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PANCREAS, BILIARY TRACT, AND LIVER

Disease-Specific Mortality Among Patients With Intraductal Papillary Mucinous Neoplasm of the Pancreas

Kazumichi Kawakubo, Minoru Tada, Hiroyuki Isayama, Naoki Sasahira, Yousuke Nakai, Naminatsu Takahara, Rie Uchino, Tsuyoshi Hamada, Koji Miyabayashi, Keisuke Yamamoto, Suguru Mizuno, Dai Mohri, Hirofumi Kogure, Takashi Sasaki, Natsuyo Yamamoto, Kenji Hirano, Hideaki Ijichi, Keisuke Tateishi, and Kazuhiko Koike

Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

BACKGROUND & AIMS: **Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is associated with synchronous and metachronous pancreatic cancer. However, the risk factors for pancreatic cancer–specific mortality have not been determined. We evaluated disease-specific mortality among patients with IPMNs harboring high-risk stigmata.**

METHODS: **We analyzed data from 243 patients diagnosed with IPMN, with indications for surgery according to the consensus criteria, at the University of Tokyo Hospital from 1995 to January 2011. By using optimal matching and propensity scores based on 16 characteristics, we matched patients who underwent surgery at diagnosis with those who did not undergo surgery. A competing risk analysis was used to assess the risk of pancreatic cancer–specific mortality.**

RESULTS: **Fifty-nine patients underwent surgery after diagnosis and 184 did not. After adjustment with propensity scores, detection of a hypo-attenuating area by computed tomography, which indicates invasive carcinoma, was associated significantly with pancreatic cancer–specific mortality (adjusted hazard ratio, 16.75; 95% confidence interval, 2.72–103.3; $P = .002$). Cyst diameter, main pancreatic duct diameter, and the presence of a mural nodule were not associated significantly with pancreatic cancer–specific mortality. Surgical management was found to reduce pancreatic cancer–specific mortality, especially in patients with hypo-attenuating areas ($P = .038$).**

CONCLUSIONS: **Detection of a hypo-attenuating area by computed tomography significantly increases the risk for pancreatic cancer–specific mortality among IPMN patients with consensus indications for surgery. Surgical resection significantly reduces this risk.**

Keywords: Pancreatic Carcinoma; Treatment; Imaging; Outcome.

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Since its first description in 1982,[1] intraductal papillary mucinous neoplasm (IPMN) of the pancreas has been recognized increasingly without symptoms by radiologic imaging.[2] IPMN has a favorable prognosis compared with ductal adenocarcinoma of the pancreas. However, IPMN not only has malignant potential itself but also is associated significantly with pancreatic carcinogenesis in the entire gland.[3] Consensus guidelines recommend the surgical management of IPMN with high-risk stigmata,[4,5] but the relatively low specificity remains unresolved.[6] Although previous reports evaluated pancreatic cancer–specific mortality in patients with surgically resected IPMN,[7–9] the long-term prognosis of patients with IPMN harboring high-risk stigmata in the absence of surgical resection has not been elucidated. Furthermore, because of treatment selection bias, it is not known how surgical resection affects pancreatic cancer–specific mortality in these patients.

The aim of this study was to examine the risk of disease-specific mortality in patients with IPMN harboring high-risk stigmata using a propensity score optimal matching analysis to control for inherent bias in treatment selection.

Abbreviations used in this paper: **CI, confidence interval; CT, computed tomography; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.**

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Methods

Patients

From 1995 to January 2011, there were 923 patients diagnosed with IPMN at the University of Tokyo Hospital and prospectively registered in our database. Written informed consent for registration in the database was obtained from all patients. The diagnosis of IPMN was based on radiologic imaging according to the definition in the consensus criteria.[4,10] Branch-duct IPMN was defined by the presence of a pancreatic cystic lesion obviously communicating with the main pancreatic duct (MPD). IPMNs with indications for surgery according to the 2006 consensus criteria were included in this study; cases included any main-duct IPMN and branch-duct IPMN with high-risk stigmata.[4] Branch-duct IPMNs with cyst size greater than 30 mm also were included. After diagnosis, patients were recommended for surgery as described in our previous study,[11,12] but patients with contraindications for general anesthesia and those who refused surgery were followed up without surgery.

