intermediate invasion as PNI2. However, only 20 percent of PNI cases were classified as PNI2 and 3, and there were no significant differences in outcome among these grades (data not shown). This indicates that the presence, rather than the extent, of cancer invasion to Auerbach's plexus is important for prognosis.

CONCLUSIONS

Cancer invasion to Auerbach's plexus is an important prognostic factor for colorectal cancer, and this should form the basis for defining PNI.

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J Hepatobiliary Pancreat Surg
DOI 10.1007/s00534-009-0173-8

Inferior head resection of the pancreas for intraductal papillary mucinous neoplasms

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Received: 1 July 2009 / Accepted: 10 July 2009

Abstract
Background Previous reports have suggested that patients with intraductal papillary mucinous neoplasm (IPMN) have a favorable prognosis after surgical resection. Thus, a variety of types of partial pancreatic resections have been advocated for treating these low-grade malignant tumors. However, the surgical outcome of IPMN after such limited pancreatectomy has not been fully clarified.
Methods We performed a retrospective review of the clinicopathologic features and surgical outcome in 15 patients who underwent inferior head resection for IPMN at the Chiba University Hospital and National Cancer Center Hospital East between July 1994 and January 2007.
Results There were 13 patients with noninvasive IPMNs (10 adenomas and 3 noninvasive carcinomas) and 2 patients with minimally invasive intraductal papillary mucinous carcinoma (minimally invasive IPMNs). Complete tumor removal (R0 resection) was performed in four patients (80%) with intraductal papillary mucinous carcinoma. Subsequent pancreatoduodenectomy was performed in one patient because of noninvasive carcinoma with multiple mucous lakes in the pancreatic parenchyma. Values for *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid excretion test results before ($n = 13$) and after ($n = 13$) the operation were 70.7 and 66.1, showing no significant difference. The 2-h glucose levels in the 75 g oral glucose tolerance test before ($n = 13$) and after ($n = 13$) the operation were 133 and 146 mg/dl, respectively, showing no significant difference. Pancreatic fistula occurred in 7 (47%) patients. Overall morbidity and mortality rates were 67 and 0%, respectively. The overall 1-, 3-, 5-, and 10-year survival rates for the 15 patients were 100, 79, 79, and 71%, respectively. The 1-, 3-, 5-, and 10-year survival rates for patients with noninvasive IPMN ($n = 13$) and those with minimally invasive IPMN ($n = 2$) were 100, 92, 92, and 83%; and 100, 0, 0, and 0%, respectively. There was a significant difference in survival between patients with noninvasive IPMN and those with minimally invasive IPMN ($p = 0.0005$). No patient with noninvasive IPMN developed recurrent disease. One patient with minimally invasive IPMN died of recurrent peritoneal dissemination 18 months after margin-positive R1 resection. Two patients died of pancreatic ductal adenocarcinoma, 30 and 78 months after inferior head resection.
Conclusions Pancreatic endocrine and exocrine function was well preserved after inferior head resection. Pancreatic fistula occurred more frequently after inferior head resection than with conventional pancreatoduodenectomy. Patients with noninvasive IPMN had favorable survivals after this procedure. However, one patient with minimally invasive IPMN with margin-positive R1 resection died of recurrent disease. Thus, margin-negative R0 resection should be performed for IPMN.

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Published online: 29 August 2009

Keywords Intraductal papillary mucinous neoplasm · Resection of inferior head of the pancreas · Ventral pancreatectomy · Pancreatic resection · Pancreatic ductal adenocarcinoma

Introduction

An increasing number of cases of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas have been reported in recent years [1–13]. Histopathologic studies have revealed that IPMN shows a spectrum of epithelial dysplasia ranging from adenoma to invasive carcinoma. The presence of an invasive component is strongly associated with poor survival [14–17]. In contrast, patients with a noninvasive neoplasm, such as adenoma or noninvasive carcinoma, have a favorable prognosis after surgical resection [17–19]. Thus, a variety of types of partial pancreatic resections have been advocated for treating these low-grade malignant tumors [20–24]. However, the appropriate indications and the surgical outcome of such limited partial pancreatectomies have not been fully clarified because of the limited number of cases. Accordingly, we performed a retrospective review of the clinicopathologic features and outcome in 15 patients who underwent inferior head resection for IPMN.

Patients and methods

Fifteen consecutive patients with IPMN who underwent inferior head resection at the Chiba University Hospital and National Cancer Center Hospital East between July 1994 and January 2007 were retrospectively analyzed. Both the uncinate process and the pancreatic parenchyma around the duct of Wirsung were resected in the inferior head resections. After excision of the inferior head of the pancreas, pancreaticojejunostomy or pancreaticoduodenostomy was performed. The details of this procedure have been described in a previous report [22]. Patient follow up ranged from 24 to 164 months (median 81 months). Overall survival analysis included all deaths, including deaths due to an unrelated cause. IPMN was classified as noninvasive IPMN ($n = 13$) or minimally invasive intraductal papillary mucinous carcinoma (minimally invasive IPMN) ($n = 2$). Noninvasive IPMN was subdivided into adenoma ($n = 10$) and noninvasive carcinoma ($n = 3$) according to the *Classification of pancreatic carcinoma* proposed by the Japan Pancreas Society [25]. Histopathologic findings were evaluated according to this classification.

Exocrine and endocrine pancreatic function was evaluated by the *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (BT-PABA) excretion test and the 75-g oral glucose tolerance test (OGTT). Statistical analysis was performed by Student's *t* test. Cumulative survival rates were generated by the Kaplan–Meier method. The survival curves were compared by the log-rank test. Differences were considered significant at $p < 0.05$.

Results

The characteristics of the patients with IPMN who underwent inferior head resection are shown in Table 1. There were 13 men and 2 women, and the mean age of patients with IPMN was 64 years. Six patients (40%) had abdominal pain and 9 (60%) had no symptoms. The mean size of the tumor was 3.2 cm (range 1.0–6.4 cm), and the mean diameter of the main pancreatic duct was 5.8 mm (range 2.0–13 mm). There was no significant difference in tumor size or in the diameter of the main pancreatic duct between patients with noninvasive IPMN and those with minimally invasive IPMN. All tumors were classified as branch-duct type. The surgical margin was positive for adenoma in three patients with noninvasive IPMN and one patient with minimally invasive IPMN. The surgical margin was positive for carcinoma in one patient with minimally invasive IPMN. Intraoperative frozen section was not performed in this patient. Complete tumor removal (R0 resection) was performed in four patients (80%) with intraductal papillary mucinous carcinoma. No patient had lymph node metastasis. Subsequent pancreatoduodenectomy was performed in one patient because of noninvasive carcinoma with multiple mucous lakes in the pancreatic parenchyma. BT-PABA excretion test results before ($n = 13$) and after ($n = 13$) the operation were 70.7 and 66.1, showing no significant difference. The 2-h glucose levels of the 75-g OGTT before ($n = 13$) and after ($n = 13$) the operation were 133 and 146 mg/dl, respectively, showing no significant difference.

Pancreatic fistula occurred in 7 of the 15 patients (47%). Two patients underwent reoperation for intraabdominal hemorrhage due to pancreatic fistula. Delayed gastric emptying and bile leakage occurred in one patient. There were no in-hospital deaths. Overall morbidity and mortality rates were 67 and 0%, respectively.

The survival curves following inferior head resection are shown in Fig. 1. The overall 1-, 3-, 5-, and 10-year survival rates for the 15 patients were 100, 79, 79, and 71%, respectively. The 1-, 3-, 5-, and 10-year survival rates for patients with noninvasive IPMN ($n = 13$) and those with minimally invasive IPMN ($n = 2$) were 100, 92, 92, and 83%; and 100, 0, 0, and 0%, respectively. There was a significant difference in survival between the patients with noninvasive IPMN and those with minimally invasive IPMN. Regardless of the margin status for adenoma, no patient with noninvasive IPMN developed recurrent

Table 1 Characteristics of patients with intraductal papillary mucinous neoplasm who underwent inferior head resection

	Total ($n = 15$)	Noninvasive ($n = 13$)	Minimally invasive ($n = 2$)
Age, years (mean)	64	64	64
Gender (male/female)	13/2	11/2	2/0
Symptoms (%)			
Abdominal pain	6 (40%)	5 (38%)	1 (50%)
Back pain	1 (7%)	0	1 (50%)
General malaise	1 (7%)	1 (8%)	0
No symptoms	9 (60%)	8 (62%)	1 (50%)
Size, cm (mean)	3.2 (range 1.0–6.4)	3.1 (range 1.0–6.4)	3.7 (range 2.5–4.8)
Diameter of MPD, mm (mean)	5.8 (range 2.0–13)	5.4 (range 2.0–8.0)	8.0 (range 3.0–13)
Tumor type			
Branch-duct type	15	13	2
Histological findings			
Adenoma	10	10	0
Adenocarcinoma	5	3	2
Margin status			
Positive for adenoma	4	3	1
Positive for carcinoma	1	0	1
Subsequent PD	1	1	0
Number of recurrences	1	0	1

PD pancreatoduodenectomy, *MPD* main pancreatic duct

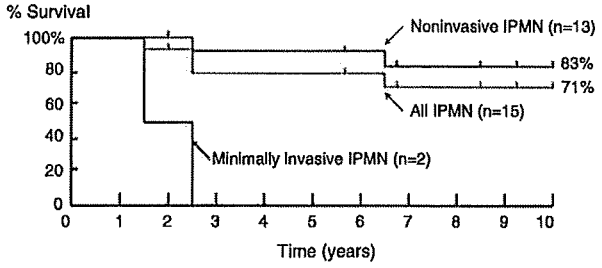

Fig. 1 Survival rates for patients with noninvasive intraductal papillary mucinous neoplasm (*IPMN*; $n = 13$) and those with minimally invasive IPMN ($n = 2$)

disease. In contrast, one patient with minimally invasive IPMN died of recurrent peritoneal dissemination 18 months after margin-positive R1 resection. Two disease-free patients with adenoma died of unrelated causes; invasive ductal adenocarcinoma of the body of the pancreas 78 months after the inferior head resection, and respiratory failure 30 months after the operation. One disease-free patient with noninvasive carcinoma died of cerebral infarction 164 months after the operation. One disease-free patient with minimally invasive carcinoma died of invasive ductal adenocarcinoma of the head of the pancreas 30 months after the inferior head resection. Histological examination revealed a distinct difference in findings between minimally invasive IPMN and invasive ductal adenocarcinoma (Fig. 2a, b).

