancer[4,5]. Whatever definition is chosen, surgeons should plan the treatment modality and design the operative approach for curative resection based on preoperative radiologic assessment. In addition, they need to explain the

patients' chance of survival and prognosis based on clinically available information. However, there is no generalized preoperative defining system effectively showing the extent of pancreatic cancer and tumor biology.

It would be very helpful if a well-designed preoperative defining system of pancreatic cancer could: (1) estimate the clinical stage of cancer (tumor extension); (2) give practical information for designing the extent of surgery and choosing the treatment modality; (3) play a role as an effective communication tool among multidisciplinary team members; and (4) help predict oncologic outcomes.

In this study, we propose a preoperative defining system in patients with pancreatic head cancer considering curative resection. Our system may be useful in improving communication and developing strategies for treating pancreatic cancer.

MATERIALS AND METHODS

Principles of the new preoperative defining system

Based on radiological interpretation of preoperative images, resected pancreatic head cancers are intended to be described as the following structures: Pancreatic head cancer; "Resectability (tumor size, cm) - Tumor location-vascular relationship (length of involved segment (cm)/Circumferential involvement (%) - Adjacent organ involvement - Preoperative CA19-9 (initial bilirubin level) - Vascular anomaly".

Radiological resectability follows the National Comprehensive Cancer Network (NCCN) guideline[5]. If there is no vascular involvement, no adjacent organ invasion, and no clinical metastasis, no descriptions were added to this defining system for explaining this negative information. Important abbreviations are listed in Table 1.

Organs such as the duodenum and bile duct that will be removed by standard pancreaticoduodenectomy were not described even in cases of cancer invasion. However, if the tumor invaded the pylorus or antrum, it was added as a factor of adjacent organ invasion. Figure 1 shows the examples for application of the new defining system in patients with pancreatic head cancer.

Patient data collection

From January 2008 to December 2012, medical records and preoperative image studies of patients with resected pancreatic cancer were retrospectively reviewed. The clinic-pathological variables were checked. In particular, preoperative clinical information such as resectability, radiologic tumor size, tumor location, preoperative serum CA19-9, preoperative serum bilirubin, and adjusted CA19-9 (initial serum level of CA19-9 divided by initial serum level of bilirubin)[6] were also evaluated. The new defining system was applied to check if it could describe the tumor extent at the initial diagnosis.
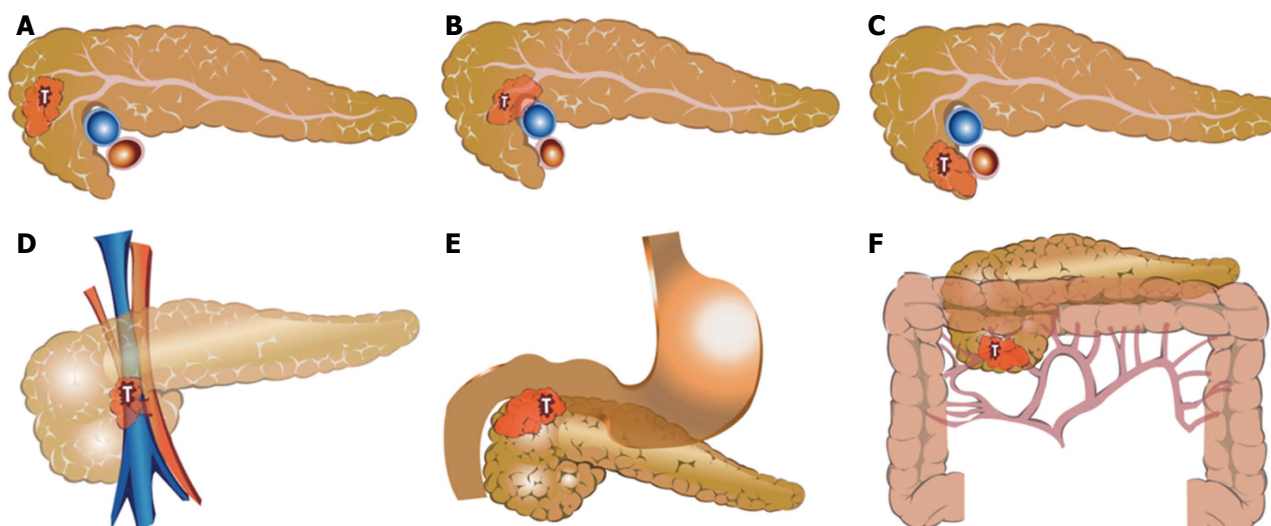
Figure 1 Clinical application of the new defining system in resected pancreatic head cancer. For example, a patient who has a 2 cm-sized tumor with preoperative CA19-9 120 U/mL and initial total bilirubin 1.2 mg/dL can be described according to the proposed new defining system as follows: (A) R2cm-H-120 (1.2); (B) BR2cm-Hn-SMV (0.5cm/30%)-120 (1.2); (C) BR2cm-Hu-SMA (0.5 cm/20%)-120(1.2); (D) BR2cm-Hn-SMV (0.5cm/50%)-120 (1.2)-Arha; (E) R2cm-H-pylorus-120 (1.2); (F) R2cm-H-T colon mesentery-120 (1.2).