Data Collection and Analysis

We collected patient data from our database and evaluated the cause of death. In patients who were lost to follow-up evaluation from our hospital, we performed telephone interviews of the patient, patient's family, or referred hospital about the clinical course and the cause of death. Pancreatic cancer death was defined as histologic evidence of pancreatic adenocarcinoma or documented peritoneal carcinomatosis or metastasis before death. All other deaths were considered non–pancreatic cancer–related deaths. We compared the baseline characteristics of patients who underwent surgery (surgery group) and those who did not (nonsurgery group), and then evaluated the cumulative incidence of pancreatic cancer death in patients who did and did not undergo surgery by using the Fine and Gray competing risk regression model.

Propensity Score Matching

To eliminate bias caused by treatment selection at the time of IPMN diagnosis, we calculated the propensity score for undergoing surgery at the time of diagnosis for each patient by multiple logistic regression models. The following variables were used in calculation of the propensity score: age, sex, body mass index, diagnostic clues, history of smoking, family history of pancreatic cancer, history of diabetes mellitus, comorbidity score by adult comorbidity evaluation-27,[13] cyst diameter, MPD diameter, mural nodules, multiple IPMNs, location of IPMN, MPD-type IPMN, a hypoattenuating area on computed tomography (CT) that suggests invasive cancer,[14,15] and date of diagnosis. We matched the patients in the surgery group with those in the nonsurgery group in up to a 1:1 ratio using the calculated propensity score by optimal matching methods. This approach minimized the overall distance between observations and was conducted using a Mahalanobis distance within 0.2 SDs of propensity score calipers (no matches outside the calipers). After optimal matching, we compared the baseline characteristics and the adjusted cumulative incidence of pancreatic cancer death between groups.

Statistical Analysis

Continuous variables were described using medians and interquartile ranges and compared using the Student *t* test or the Wilcoxon–Mann–Whitney test. Categoric variables were given as proportions and compared using the chi-square test or the Fisher exact test. The adjusted hazard ratios for pancreatic cancer–specific mortality with the associated 95% confidence intervals (CIs) and *P* values

Table 1. Patient Characteristics Before Matching (N = 243)

	Surgery (59 patients)	Nonsurgery (184 patients)	*P* value
Mean age, *y* (SD)	66.6 (9.1)	69.8 (10.4)	.034
Male, n (%)	42 (71)	114 (62)	.193
Mean BMI, kg/m^2 (SD)	22.1 (2.9)	22.0 (3.4)	.916
Diagnostic clues, n (%)			.124
Symptoms	13 (22)	19 (10)	
Medical check-up	14 (24)	39 (21)	
Other diseases	27 (46)	108 (59)	
Unknown	5 (8)	18 (10)	
Smoking history, n (%)	39 (66)	89 (49)	.017
Family history of PC, n (%)	1 (2)	10 (5)	.304
Diabetes mellitus, n (%)	18 (31)	59 (32)	.823
Comorbidity (ACE-27), n (%)			.160
None	15 (25)	55 (31)	
Mild	22 (37)	49 (27)	
Moderate	14 (24)	33 (18)	
Severe	8 (14)	44 (24)	
Median diameter of cyst, *mm* (IQR)	35 (20–42)	31 (24–38)	.628
Cyst >30 mm, n (%)	38 (64)	131 (71)	.329
Median diameter of MPD, *mm* (IQR)	7 (3–10)	3 (2–6)	.001
MPD >6 mm, n (%)	35 (59)	47 (26)	<.001
Presence of mural nodule, n (%)	33 (56)	37 (20)	<.001
Multiple, n (%)	17 (29)	75 (41)	.096
Location of IPMN, head, n (%)	37 (63)	145 (79)	.016
MPD type, n (%)	14 (24)	20 (11)	.018
Hypoattenuating area on CT, n (%)	10 (17)	10 (5)	.009
Date of diagnosis			.563
≤2001	10 (17)	38 (21)	
2002–2006	20 (34)	70 (38)	
≥2007	29 (49)	76 (41)	
Median follow-up period, mo (IQR)	44 (27–88)	46 (24–81)	.478
Mean propensity score (SD)	0.448 (0.253)	0.176 (0.175)	<.001

ACE, adult comorbidity evaluation; BMI, body mass index; IQR, interquartile range; PC, pancreatic cancer; SD, standard deviation.