Discussion

We have herein reported the surgical outcome of IPMN after inferior head resection of the pancreas. This procedure removes the uncinate process and the pancreatic parenchyma around the duct of Wirsung [22]. The duodenum, bile duct, and superior part of the pancreatic head around the duct of Santorini are preserved. Thus, this is a type of duodenum-preserving partial pancreatic head resection. Because the field of resection is reduced in this procedure, pancreatic endocrine and exocrine function is well preserved after the operation.

Previous reports have suggested that patients with noninvasive IPMN have a favorable prognosis after surgical resection [16–19]. Thus, a variety of types of partial pancreatic resections have been advocated for treating these low-grade malignant tumors [20–24]. Takada [20] presented the procedure of ventral pancreatectomy. He resected only the ventral segment of the pancreas, without an anastomosis between the main pancreatic duct and the gastrointestinal tract. The field of resection in inferior head resection is similar to that in ventral pancreatectomy. Takada [20] and Ryu et al. [21] reported that the ventral and dorsal segment could be surgically separated, because the pancreas is formed by the fusion of the ventral and dorsal pancreatic anlagens. However, it might be difficult to accurately determine the demarcation between the ventral segment and the dorsal segment.

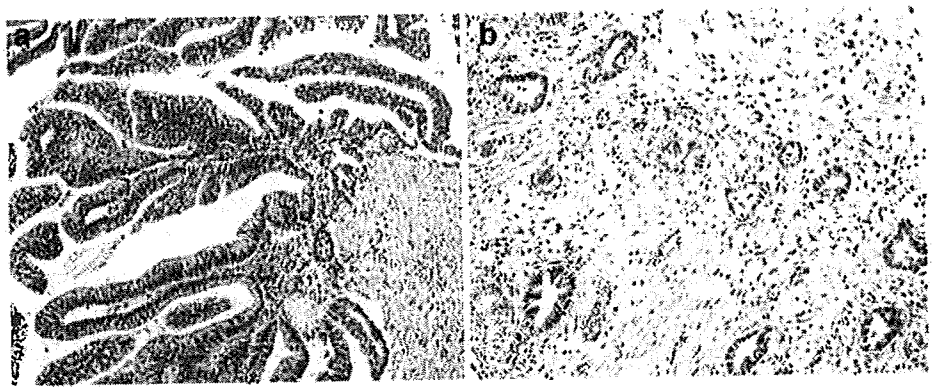

Fig. 2 Histological examination revealed a distinct difference in findings between minimally invasive IPMN and invasive ductal adenocarcinoma. **a** Microscopic findings of IPMN. Histological examination revealed marked papilla formation with significant architectural and nuclear atypia (hematoxylin and eosin, magnification ×100). **b** Microscopic findings of peritoneal dissemination from invasive ductal adenocarcinoma of the head of the pancreas. Histological examination showed moderately differentiated tubular adenocarcinoma with an intense desmoplastic reaction (hematoxylin and eosin, magnification ×100)

In the present study, overall morbidity and mortality after inferior head resection were 67 and 0%, respectively. Pancreatic fistula occurred more frequently with the inferior head resection than with conventional pancreatoduodenectomy. The wider cut surface of the pancreas after inferior head resection may lead to more frequent pancreatic fistula formation. Small branches of the pancreatic duct should be ligated or transfixed with many fine sutures during division of the pancreatic head. Furthermore, subsequent pancreatoduodenectomy was performed in one patient with noninvasive IPMN, because histological examination revealed multiple mucous lakes in the pancreatic parenchyma.

Intraductal papillary mucinous neoplasm is frequently classified as noninvasive IPMN and invasive IPMN. An indolent character and favorable outcome for noninvasive IPMN have been described recently [16–19]. In contrast, poor survival results have been reported for invasive IPMN [14–16, 26]. In the present study, the 5-year survival rate for noninvasive IPMN was 92%. In this study, regardless of the margin status for adenoma, no patient with noninvasive IPMN developed recurrent disease. Patients with noninvasive IPMN showed favorable survival after inferior head resection. However, one patient with minimally invasive IPMN with margin-positive R1 resection died of recurrent disease. Previous reports have suggested that patients with minimally invasive IPMN had favorable survivals compared with survivals in those with noninvasive IPMN [17–19]. Thus, better survival results could be achieved by margin-negative R0 resection even in minimally invasive IPMN. Care must be taken to ensure complete extirpation with a free margin. Frozen sections of the surgical margin would be useful for evaluating the margin status of IPMN [27]. If the transection margins in frozen sections are involved with carcinoma, such limited resections should be avoided, and pancreatoduodenectomy should be performed for IPMN. Further studies are needed to evaluate the efficacy of limited partial pancreatic resection for IPMN.

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Evaluation of the Prognostic Factors and Significance of Lymph Node Status in Invasive Ductal Carcinoma of the Body or Tail of the Pancreas

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Objective: We evaluated prognostic indicators for distal pancreatectomy with regional lymph node dissection in pancreatic body or tail carcinoma.

Methods: Between 1993 and 2008, 50 patients with ductal carcinoma of the body or tail of the pancreas who underwent distal pancreatectomy with regional lymph node dissection were retrospectively analyzed. Clinicopathological factors associated with patient survival were evaluated.

Results: No in-hospital deaths occurred among the study patients. The overall 5-year survival rate was 19.3%, and median survival was 22.6 months. Univariate analysis revealed that lymph node metastasis, intrapancreatic neural infiltration, peripancreatic nerve plexus infiltration, and tumor differentiation affected patient survival significantly. Multivariate analysis validated lymph node metastasis as an independent prognostic factor. Moreover, the lymph nodes attached to the pancreas were the most frequent metastatic nodes, and the number of metastasis in the lymph nodes attached to the pancreas was significantly associated with survival after surgical resection.

Conclusions: Lymph node metastasis was a significant and independent prognostic factor for the surgically resected pancreatic body or tail carcinoma. Furthermore, the lymph nodes attached to the pancreas were the most frequent metastatic nodes, and these lymph nodes were potential indicators predicting both tumor extension and survival after surgery for pancreatic body or tail carcinoma.

Key Words: pancreas cancer, distal pancreatectomy, lymph node metastasis, pancreatic body and tail of carcinoma, lymph nodes attached to the pancreas

(*Pancreas* 2010;39: e48–e54)

Despite recent advances in diagnostic imaging and chemotherapeutic treatment strategies, carcinoma of the pancreas remains a challenging disease. In particular, carcinoma located in the distal pancreas is usually diagnosed at an advanced stage, and a lower survival rate has been reported even in surgically resected cases.[1–3] Accumulating evidence suggests that successful surgical resection is one of the most important parameters in the treatment of pancreatic cancers.[4,5] For pancreatic carcinoma of the body or tail, distal pancreatectomy with dissection of the regional lymph nodes is a common procedure. However, regardless of the multidisciplinary treatment strategy, the outcomes for patients with pancreatic body or tail carcinoma are unsatisfactory, even when aggressive surgical resection is performed.[4,5]

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Previous studies involving a small number of patients have demonstrated that 5-year survival rates are around 10% in pancreatic cancer resected by distal pancreatectomy.[2,5] However, little is known about the prognostic indicators in patients who undergo surgery for carcinoma of the pancreatic body or tail. Moreover, although the status of lymph node involvement is an important parameter in determining progression of the disease, few reports demonstrate the frequency and pathway of lymph node metastasis in pancreatic body and tail carcinoma. The aim of this study was to evaluate the clinicopathological features and long-term outcomes in patients with pancreatic body or tail carcinoma after distal pancreatectomy with regional lymph node dissection. Furthermore, we discuss the frequency of lymph node involvement and its significance with respect to patient survival.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of patients who underwent distal pancreatectomy for pancreatic body or tail carcinoma between November 1993 and June 2008. During this period, a total of 534 patients had a diagnosis and underwent pancreatic resection. Among these, 67 (12.5%) underwent distal pancreatectomy, and 58 (10.8%) were histologically proven to have ductal adenocarcinoma of the pancreatic body or tail. The patients' medical records were reviewed to identify the clinical stage of the disease, surgical procedures, histopathological findings of the lesions, incidence of postoperative events, and outcome.

Diagnostic Studies

Extent of the tumors was examined preoperatively using conventional ultrasonography, dynamic thin-slice computed tomography, and magnetic resonance imaging. In some cases, endoscopic retrograde pancreatography and angiographic imaging studies were combined to evaluate local tumor extension to major vessels and small hepatic metastases.

In most cases, perioperative washing cytological examination was carried out routinely immediately after laparotomy. Briefly, saline solution was instilled into the pelvis using a bulb syringe, and after agitation of the abdomen, the cytological specimens were aspirated from the pouch of Douglas into a sterile tube. A positive peritoneal cytological finding was not considered to be a contraindication for surgery. Perioperative assessment remained consistent throughout the period of the study.

Surgical Procedure

Surgical procedures consisted of distal pancreatectomy with regional lymph node dissection. Regional (N1) and peripancreatic lymph nodes (N2) were routinely dissected.[6] Lymph nodes

TABLE 1. Patient Characteristics

Variables	n	%
Age, yr		
≤60	18	36
60<	32	64
Sex		
Male	28	56
Female	22	44
Tumor size		
≤4 cm	33	66
>4 cm	17	34
Lymph node status		
Node positive	30	60
Node negative	20	40
Stage of disease*		
IA	3	6
IB	4	8
IIA	8	16
IIB	31	62
III and IV	4	8

*Sixth UICC classification system.

along the common hepatic artery, splenic artery, or inferior margin of the pancreas, or those at the splenic hilum, were classified as belonging to the regional lymph node group, N1. Lymph nodes along the left gastric artery, around the celiac artery, along the superior mesenteric artery, or along the middle colic artery were classified as belonging to the peripancreatic lymph node group, N2. The precise areas of the paraaortic lymph nodes (N3) were defined according to the fifth edition of the *General Rules for the Study of Pancreas Cancer*,[7] in which lymph nodes located along the aorta and between the superior and inferior mesenteric arteries are classified as N3 paraaortic nodes.