Table 1 Important abbreviations used in the new preoperative defining system for pancreatic cancer

Symbol	Description	Comments
Resectability		
R	Resectable	
BR	Borderline resectable	
LA	Locally advanced	
Location		
H	Pancreatic head	Hu: uncinate process, Hn: neck portion
Vascular structure		
CA	Celiac axis	
CHA	Common hepatic artery	
GDA	Gastroduodenal artery	OGA: origin of gastroduodenal artery
aRHA	Aberrant right hepatic artery	
Rt/Lt	Right/left	
SMA	Superior mesenteric artery	
SMV	Superior mesenteric vein	
SMV-SV-PV	Superior mesenteric vein-splenic vein-portal vein	

R: Resectable pancreatic cancer; BR: Resectable pancreatic cancer; LA: Locally advanced pancreatic cancer.

Correlation between new preoperative defining system and clinico-oncologic outcomes

Individual clinical components existing in the new preoperative defining system, such as radiological resectability, tumor size, tumor location, vascular involvement, adjacent organ invasion, preoperative initial serum CA19-9 level, and initial serum bilirubin were correlated with treatment strategy and oncologic outcomes.

Statistical analysis

All statistical analyses were performed using IBM® SPSS Statistics version 20. Continuous variables were indicated as mean ± SD and categorical variables as frequency and percentage (%). Student's *t*-tests and χ^2 tests were used. Logistic regression analysis was applied for multivariate analysis. Kaplan-Meier and Cox-proportional hazard models were applied for disease-free survival as univariate and multivariate analysis. *P* values < 0.05 were considered as statistically significant.

RESULTS

Clinical feasibility of the new preoperative defining system

During the study period, 119 patients underwent potentially curative resection of pancreatic head cancer. All were confirmed as ductal adenocarcinoma by pathologic examination. Among them, six patients without available preoperative image studies were excluded, totally 113 patients were enrolled. The new preoperative defining system was applied to describe the extent of the tumor and some clinical information for all patients. Resectable pancreatic cancer (R) was noted in 75 patients (66.4%), borderline resectable pancreatic cancer (BR) in 34 (30.1%), and locally advanced pancreatic cancer (LA) in four patients (3.5%). The mean radiologic tumor size was measured as 2.4 ± 0.8 cm in the maximum diameter. Seventy-three tumors (64.6%) were located in the pancreatic head, 35 (31%) in the uncinate process, and five (4.4%) in the pancreatic head and neck area. Forty patients (35.4%) were found to have tumors involving

Table 2 Univariate analysis to predict combined venous vascular resection in treating pancreatic head cancer

	Combined venous vascular resection		*P* value
	No	Yes	
Resectability			
R	54	21	
BR	17	17	
LA	2	2	0.054
Radiologic tumor size (cm)	2.3 ± 0.7	2.6 ± 0.8	0.044
Tumor location			
Head	49	24	
Uncinate	22	13	
Including neck	2	3	0.485
Radiologic vascular component			
No	52	21	
Yes	21	19	0.002
Initial preoperative serum CA19-9	846.7 ± 2193.9	805.3 ± 1761.9	0.919
Initial serum total bilirubin	4.3 ± 5.0	4.9 ± 4.6	0.528

R: Resectable pancreatic cancer; BR: Resectable pancreatic cancer; LA: Locally advanced pancreatic cancer.

Table 3 Univariate analysis to predict neoadjuvant treatment for pancreatic head cancer

	Neoadjuvant treatment		*P* value
	No	Yes	
Resectability			
R	52	23	
BR	10	24	
LA	1	3	< 0.001
Radiologic tumor size (cm)	2.1 ± 5.7	2.7 ± 0.9	< 0.001
Tumor location			
Head	46	27	
Uncinate	15	20	
Including neck	2	3	0.049
Radiologic vascular component			
No	52	21	
Yes	11	29	< 0.001
Initial preoperative serum CA19-9	600.8 ± 1640.6	1109.0 ± 2437.1	0.189
Initial serum total bilirubin	3.9 ± 4.9	5.5 ± 4.9	0.087

R: Resectable pancreatic cancer; BR: Resectable pancreatic cancer; LA: Locally advanced pancreatic cancer.

major vascular structures. Mean initial serum level of CA19-9 was found to be 825.7 ± 2037.8 (U/mL), and initial serum bilirubin was 4.6 ± 5.0 (mg/dL). Adjusted CA19-9 was calculated as 401.9 ± 872.8 (U/mL).

Correlation between clinical components and surgical strategy
It was found that the new preoperative defining system can help in decision-making about treatment strategies and surgical extent in pancreatic cancer management.

Thirty-nine patients (34.5%) underwent combined venous vascular resection. SMV/PV wedge resection was performed in 15 patients, and 24 patients underwent segmental resection of the PV system. Among the clinical factors used in the new preoperative defining system, radiologic tumor size, vascular components were associated with combined venous vascular resection (*P* < 0.05, Table 2). However, in multivariate analysis, only radiologic tumor size ≥ 2.4 cm [Exp(B) = 2.288, 95%CI: 1.029-5.087, *P* = 0.042] was noted to be independent clinical factor to predict combined venous vascular resection.

It was also found that resectability, radiologic tumor size, tumor location, and radiologic vascular component were related to neoadjuvant treatment before surgical resection (*P* < 0.05, Table 3). In multivariate analysis, radiologic tumor size ≥ 2.4 cm [Exp(B) = 3.608, 95%CI: 1.512-8.609, *P* = 0.004], and radiologic vascular component [Exp(B) = 5.553, 95%CI: 2.269-14.589, *P* < 0.001] were found to be independent predictive factors for preoperative neoadjuvant treatment in this study population.

Correlation between clinical components and long-term oncologic outcomes
It was also noted that the proposed new defining system can be useful in predicting oncologic outcome even before confirming pathologic characteristics of the resected pancreatic cancer.

Mean disease-free survival was 24.8 mo (95%CI: 19.6-30.1) with a 5-year disease-free survival rate of 13.5%. Interestingly, when putting clinical variables used in the preoperative defining system into a Cox hazard regression model, it was found that anatomic resectability, especially borderline resectable pancreatic cancer [Exp(B) = 0.222]; radiologic tumor size ≥ 2.4cm [Exp(B) = 1.696], tumor location, especially pancreatic head cancer involving the pancreatic neck portion [Exp(B) = 9.461]; radiologic venous vascular component [Exp(B) = 2.788]; arterial component [Exp(B) = 6.208]; initial total bilirubin ≥ 4.6 [Exp(B) = 0.588]; and adjusted CA19-9 ≥ 50 [Exp(B) = 1.972] were identified as prognostic clinical factors to predict tumor recurrence (Table 4).