Histopathological Evaluation of the Resected Specimens

Histopathological findings that potentially affect patient survival were classified as follows: tumor size, serosal invasion, retropancreatic tissue invasion, splenic or portal vein invasion, splenic artery invasion, extrahepatic nerve plexus invasion, lymph node involvement, differentiation of the tumor, lymphatic invasion, venous invasion, and intrapancreatic nerve invasion. Histopathological evaluation was carried out by at least 2 specialized pathologists. Pancreatic cancer occasionally involves small lymph nodes located below the serosal layer of the pancreas with close attachment to the pancreatic parenchyma, and precise determination of the anatomical location of these nodes is usually difficult. Therefore, for detailed evaluation of lymph node metastasis, we subdivided the regional N1 lymph nodes into the lymph nodes attached to the pancreas and other nodes. Lymph nodes attached to the pancreas were defined as a group of lymph nodes having both of the following features: (1) located under the serosal layer of the pancreas and (2) within 3 mm of the parenchyma, being recognized only on histopathological evaluation. The tumors were staged according to the sixth edition of the Union Internationale Contre le Cancer (UICC) TNM classification system.[8]

Statistical Analysis

Survival estimates were calculated using the Kaplan-Meier method. All univariate comparisons of the survival curves were made using the log-rank test. Associations were considered statistically significant if $P \leq 0.05$. A multivariate regression analysis was carried out using the Cox proportional hazards model, and variables with a $P < 0.05$ were entered into the final model. All statistical analyses were performed using SPSS for Windows version 11.5 software (SPSS, Chicago, Ill).

RESULTS

Follow-up of the patients, including clinical evaluation and laboratory tests, was carried out, and adequate survival data were obtained for 50 of 58 patients who underwent distal pancreatectomy and had a histological diagnosis of ductal adenocarcinoma of the body or tail of the pancreas.

Patient characteristics of these 50 patients are shown in Table 1. Fifty-six percent of the patients were men, and 44% were women; the mean age of all patients was 64.2 years (range, 40–81 years). Thirty-three patients (66%) had tumors smaller than 4 cm in diameter, and 27 patients (34%) had larger tumors, and mean diameter was 40.2 cm. Ninety percent of patients underwent R0 resection of the tumor, whereas the remaining 10% of the patients underwent R1 resection. No in-hospital deaths occurred. Histopathological evaluation of the resected specimens revealed that 30 patients (60%) had metastatic lymph nodes. The disease stage was classified according to the sixth edition of the UICC TMN classification system.[8] Three patients (6%) had a diagnosis of stage IA; 4 (8%), stage IB; 8 (16%), stage IIA; 31 (62%), stage IIB; and 4 (8%), stage III or IV.

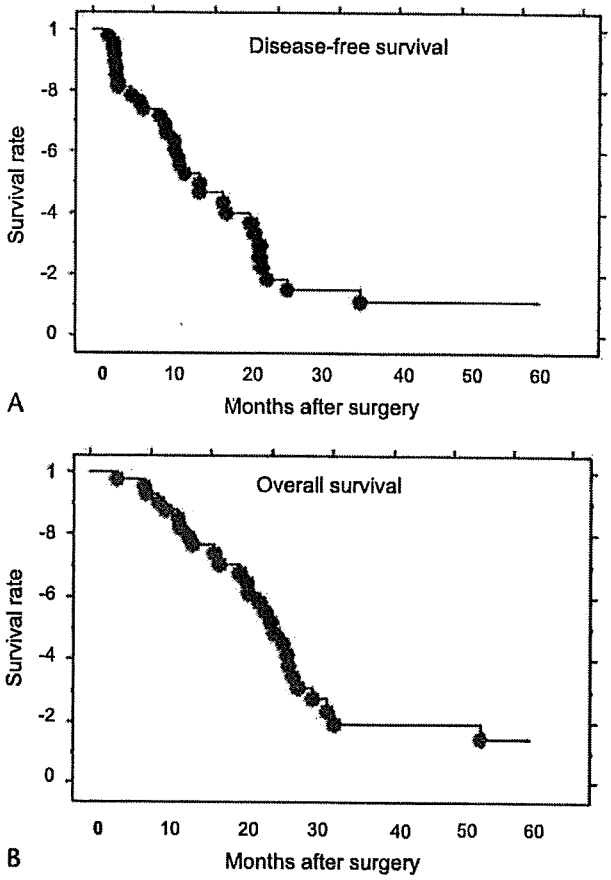


FIGURE 1. Five-year disease-free (A) and overall survival (B) curves (Kaplan-Meier) for 50 patients who underwent pancreatectomy for ductal adenocarcinoma of the body or tail of the pancreas.

Cumulative survival curves are shown in Figure 1. Disease-free survival rates were 52.6%, 14.7%, and 11.1%, and overall survival rates were 84.8%, 55.1%, and 19.3%, at 1, 3, and 5 years, respectively. The median survival time was 22.6 months. One patient (2.0%) survived for more than 10 years, and 3 patients (6.0%) survived for more than 5 years. Eighteen patients (36%) had no postoperative tumor recurrence during the follow-up period. The median follow-up period was 22.2 months (range, 1–139.8 months).

To explore their potential prognostic significance, various clinical and pathological parameters (tumor size; serosal, retropancreatic tissue, splenic vein, splenic artery, extrapancreatic nerve plexus, lymphatic, venous, and intrapancreatic nerve invasions; tumor differentiation; and lymph node metastasis) were investigated. The results of the log-rank test are shown in Table 2. Results of the univariate analysis revealed that factors such as extrapancreatic nerve plexus invasion ($P = 0.006$), intrapancreatic nerve invasion ($P = 0.024$), tumor differentiation (grade 1 vs 2 or 3; $P = 0.018$), and the status of lymph node metastasis ($P = 0.011$) were significant indicators of survival in patients after operation.

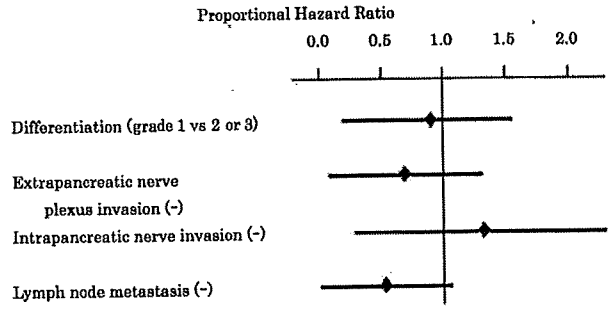
TABLE 2. Prognostic Factors of Survival in Distal Pancreatectomy Univariate Analysis

Variables	n	1-yr Survival, %	5-yr Survival, %	P
Tumor size				NS
≤4 cm	33	86.7	24.0	
<4 cm	17	79.2	16.4	
Serosal invasion				NS
Negative	38	83.2	20.6	
Positive	12	82.2	10.4	
Retropancreatic tissue invasion				NS
Negative	17	81.3	27.5	
Positive	33	82.2	10.4	
Splenic vein invasion				NS
Negative	26	82.9	28.9	
Positive	24	88.2	0.0	
Splenic artery invasion				NS
Negative	37	100	20.7	
Positive	13	81.1	0.0	
Extrapancreatic nerve plexus invasion				$P = 0.0067$
Negative	35	88.2	26.6	
Positive	15	76.9	0.0	
Lymphatic invasion				NS
Negative	33	89.5	20.6	
Positive	17	72.9	15.2	
Venous invasion				NS
Negative	19	82.5	36.1	
Positive	31	81.9	12.0	
Intrapancreatic nerve invasion (ne0, 1 vs ne2, 3)				$P = 0.0246$
Negative	23	84.5	36.2	
Positive	27	85.2	6.7	
Differentiation				$P = 0.0183$
Well differentiation	14	100	36.7	
Moderate or poor differentiation	36	77.6	9.1	
Lymph node metastasis				$P = 0.012$
Negative	20	86.7	43.8	
Positive	30	83.9	0.0	

ne indicates intrapancreatic nerve plexus invasion; NS: not significant.

TABLE 3. Multivariate Analysis Using Cox Proportional Hazards Model

Variables	Hazard Ratio	95% CI	P
Differentiation (grade 1 vs 2 or 3)	0.570	0.210–1.548	0.26
Extrapancreatic nerve plexus invasion	0.444	0.160–1.230	0.11
Intrapancreatic nerve invasion (ne0, 1 vs ne2, 3)	0.912	0.315–2.367	0.86
Lymph node metastasis	0.387	0.139–1.035	0.05



The multivariate analysis showed that lymph node status was one of the most important prognostic factors. To evaluate the significance of the status of lymph node metastasis, we further investigated the lymph node status according to the anatomical location of the tumor, based on the categories used to subdivide regional N1 lymph nodes into the lymph nodes attached to the pancreas and other nodes, as described in Materials and Methods. The results for the lymph node status are shown in Figure 2. In total, 1461 lymph nodes were resected from 50 patients (mean, 29.2 nodes per patient), and 89 lymph nodes (6.1%; mean, 1.8 nodes per patient) were histologically diagnosed as metastatic nodes. Of these, the lymph nodes attached to the pancreas were the most frequent node both in the total number of dissected nodes (633/1461 nodes, 43.3%) and in the number of total metastatic lymph nodes (69/89 nodes, 77.5%).