DISCUSSION

TNM staging system is widely accepted, and it is aimed at predicting survival. Some kinds of cancer cannot be simplified down to a TNM stage because of unique anatomical characteristics. One of these is hilar cholangiocarcinoma (HCCA) and another is pancreas head cancer. For hilar cholangiocarcinoma, there is already a presurgical staging system that considers surrounding anatomical structures[7]. The Jarnagin-Blumgart (J-B) classification has been used for deciding treatment plans and developing a prognosis

Table 4 Oncologic impact of clinical variables used in the new preoperative defining system

Clinical variables	Exp(B)	95%CI	P value
Resectability			0.019
BR	0.222	0.073-0.676	0.008
LA	0.557	0.105-2.955	0.492
Radiologic tumor size (cm) ≥ 2.4	1.696	0.993-2.897	0.053
Tumor location			0.007
Hu	0.952	0.557-1.629	0.858
Hn	9.461	2.634-33.976	0.001
Vascular relationship with			0.064
Venous system	2.788	0.952-8.165	0.061
Arterial system	6.208	1.562-24.669	0.010
Both	2.200	0.484-10.006	0.307
CA19-9 ≥ 825	1.709	0.777-3.761	0.183
Total bilirubin ≥ 4.6	0.588	0.339-1.022	0.060
Adjusted CA19-9 ≥ 50	1.972	1.118-3.480	0.019

BR: Resectable pancreatic cancer; LA: Locally advanced pancreatic cancer.

of HCCA[8]. We need a more appropriate defining system for pancreas head cancer rather than the TNM stage, something similar to the J-B classification for HCCA.

The presented new preoperative defining system can suggest the treatment strategy, extent of surgery, and even tumor biology in resected pancreatic head cancer. It was found that all resected pancreatic head cancers could be described according to the new preoperative defining system based on a preoperative CT scan. In addition, in multivariate analysis, radiologic tumor size ≥ 2.4 cm [Exp(B) = 3.608, P = 0.004], and radiologic vascular component [Exp(B) = 5.553, P < 0.001] were independent predictive factors for preoperative neoadjuvant treatment. In particular, larger tumor size (tumor size ≥ 2.4 cm) was associated with combined venous vascular resection [Exp(B) = 2.288, P = 0.042], suggesting that clinical components used for the currently proposed new defining system can provide important clinical clues about treatment strategy and the extent of surgery in treating pancreatic cancer.

Most importantly, the current system can predict patients' outcomes without requiring confirmation of the clinical stage of the cancer. Considering that most prognostic factors are based on pathologic characteristics[9-13], such as lymph node metastasis, lymph node ratio, perineural invasion, lymphovascular invasion, and cell differentiation, the proposing preoperative defining system showed that even clinical characteristics, such as anatomic resectability (P = 0.019), tumor location (P = 0.007), and adjusted CA19-9 (P = 0.019), which can be estimated before surgical intervention, were identified as good prognostic markers for predicting tumor recurrence (Table 4).

Adjusted CA19-9 is defined as the value of initial CA19-9 level divided by serum total bilirubin. This concept was developed because the actual serum level

of CA19-9 is not reliable in patients with jaundice. We already demonstrated that adjusted CA19-9 was a prognostic clinical marker in resected pancreatic cancer[6], which was shown again in the present study. Further clinical investigation based on a large population is necessary to define the oncologic significance of preoperative adjusted CA19-9.