Next, to address the correlation between the location of the tumor and the lymph node status, we classified the tumor location in the pancreas as follows: the body of the pancreas (Pb), the tail of the pancreas (Pt), and both the body and the tail of the pancreas (Pbt). Among the 50 patients, 25 patients (50%) were classified as Pb, 17 patients (34%) as Pbt, and 8 patients (16%) as Pt. Among the Pb cases, 47 lymph nodes were histologically diagnosed as metastatic lymph nodes, primarily comprising the lymph nodes attached to the pancreas (37/47, 78.7%), the lymph nodes along the superior mesenteric artery (3/47, 6.3%), and the lymph nodes around the paraaortic area

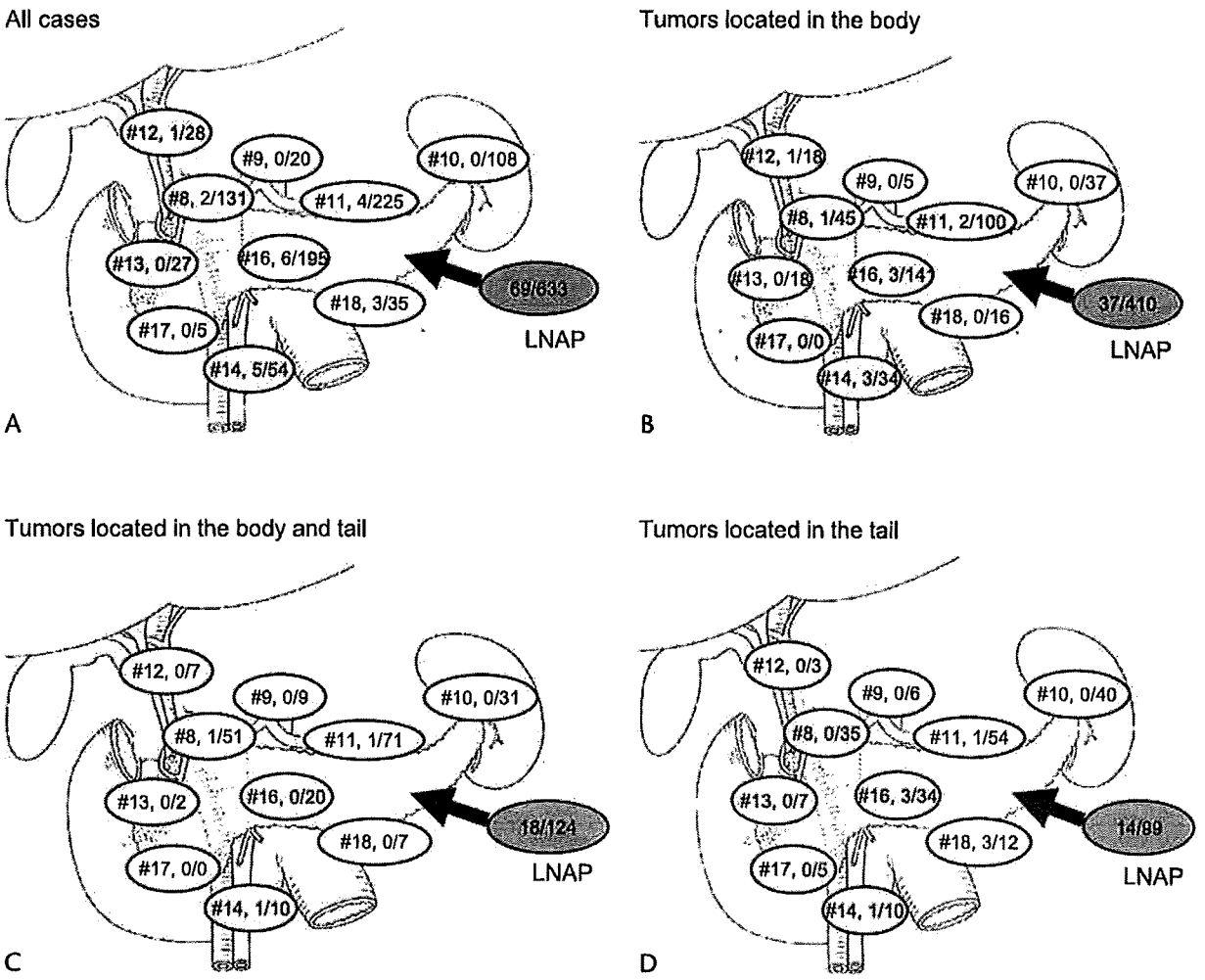


FIGURE 2. Lymph node mapping in distal pancreatectomy in patient with pancreatic body or tail carcinoma (A, all cases; B, tumors located in the body of pancreas; C, tumors located in the body and tail of pancreas; D, tumors located in the tail of pancreas).

(3/47, 6.3%; Fig. 2B). Among the Pbt cases, 21 lymph nodes were microscopically diagnosed as showing tumor metastasis. Most of these metastatic lymph nodes were the lymph nodes attached to the pancreas (18/21, 85.7%), and the remaining metastatic lymph nodes were located along the common hepatic (1/21, 4.7%), splenic (1/21, 4.7%), and superior mesenteric arteries (1/21, 4.7%; Fig. 2C). Among the Pt cases, 22 lymph nodes were microscopically diagnosed as showing tumor metastasis, and these metastatic nodes mostly comprised the lymph nodes attached to the pancreas (14/22, 63.3%), the nodes located around the inferior margin of the pancreas (3/22, 13.6%), and the nodes located around the paraaortic area (3/22, 13.6%; Fig. 2D).

Table 4 shows the distribution and the percentage of the metastatic lymph nodes. For Pb tumors, percentages of lymph node metastasis were higher in the lymph nodes attached to the pancreas (9.0%) and in nodes located along the superior mesenteric artery (8.8%). For Pbt tumors, although the total number of metastatic nodes was small, the nodes attached to the pancreas (14%) and along the superior mesenteric artery (10%) showed a higher percentage of tumor metastasis. For Pt tumors, the lymph nodes attached to the pancreas (9.6%), the nodes along the superior mesenteric artery (9.5%), and the nodes around the inferior margin of the pancreas (8.5%) showed a higher percentage of tumor metastasis. Taken together, the

TABLE 4. Distribution and Percentage of Metastatic Lymph Node in Distal Pancreatectomy for Pancreatic Body or Tail Carcinoma

Lymph Nodes	Pb (%)	Pbt (%)	Pt (%)	Total (%)
8*	1 (2.2)	1 (1.9)	0 (0)	2 (1.5)
9†	0 (0)	0 (0)	0 (0)	0 (0)
10‡	0 (0)	0 (0)	0 (0)	0 (0)
11§	2 (2.0)	1 (1.4)	1 (1.8)	4 (1.7)
12‖	1 (5.5)	0 (0)	0 (0)	1 (3.5)
13¶	0 (0)	0 (0)	0 (0)	0 (0)
14#	3 (8.8)	1 (10)	1 (10)	5 (9.2)
16**	3 (2.1)	0 (0)	3 (8.8)	6 (3.0)
17††	0 (0)	0 (0)	0 (0)	0 (0)
18‡‡	0 (0)	0 (0)	3 (25)	3 (8.5)
Nodes attached to the pancreas	37 (9.0)	18 (14)	14 (14)	69 (9.6)
Total	47 (5.7)	21 (6.3)	22 (7.2)	90 (6.1)

*Lymph nodes along the common hepatic artery.
†Lymph nodes around the celiac artery.
‡Lymph nodes at the splenic hilum.
§Lymph nodes along the splenic artery.
‖Lymph nodes around the hepatoduodenal ligament.
¶Lymph nodes around the dorsal head of the pancreas.
#Lymph nodes around the superior mesenteric artery.
**Lymph nodes around the paraaortic area.
††Lymph nodes around the ventral head of the pancreas.
‡‡Lymph nodes at the inferior margin of the pancreas.

percentage of the metastatic lymph nodes was 6.1% among all the dissected lymph nodes, and both the number and the percentage of metastatic lymph nodes were highest in the lymph nodes attached to the pancreas for all tumor locations.

Because both the number and the percentage of metastases in the lymph nodes attached to the pancreas were greater compared with that in the other N1 regional nodes, regardless of tumor location, and because lymph node metastasis was an important prognostic indicator in pancreatic body or tail carcinoma, we focused further on the lymph nodes attached to the pancreas to evaluate their potential prognostic impact in patients who underwent distal pancreatectomy. Figure 3 shows the overall survival curves related to the status of the lymph nodes attached to the pancreas in patients who underwent distal pancreatectomy. As shown in Figure 3A, significantly better survival ($P < 0.05$) was observed in patients with no metastasis in the lymph nodes attached to the pancreas. Furthermore, we examined the status of the lymph node attached to the pancreas to determine whether it affected the frequency of metastasis in extrapancreatic nodes. As shown in Figure 3B, among patients with no positive lymph nodes attached to the pancreas, 6.5% showed extrapancreatic lymph node metastasis, whereas 48.5% of patients with positive lymph nodes attached to the pancreas showed extrapancreatic metastasis, a statistically significant result ($P < 0.05$). Figure 3C shows the overall survival curves in patients with no metastatic nodes attached to the pancreas, with 1 to 2 metastatic nodes attached to the pancreas and with 3 or more metastatic lymph nodes. Significantly worse survival was observed in patients with 3 or more positive lymph nodes attached to the pancreas ($P < 0.01$) compared with the other groups. Indeed, when patients were categorized into 2 groups (metastasis involving 0–2 nodes attached to the pancreas vs ≥3 nodes attached to the pancreas), significantly better survival was observed in patients with metastasis involving 0 to 2 lymph nodes attached to the pancreas ($P < 0.001$; Fig. 3D). The multivariate analysis using the Cox proportional hazards model demonstrated that the presence of 3 or more positive lymph nodes attached to the pancreas was an independent prognostic factor in patients who underwent distal pancreatectomy for pancreatic carcinoma of the body or tail (HR, 0.349; 95% CI, 0.134–0.906; $P = 0.03$; Table 5).

DISCUSSION

Ductal adenocarcinomas of the body or tail of the pancreas are usually diagnosed at an advanced stage, which frequently results in unresectable disease due to extrapancreatic tumor involvement or distant metastasis. A prior study evaluating a large series of patients in the United Kingdom demonstrated that resection of pancreatic carcinoma of the body or tail was achieved in less than 10% of patients.[9–11] Despite multidisciplinary treatment strategies, the prognosis for patients with ductal adenocarcinoma of the body or tail of the pancreas is dismal. Previous studies have reported that 5-year survival rates ranged from 10% to 22%, and median postoperative survival was 11 to 16 months for patients with pancreatic body or tail carcinoma.[1,3–5,12,13] A recent report from a Japanese investigator demonstrated a 5-year survival rate of 19% and median survival of 22 months for patients who underwent pancreatectomy with extended lymphadenectomy for ductal adenocarcinoma of the body or tail of the pancreas. In the present study, 5-year overall survival was 19.3% and median survival term was 22.6 months,[4] which is compatible with the results of the previous studies.

In the treatment of pancreatic carcinoma, chemotherapeutic agents are becoming a more important option. The results of recent studies demonstrated that adjuvant chemotherapy could improve patient survival in pancreatic cancers.[14,15] Previous studies have shown significant improvement in survival for patients with pancreatic cancer who received adjuvant chemotherapy after R0/R1 resection for pancreatic cancer,[16] and a recent trial has also demonstrated the beneficial effect of adjuvant chemotherapy.[17] Thus, although the improvement in survival obtained by adjuvant chemotherapy is not yet satisfactory, it is clear that adjuvant chemotherapy is essential in the treatment of pancreatic cancer.

Clinicopathological features in patients with ductal adenocarcinoma of the head of the pancreas have been widely investigated, whereas prognostic factors in patients with ductal adenocarcinoma of the body or tail of the pancreas, particularly based on evaluation of the frequency of lymph involvement, have not been fully addressed. Therefore, further investigation is required to elucidate the potential prognostic indicators in patients who undergo surgery for pancreatic carcinoma of the body and tail. To identify the potential prognostic factors, it is necessary to understand the clinicopathological features and patterns of the tumor spread in the distal pancreas. Reflecting the complexity of the anatomical location of the pancreas, extension of the tumors is determined by multiple factors such as vascular or nerve plexus invasion. In the present study, the status of lymph node involvement was found to be one of the most important indicators predicting patient survival after surgery. Indeed, supporting our observation, current reports have indicated that lymph node metastasis is a critical determinant of long-term survival in patients after surgery for pancreatic carcinoma of the body or tail.[4,5] Based on detailed analysis

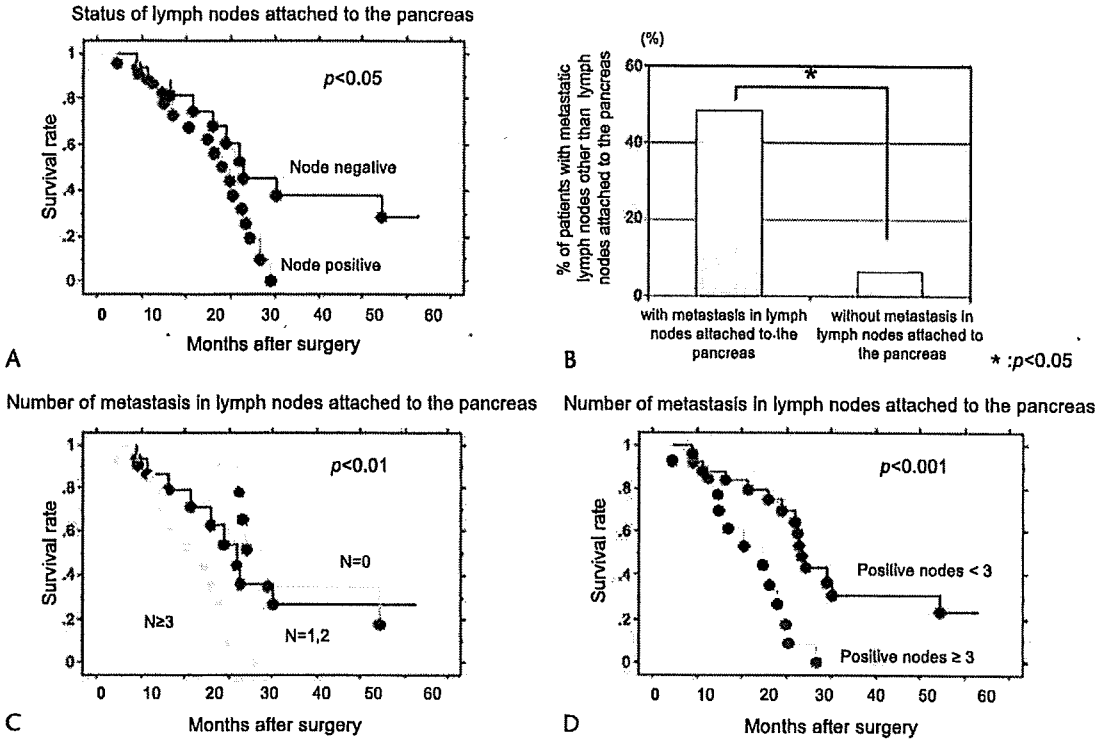


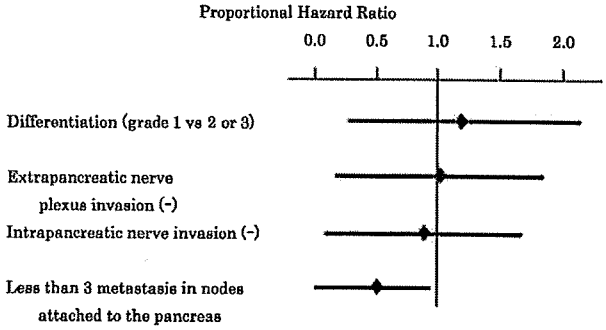
FIGURE 3. Overall survival regarding the status of lymph nodes attached to the pancreas in patients who underwent distal pancreatectomy for pancreatic body or tail carcinoma. A, Five-year overall survival curve for patients who underwent distal pancreatectomy regarding the status of lymph node metastasis. Significant differences are observed between the 2 groups (node positive vs node negative). B, Percentage of patients with metastatic lymph nodes other than lymph nodes attached to the pancreas, regarding the status of the lymph nodes attached to the pancreas. Incidences of metastasis in lymph nodes other than the lymph nodes attached to the pancreas are significantly higher in patients with metastasis in the lymph nodes attached to the pancreas. C, Significantly lower survival rate is observed for patients with 3 or more metastatic lymph nodes attached to the pancreas compared with those with less than 3 metastasis in the lymph node attached to the pancreas. D, Significantly better survival is observed for patients with more than 3 metastases in the lymph node attached to the pancreas.

of surgically resected specimens of pancreatic body or tail carcinoma, Nakao et al[13] reported that a higher incidence of lymph node involvement was observed along the splenic artery and around the superior mesenteric artery. Conversely, a low incidence of lymph node involvement was observed on the inferior pancreatic body, around the common hepatic artery, at the hilum of the spleen, and on the anterior surface of the head of pancreas. Consistent with their observations, the results of our study demonstrated a higher incidence of lymph node metastasis along the superior mesenteric artery and a lower incidence around the anterior surface of the head of pancreas, at the splenic hilum, and along the common hepatic artery. In ductal adenocarcinoma of the pancreatic head, it has been reported that lymphatic flow is strongly suspected from the tumor to the paraaortic lymph nodes via the posterior surface of the pancreatic head and around the superior mesenteric artery.[13,18] The results of the present study suggest that, on the contrary, lymph nodes around the superior mesenteric artery may be one of the major pathways to the paraaortic lymph nodes in ductal adenocarcinoma of the body or tail of the pancreas.

In the present study, the lymph nodes attached to the pancreas were the most frequently dissected nodes among the other regional nodes. For this reason, we investigated the association between tumor progression and the status of these nodes, which were only detectable on histological examination. The existence

TABLE 5. Multivariate Analysis Using Cox Proportional Hazards Model

Variables	Hazard Ratio	95% CI	P
Differentiation (grade 1 vs 2 or 3)	0.724	0.243–2.160	0.56
Extrapancreatic nerve plexus invasion	0.640	0.222–1.846	0.40
Intrapancreatic nerve invasion (ne0, 1 vs ne2, 3)	0.549	0.178–1.698	0.29
Less than 3 metastasis in nodes attached to the pancreas	0.349	0.134–0.906	0.03



of the lymph nodes attached to the pancreas had not been described previously. These nodes can be categorized as lymph nodes along the common hepatic artery, lymph nodes along the splenic artery, or lymph nodes around the inferior margin of the pancreas. Definitive classification of these nodes is difficult; however, based on microscopic evaluation, the regional N1 nodes were subdivided as lymph nodes attached to the pancreas or the other nodes. On microscopic examination, these nodes were found to be (mean ± SD) 2.75 ± 0.73 mm in size, located at a distance of 1.93 ± 0.44 mm from the parenchyma of the pancreas, and mostly undetectable by intraoperative or macroscopic observations. Notably, in both the number of dissected nodes and percentage of metastasis, the lymph nodes attached to the pancreas were found to be the most frequent nodes being considered major lymph nodes in pancreatic body or tail carcinoma.

Several studies have demonstrated the detailed lymphatic pathway of the pancreas.[2,19] The smallest lymphatic vessels, termed *intralobular lymphatics*, start within the lobules of the pancreas, and their blind beginnings lie in the thin and delicate connective tissues surrounding the smallest pancreatic ducts and blood vessels. These earliest lymphatics open into interlobular lymphatics, and larger interlobular lymphatics reach to the surface of the pancreas and enter a surface network of the lymphatic vessels that converge at the lymph node.[19] In the present study, detailed analysis of the distribution of metastatic lymph nodes revealed that the lymph nodes attached to the pancreas are the most frequent nodes removed after distal pancreatectomy. Because the lymph nodes attached to the pancreas are located nearest to the parenchyma of the pancreas among the other regional nodes, it is reasonable to suppose that the lymph nodes attached to the pancreas could be categorized as the earliest surface network nodes to which cancer cells first migrate and create metastatic foci. Furthermore, the results of the present study demonstrated that only 6.5% of patients with no positive nodes attached to the pancreas had extrapancreatic lymph metastasis, whereas 45% of patients with positive nodes attached to the pancreas had extrapancreatic nodal metastasis, a statistically significant result (Fig. 3). Moreover, among patients with positive extrapancreatic nodes, 91.6% (data not shown) of patients demonstrated lymph metastasis in the nodes attached to the pancreas. Given that paraffin-embedded pancreatic tissues were prepared as 5-mm slices and the mean diameter of the lymph nodes attached to the pancreas was less than 3 mm, metastasis in the lymph nodes attached to the pancreas was potentially more frequent in patients with positive extrapancreatic nodes.

Our study had several limitations. Some conditions of the patients may have been falsely diagnosed as negative for the lymph nodes attached to the pancreas because of the small size of both the nodes and the slices prepared for histological evaluation; therefore, excluded information could have biased the results of the study. Furthermore, our study covered an almost 15-year period, during which preoperative diagnostic accuracy and postoperative follow-up regimens differed. However, histopathological explorations were performed consistently, which may even be considered a strength of the study.