When applying this new system in cases of neoadjuvant treatment, it would be easy and more subjective to detect the radiologic responsiveness after neoadjuvant treatment in borderline resectable pancreatic cancer. If a radiologist described the radiologic changes according to the new defining system, the surgeon could be well aware of the current tumor status compared with the pre-neoadjuvant treatment status, which is one of many advantages of new system. For example, it can be described in this way: BR2cm-Hu-SMV2.5cm/30%-219 (8) → Neo-BR2cm-Hu-SMV2.0cm/10%-58 (2).

In spite of oncologic significance of lymph node metastasis, clinical N-stage (cN-stage) was not considered in this system because the accuracy of radiologic estimation of lymph node metastasis is not high[14,15]. In addition, preoperative cholangitis, pancreatitis, and interventional approaches due to obstructive cholangio-pancreatopathy can induce secondary lymph node enlargement. In fact, lymph node metastasis is one of the important prognostic factors in resected pancreatic cancer; however, several important randomized controlled studies have proven that the extent of lymph node dissection could not contribute to increasing oncologic outcome[16-18]. Therefore, cN-stage will not influence either prognosis or the clinical treatment strategy when the tumor is regarded as a resectable pancreatic cancer.

Instead, clinical information on the possibility of pylorus involvement or right colonic mesentery would be more useful in designing surgical extent. Recently, techniques for pyloric-ring resected pancreati-coduodenectomy[19], subtotal stomach-preserving pancreaticoduodenectomy[20], and combined resection of ascending colon are clinically available. In addition, descriptions of associated vascular anomaly, especially an aberrant right hepatic artery, will be another good guide for performing safe pancreaticoduodenectomy, because this artery is at risk for accidental injury during dissection of the hepatoduodenal ligament[21]. To design an optimal operation, it is mandatory to have exact anatomical delineation preoperatively. This proposed preoperative defining system can give compact and critical anatomical information to the surgical team.

There are several important flaws in our study. First, the new defining system is only based on retrospective data of operated patients. Therefore, this could not be reflective of all patients seen for consideration of surgery. It is needed to validate this defining system with all pancreas head cancer

surgery candidates prospectively. Second, it seems to be complicated and difficult to describe. Third, this system cannot estimate actual lymph node status. However, in the era of the multidisciplinary team approach for treating pancreatic cancer, this defining system can be useful for improving communication among team members, planning the extent of surgery, developing the treatment strategy, and defining tumor biology. This system needs to be validated on different sets of patient data to confirm its clinical feasibility, reproducibility, and oncologic meanings.

COMMENTS

Background

In this multidisciplinary treatment era, it is most important to share the exact disease status among multidisciplinary team members for making appropriate treatment pathway. When it comes to pancreas head cancer, the anatomical complexity surrounding tumor can make it difficult not only to communicate with each members of team, but also to decide treatment plan. In this study, the authors suggested a preoperative defining system which contained the important anatomical and laboratory findings associated with pancreas head cancer. Then they evaluated the efficacy of this system for designing treatment plan and predict oncologic outcomes.

Research frontiers

The National Comprehensive Cancer Network (NCCN) categorized the pancreas head cancer cases into resectable, borderline resectable or unresectable diseases. But this classification solely depends on vascular relationship in the preoperative radiologic evaluation. Several studies reported that tumor characteristics, adjusted preoperative CA19-9, vascular anomalies also should be considered preoperatively.

Innovations and breakthroughs

With the suggested defining system, they authors can estimate necessary of the neoadjuvant therapy or the combined vascular resection for pancreas head cancer. Moreover, the contents of this system are strongly related to the tumor recurrence.

Applications

This study demonstrates the new defining system for pancreas head cancer and will help the multidisciplinary board to communicate with each other about the individual disease status in a comprehensive way.

Terminology

Borderline resectable pancreas cancer means there is a possibility of incomplete resection because of adjacent vital vessel invasion such as superior mesenteric vein, gastroduodenal artery, hepatic artery and superior mesenteric artery.

Peer-review

The authors recommended a good preoperative description system for pancreatic cancer patients. This proposal with possible implication in neoadjuvant treatment is very remarkable.

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