In conclusion, the results of our study indicate that (1) the status of lymph node metastasis was an important prognostic factor in patients who underwent distal pancreatectomy for ductal adenocarcinoma of the pancreatic body or tail and (2) the lymph nodes attached to the pancreas were the most frequent nodes in both the number of dissected nodes and percentage of metastasis, and these nodes were potential indicators predicting tumor extension and survival after surgery for patients with carcinoma of the pancreatic body or tail.

ACKNOWLEDGMENTS

The authors thank the members of the Division of Digestive Surgery for their critical discussion of this study. The authors greatly appreciate Drs Atsushi Ochiai and Satoshi Fujii for providing histopathological suggestions. The authors also thank the members of the Division of Hepatobiliary Pancreatic Oncology for providing the clinical information.

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J Hepatobiliary Pancreat Surg
DOI 10.1007/s00534-009-0115-5

ORIGINAL ARTICLE

Incidence, clinical presentation and pathological features of benign sclerosing cholangitis of unknown origin masquerading as biliary carcinoma

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Received: 25 January 2009 / Accepted: 10 March 2009

Abstract
Background Benign obstructions of the liver hilum are occasionally encountered in surgically resected cases. Some of these cases are pathologically classified as benign sclerosing cholangitis and are not clearly categorized. This study aims to elucidate the clinicopathological features of benign sclerosing cholangitis of unknown origin.
Methods Patients who had undergone surgery of the proximal bile duct from 1993 to 2008 on suspicion of proximal bile carcinoma were evaluated, then their clinical presentation, histopathological and immunohistochemical findings were retrospectively analyzed.
Results One hundred seventy-six patients underwent surgery during this period. Of these, five patients were diagnosed with benign sclerosing cholangitis of unknown origin. All five patients were middle-aged with no history of autoimmune disease. One patient died of recurrent cholangitis after surgery. Histopathologically, lymphoplasmacytic infiltrations were observed in all five cases. Among them, the clinicopathological findings of one patient were compatible with IgG4-related sclerosing cholangitis, and the other two patients had unusual histopathological findings with prominent lymph follicular formation.
Conclusions Although patients with benign sclerosing cholangitis of unknown origin comprise a heterogeneous population, they can be further classified into subgroups. The response to immunosuppressive therapy, long-term prognosis and histological morphology of the disease should be considered in order to classify these cases of sclerosing cholangitis.

Keywords Hilar cholangiocarcinoma · Sclerosing cholangitis · IgG4-associated sclerosing pancreatocholangitis · Malignant hilar masquerade

Abbreviations
PSC Primary sclerosing cholangitis
IgG4-SC IgG4-associated sclerosing cholangitis

Introduction

The incidence of benign stricture of the hilar bile duct was reported in approximately 10% of surgically resected cases that were preoperatively diagnosed as cholangiocarcinoma [1–8]. Although secondary sclerosing cholangitis associated with choledocholithiasis and hepatolithiasis is responsible for bile duct stenosis [9, 10], there are still certain benign biliary obstructive conditions whose exact pathogenesis remains unclear and are occasionally diagnosed as non-specific sclerosing cholangitis. Of these, IgG4-related lymphoplasmacytic sclerosing disease was recently found to be responsible for stricture of the bile duct in the context of autoimmune pancreatitis [11, 12]. Current reports have also suggested that IgG4-related lymphoplasmacytic sclerosing disease is responsible for hilar bile obstruction and even for extra-hepatobiliarypancreatic lesions [11, 13].

IgG4-associated autoimmune disease was advocated in the field of autoimmune pancreatitis [12] when focal stricture of the main pancreatic duct was observed not only

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Published online: 28 April 2009

in pancreatic cancer, but also in benign diseases with an autoimmune origin frequently associated with elevation of serum IgG4 levels. Histopathological findings of autoimmune pancreatitis were characterized by lymphoplasmacytic infiltration and categorized as lymphoplasmacytic sclerosing pancreatitis [11, 14]. In nearly half of the autoimmune pancreatitis cases, there are more than 20 IgG4-positive plasma cells per high-power field (h.p.f) [15–17]. Likewise, IgG4-positive plasma cells are prominently observed in lymphoplasmacytic sclerosing cholangitis. However, the way in which large lymphoplasmacytic sclerosing cholangitis is responsible for proximal stricture of the bile duct, which masquerades as hilar cholangiocarcinoma, has not been clarified. In fact, recent reports suggest that inflammatory biliary strictures probably represent a wider variety of pathological processes [3, 4]. This suggests that there are other types of sclerosing cholangitis regardless of the status of IgG4.

This study aims to evaluate the incidence of IgG4-positive sclerosing cholangitis among patients diagnosed with benign sclerosing cholangitis of unknown origin and to summarize the clinicopathological features of this condition. Furthermore, we review the literature and discuss the potential characteristics of this as yet uncategorized disease.

Methods

Patients

Patients who had undergone surgery for proximal biliary strictures were identified retrospectively from the database of the clinical pathology unit of the National Cancer Center Hospital East from October 1993 to July 2008.

Clinical presentation

The preoperative diagnosis was based on preoperative imaging studies, including percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography and conventional cross-sectional imaging studies (computed tomography and magnetic resonance imaging). Proximal bile duct strictures were classified according to the Bismuth–Corlette classification system. The patients' medical records were reviewed for clinical symptoms, surgical procedures, postoperative complications and long-term outcome.

Histopathological and immunohistochemical analysis

With the use of serial sections from paraffin-embedded tissue blocks, immunohistochemical analyses were performed using anti-CD3, CD4, CD8, CD20, CD79a and IgG4 antibodies (Santa Cruz Co., Santa Cruz, CA). Monoclonal antibodies against IgG4 were obtained from The Binding Site (Birmingham, UK). Immunohistochemical staining was performed in the usual manner. Briefly, the deparaffinized sections were microwaved for 20 min in EDTA buffer. After blocking the endogenous peroxidase and incubating in blocking buffer, the sections were incubated overnight with the primary antibody at 4°C. Thereafter, these sections were incubated for 2 h with the secondary antibody at room temperature. Diaminobenzidine tetrahydrochloride was used as the chromogen before counterstaining with hematoxylin (Sigma-Aldrich, St Louis, MO).

The numbers of IgG4-positive cells were counted and evaluated in at least 10 h.p.f and determined as positive in cases with more than 10 cells per h.p.f (Olympus, Tokyo, Japan). The degree of immunohistochemical positivity of cells was classified semiquantitatively. Statistical analysis was performed using the chi-square test, and $P < 0.05$ was considered statistically significant.

Two specialized pathologists (MK and TH) histologically evaluated all stained slides of the lesions. The following features were assessed during the histopathological re-evaluation on a semiquantitative basis: fibrosis (absent, minimal, mild, moderate, severe), lymphoplasmacytic infiltration (absent, minimal, mild, moderate, severe) and formation of lymph follicles (absent, mild, moderate, severe), germinal centers (absent, mild, moderate, severe) and vascular thrombi (absent, mild, moderate, severe). Evaluation of immunohistochemical staining was performed based on the presence or absence of cells positive for the markers. Distributions of IgG4-positive cells were classified as diffuse, focal and scattered.

Results

Patients

From October 1993 to June 2008, 176 patients with proximal biliary strictures underwent surgery at the National Cancer Center Hospital East. Results of histopathological analysis of the resected specimens showed that 155 (88.1%) patients had malignant neoplasms. Seven (4.0%) patients had biliary obstructive disease related to congenital biliary dilatation, two (1.1%) had biliary hamartoma, two (1.1%) had stone disease or its related glanulomatous process, five (2.8%) had other conditions, and five (2.8%) had benign bile stricture of unknown origin.

Five patients had benign nonspecific sclerosing cholangitis: three men and two women with a mean age of 54.8 (range 44–65) years. We further evaluated the clinicopathological characteristics of these five cases.

Clinical presentation

A brief summary of the clinical characteristics of the five patients with benign nonspecific sclerosing cholangitis is shown in Table 1. Obstructive jaundice was the main reason for the consultation for the symptoms in three (60%) patients, and two (40%) patients had abnormal hepatobiliary enzyme levels and a slight elevation of serum total bilirubin. None of the patients had a history of autoimmune-like disease; one patient had a history of gastric cancer. Blood examination showed no abnormal findings concerning anti-nuclear antibodies or other markers of autoimmune disease. The main lesions were located in the liver hilum in four (80%) patients. All five patients had a preoperative diagnosis of cholangiocarcinoma, and stenotic lesions were surgically removed in all cases. Of these patients, two (40%) underwent extended hepatic lobe resections, two (40%) underwent local resection of the liver hilum, and one (20%) underwent modified pancreatoduodenectomy.

The outcomes of the patients are shown in Table 2. At a median follow-up of 59.2 months (range 3–180 months), one patient had died, three were still alive, and one was lost to follow-up. As postoperative complications, two patients (40%) had moderate pancreatic fistula and transient cholangitis, both of which were successfully managed, and no special care was needed. Two patients were administered corticosteroids, and one of them showed moderate response (case 2); the other showed mild response (case 3). Case 3 had a progressive worsening of hepatobiliary enzyme levels 3 months after surgery and eventually died of liver failure of unknown origin.

Histopathological and immunohistochemical findings

A summary of the histopathological findings for these five cases is shown in Table 3. Fibroinflammatory changes were observed under the submucosal layer of the stenotic areas for all patients. Lymphoplasmacytic infiltration of

Table 1 Clinical manifestations

	Age	Gender	Symptom	Location	Surgery	AIDs	Previous history	Duration of symptom (months)
Case 1	44	M	Jaundice	Bismuth IV	Bile duct resection	−	Gastric cancer	4
Case 2	60	M	Jaundice	Bismuth IV	Bile duct resection	−	−	3
Case 3	58	F	Elevation liver enz	Bismuth III	Left hepatectomy	−	−	24
Case 4	65	F	Jaundice	Bismuth I	Pancreato-duodenectomy	−	−	4
Case 5	47	M	Elevation liver enz	Bismuth IV	Right hepatectomy	−	−	36

AIDs autoimmune disease, *NA* not applicable, + present, − absent

Table 2 Patient outcomes

	Postoperative complications	Recurrent cholangitis	Treatment with IST	Response to the IST	Late complications	Overall survival
Case 1	−	−	None	NA	None	Alive (180 months)
Case 2	−	+	Corticosteroids	Moderate	Henoch–Schonlein purpura	Unknown (75 months)
Case 3	Cholangitis	+	Corticosteroids	Mild	Liver failure	Died (24 months)
Case 4	Pancreas fistula	−	None	N/A	None	Alive (14 months)
Case 5	−	−	None	N/A	None	Alive (3 months)

IST immunosuppression therapy, *NA* not applicable

Table 3 Histopathological findings

	Histological diagnosis	Fibrosis	Lymph-plasmocycte infiltration	Lymph follicule	Germinal center	Vascular thrombus	Epithelial surface	Intrahepatic peripheral bile duct
Case 1	BSC	++	+	−	−	−	Intact	Intact
Case 2	BSC	++	++	+	−	++	Intact	Intact
Case 3	BSC	++	+++	+++	++	−	Intact	Intact
Case 4	BSC	++	±	−	−	−	Disappeared	Intact
Case 5	BSC	++	+++	+++	++	−	Intact	Intact

BSC benign sclerosing cholangitis, − absent, ± minimal, + mild, ++ moderate, +++ severe

various degrees was observed in all cases. Two patients (case 1 and 4) had prominent dense fibrosis around the stenotic bile ducts, and scattered lymphoplasmacytic inflammatory foci were observed in the fibrotic areas (Fig. 1a). However, in these two patients, the number of lymphoplasmacytes was much lower than in the other three patients; no lymph follicular formation or vascular phlebitis was observed around the lesion (Fig. 1b, c), and the margin between the fibrotic lesion and periductal area was clearly observed. However, lymph follicle formations were observed in three cases and were particularly prominent in two cases (cases 3 and 5) in which they had germinal centers (Fig. 2a). In these two cases, marked lymph follicles were circumferentially located around the fibroinflammatory layers of the periductal areas (Fig. 2b). These pathological findings were observed only in relatively large-diameter bile ducts (Fig. 2c), with no abnormal findings in the peripheral intrahepatic bile duct.

In case 2, mild lymph follicle and moderate venous thrombus formations were observed in the peripheral intrahepatic lesions (Fig. 3a). Histological examination showed vascular phlebitis and perineural lymph infiltrates (Fig. 3b, c). In all cases, nearly intact or only mildly dysplastic biliary epithelium was observed; no findings indicative of malignant neoplasms were observed. Other histopathological findings, such as "onion-skin" lesions and non-suppurative destructive cholangitis, were not observed in any of the cases.

The results of immunohistochemical staining in the five patients with nonspecific sclerosing cholangitis are summarized in Table 4. One of these patients had a small amount of lymphoplasmacytic infiltration (case 4), while in the remaining four, moderate to severe lymphoplasmacytic infiltration was observed. However, regardless of the number of infiltrating inflammatory cells, the lymphoplasmacytes of all five patients were positive for CD3, CD4, CD8, CD20 and CD79a. In contrast, IgG4-positive lymphoplasmacytes were observed in only one case (case 2) (Figs. 1d, 2d, 3d).

On the basis of histopathological and immunohistochemical analyses, we classified cases of benign sclerosing cholangitis of unknown origin as follows: (1) IgG4-related sclerosing cholangitis, (2) lymphoplasmacytic sclerosing cholangitis with prominent lymph follicules and (3) nonspecific fibroinflammatory cholangitis.

Discussion

The incidence of benign biliary strictures of unknown origin varies between 2.9 and 14.3% in cases of proximal biliary strictures masquerading as cholangiocarcinoma [18]. Two studies, including this one, have described the incidence of proximal biliary strictures masquerading as cholangiocarcinoma in Japanese populations [18]; however, no clear trends were observed in a comparison of this incidence in

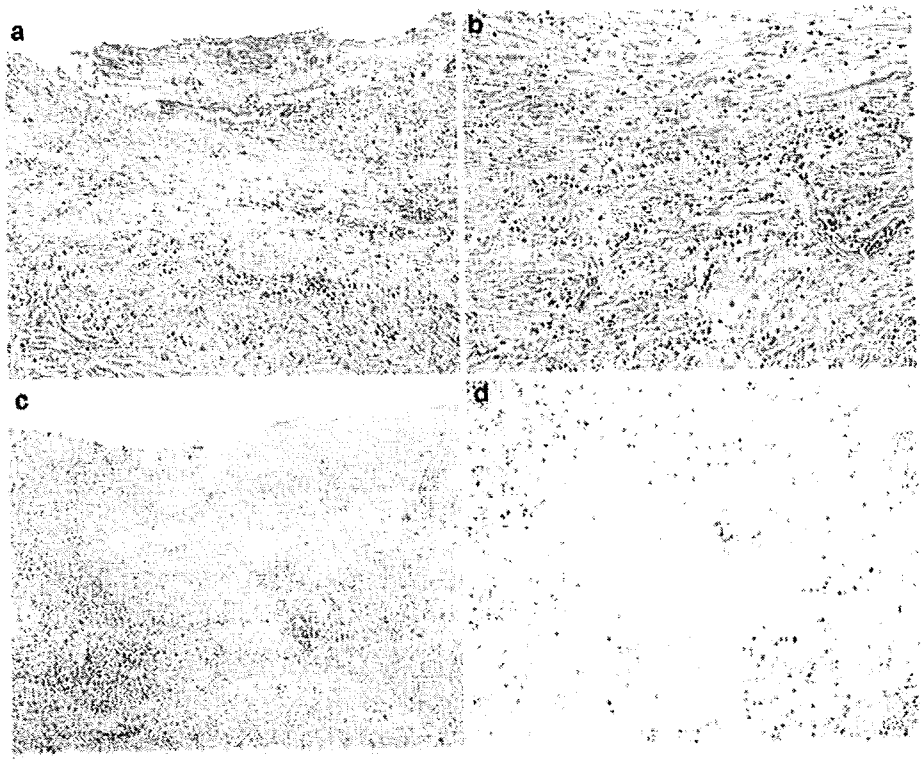

Fig. 1 Histopathological findings of case 1. **a** Stenotic area was composed of dense fibrotic tissue. **b** Scattered lymphoplasmacytic infiltrations were scattered around the inflammatory foci of the stenotic area. **c** No lymph follicular formation was observed in the inflammatory foci. **d** Immunohistochemical study found that there were no lymphoplasmacytes positive for IgG4

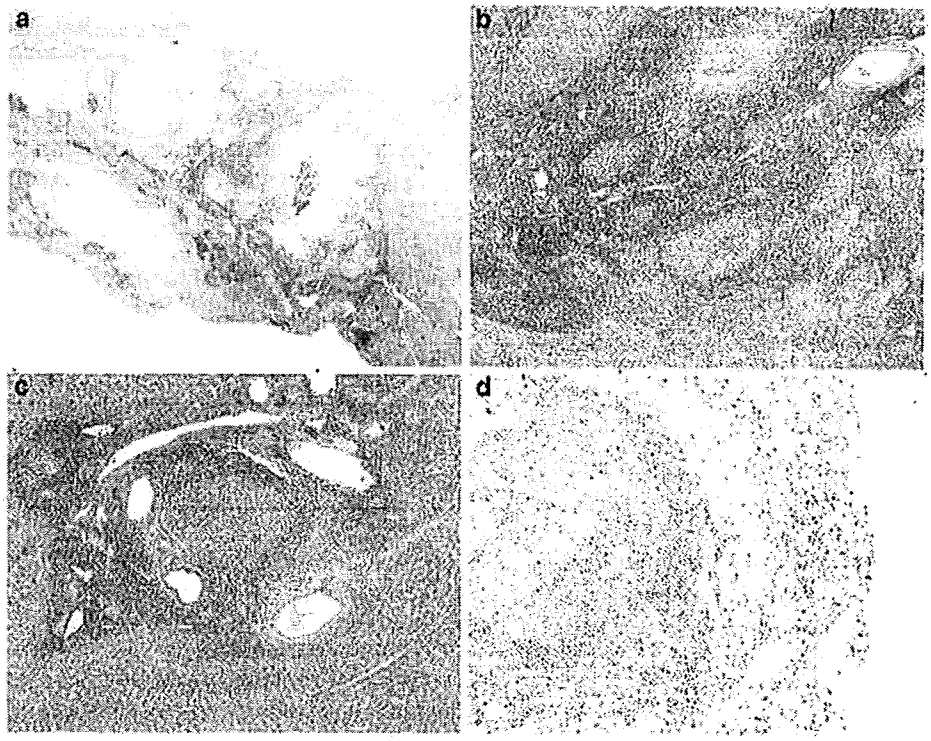

Fig. 2 Histopathological findings of case 3. **a** Inflammatory lesion was composed of follicular lymphoplasmacyte infiltration. Lymph follicule formations were prominently observed around the inflammatory lesion. **b** Lymph follicules were accompanied by germinal centers. **c** Lymphoplasmacyte infiltrations were observed only in relatively large-diameter bile ducts. **d** Immunohistochemical findings of case 3 was compatible with negative for IgG4

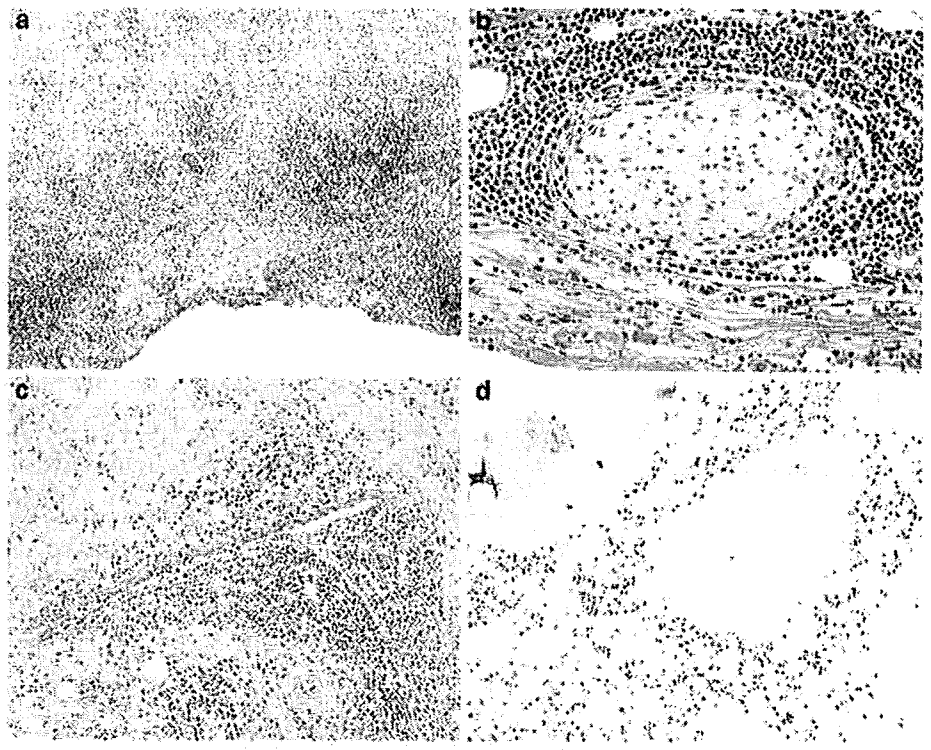

Fig. 3 Histopathological findings of case 2. **a** Inflammatory lesion was composed of diffuse lymphoplasmacyte infiltrations. Few lymph follicules were found in the lesion. **b** Histological examination showed vascular phlebitis. **c** Perineural lymph infiltrations were markedly observed around the inflammatory foci. **d** Immunohistochemical study revealed that IgG4 positive plasmacytes were diffusely observed in the lesion

Japanese, European and American patients. Most studies on benign biliary strictures of unknown origin have simply described histological findings such as chronic inflammatory infiltration. Thus, further review and a detailed histological re-evaluation may identify the epidemiological and clinicopathological features of benign biliary strictures.

Except for cases caused by obvious mechanical stimulation, most benign bile strictures are supposed to be somehow associated with the autoimmune system [9, 10, 19], and several recent studies showed that IgG4 is associated with the progression of autoimmune pancreatitis, cholangitis and other fibroinflammatory diseases [11, 20]. These intra- and extra-pancreatic lesions indicate infiltration of abundant IgG4-positive plasma cells, and treatment with steroids resulted in the disappearance of most of the IgG4 plasma cells and subsequent improvement of the affected organs [15, 21, 22].

As per our current understanding of sclerosing cholangitis, we re-evaluated the cases of benign sclerosing cholangitis of unknown origin diagnosed over the past 15 years and found that there were 5 cases among 176 patients who underwent surgery for proximal biliary stricture. Of these, case 2 had a moderate level of lymphoplasmacytic inflammation, and these plasma cells were diffusely positive for IgG4, being compatible with IgG4-related sclerosing cholangitis. On the other hand, the histopathological findings for cases 3 and 5 were similar and unusual, showing differences from those of case 2. Microscopically, in cases 3 and 5, the walls of the bile duct were thickened, and dense fibrosis as well as a marked formation of lymph follicles with germinal centers under the mucosal layer was observed. On the basis of our evaluation, both cases showed the absence of IgG4 levels; however, it is unknown whether or not these unusual cases of cholangitis consistently show the absence of IgG4. With regard to the status of IgG4, some recent reports suggest that the number of IgG4-positive plasma cells can vary depending on the status of the disease, and they further imply that there is no selective increase in IgG4-positive plasma cells in IgG4-related sclerosing cholangitis [17, 23, 24]. Therefore, we could not rule out the possibility that this lymphoplasmacytic sclerosing cholangitis with prominent lymph follicules is a variant of IgG4-related sclerosing cholangitis. Nevertheless, because the histopathological findings and profile of disease progression of this unusual lymphoplasmacytic sclerosing cholangitis varied in our study, the characteristics of the disease should be further clarified.

In our cases 1 and 4, a single focal stricture of the bile duct with no abnormal findings in other areas of the hepatobiliary system and subtle lymphoplasmacyte infiltration negative for IgG4 were found. The histological findings for these two cases indicated no vascular phlebitis or perineural lymph infiltration with no pathological findings in the peripheral intrahepatic bile duct. Thus, we could not further categorize these two cases, and they were classified as nonspecific fibroinflammatory cholangitis at this point.

Table 4 Immunohistochemical findings

	CD3	CD4	CD8	CD20	CD79a	IgG4	Distribution of IgG4(+) cells
Case 1	+	+	+	+	+	−	NA
Case 2	+	+	+	+	+	+	Diffuse
Case 3	+	+	+	+	+	−	NA
Case 4	+	+	+	+	+	−	NA
Case 5	+	+	+	+	+	−	NA

NA not applicable, + present, − absent

Table 5 Summary of cases in the literature of benign proximal stricture of the bile duct presumably diagnosed as cholangiocarcinoma

	Total number of resected specimen	Number of benign biliary stricture	Primary sclerosing cholangitis	Biliary stricture with unknown origin	Stone disease or granulomatous process
Hadjis et al. [1]	104	8 (7.7%)[a]	N/A	8 (7.7%)	0 (0%)
Wetter et al. [7]	98	8 (8.1%)[b]	N/A	3 (3.0%)	5 (5.1%)
Verbeek et al. [6]	82	11 (13.4%)[c]	N/A	11 (13.4%)	N/A
Nakayama et al. [8]	99	14 (14.1%)[d]	N/A	14 (14.1%)	N/A
Gerhards et al. [5]	132	20 (15.1%)	N/A	15 (11.3%)	3 (2.3%)
Corvera et al. [3]	275	22 (8.0%)	3 (1.1%)	8 (2.9%)	9 (3.3%)
Uhlmann et al. [25]	49	7 (14.3%)[e]	N/A	7 (14.3%)	0 (0%)
Are et al. [2]	171	9 (5.2%)[f]	N/A	8 (4.7%)	1 (0.6%)
Erdogan et al. [4]	185	32 (17.3%)	2 (1.1%)	18 (9.7%)	7 (3.8%)
Present study	176	21 (11.9%)	0 (0%)	5 (2.8%)	2 (1.1%)

NA not applicable

[a] All cases showed increase in fibrous tissues

[b] Three cases of focal ideopathetic benign fibrosis as the cause of stricture

[c] Two out of 11 cases showed localized sclerotic tissues; 9 out of 11 cases showed chronic inflammatory infiltrations

[d] All 14 cases showed extensive fibrosis with inflammatory cellular infiltration at stricture

[e] All cases showed fibrosis with nonspecific chronic inflammation

[f] Eight cases of ideopathetic stricture

Table 6 Recent reports of the incidence of benign hilar strictures in surgically resected cases

	Total number of resected specimen	Number of benign biliary stricture	Autoimmune-like sclerosing cholangitis	IgG4-related sclerosing cholangitis	Incidence of IgG4-related SC in ASC (%)
Corvera et al. [3]	275	22 (8.0%)[a]	13 (59.1%)[b]	2 (9.1%)[b]	15.4
Erdogan et al. [4]	185	32 (17.3%)[a]	15 (46.9%)[b]	2 (6.2%)[b]	13.3
Present study	176	21 (11.9%)[a]	5 (23.8%)[b]	1 (4.8%)[b]	20.0

ASC Autoimmune-like sclerosing cholangitis

[a] Percentage among total number of resected case

[b] Percentage among number of benign biliary stricture

A summary of cases in the literature of benign proximal stricture of the bile duct presumably diagnosed as cholangiocarcinoma is shown in Table 5 [1–8, 25]. Of these, PSC is an important differential diagnosis in patients with suspected proximal biliary stricture. The prevalence of PSC is estimated to be between three and eight cases per 100,000 people [26, 27]; however, the prevalence of patients with PSC varies worldwide [22, 26, 28, 29]. Moreover, due to the consistently low (0–1.1%) incidence of PSC in malignant hilar masquerade, only a few studies have clearly described the incidence of PSC as that of malignant masquerade.

Recent reports of the incidence of benign hilar strictures in surgically resected cases, particularly autoimmune-like sclerosing cholangitis and IgG4-positive chronic cholangitis preoperatively diagnosed as hilar carcinoma, are summarized in Table 6 [3, 4]. Including our results, the incidence of benign biliary strictures ranged from 8.0 to 17.3%. Among the cases diagnosed as benign biliary obstructions, the incidence of autoimmune-like disease and possible IgG4-related sclerosing cholangitis ranged from 23.8 to 59.1 and 4.8 to 9.1%, respectively. These data indicate that IgG4-related sclerosing cholangitis accounts for 13.3–20% of autoimmune-like sclerosing cholangitis, implying that potentially there are several uncategorized types of autoimmune-like sclerosing cholangitis. Indeed, histopathological or immunohistochemical findings similar to our cases (case 3 and 5) with marked lymphoplasmacytic infiltration and lymph follicle formation with germinal centers have been found in previous large studies [3]. Their presented cases could belong to the same category as our case 3 and 5.

One important reason for classifying benign sclerosing cholangitis of unknown origin is to determine an appropriate treatment strategy and estimation of the prognosis. Sclerosing cholangitis can be divided into two subtypes: (1) IgG4-related sclerosing cholangitis, which responds well to corticosteroid therapy and has a good prognosis, and (2) PSC, which responds well to corticosteroids and requires liver transplantation [11, 13, 30]. The clinical courses and outcomes of our five cases varied; case 3 developed recurrent cholangitis 2 months after the surgery, which resulted in a progressive worsening of liver function despite immunosuppressive therapy, whereas case 1 had no sign of recurrent disease after a long-term follow-up. Few studies have reported the response to immunosuppressive therapy or the long-term prognosis of patients with benign sclerosing cholangitis of hilar malignant masquerade. However, in order to classify benign sclerosing cholangitis of unknown origin, it is important to examine not only the characteristics of the disease, but also the treatment strategy and long-term prognosis.

Acknowledgments We thank Professor Yasuni Nakanuma (Department of Pathology, Kanazawa University, Kanazawa) and Professor Shunji Matsumoto (Department of Pathology, Juntendo University, Tokyo) for the review and discussion of the pathological findings. We thank Dr. T. Hasebe for the evaluation of the histopathological findings.

Conflict of interest statement No financial support or relationships posed a conflict of interest.

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