Table 3 Comparison of complications according to the type of biliary drainage

	External drainage (n = 60)	Internal drainage (n = 67)	*P* value
Preoperative cholangitis*	1 (1.7%) 15 (22.4%)	<.001	
All postoperative complications†	14 (23.3%)	28 (41.8%)	.027
0–II	2 (3.4%)	2 (3.0%)	
IIIa	10 (16.7%)	18 (26.9%)	
IIIb	0 (0%)	0 (0%)	
IVa	1 (1.7%)	4 (6.0%)	
IVb	0 (0%)	1 (1.5%)	
V	1 (1.7%)	3 (4.4%)	
Severe complications (grade III or more)	12(20%)	26 (38.8%)	.021
Infectious complications	9 (15%)	16 (23.9%)	.209
Pancreatic fistula‡	13 (21.7%)	26 (38.8%)	.037
Grade A	6 (10%)	12 (17.9%)	
Grade B	7 (11.7%)	9 (13.4%)	
Grade C	0 (0%)	5 (7.5%)	
Delayed gastric emptying§	4 (6.7%)	7 (10.4%)	.449
Grade A	2 (3.3%)	3 (4.5%)	
Grade B	1 (1.7%)	3 (4.5%)	
Grade C	1 (1.7%)	1 (1.4%)	
Bile leakage	1 (1.7%)	1 (1.4%)	.937
0–II	0 (0%)	0 (0%)	
IIIa	1 (1.7%)	1 (1.4%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	0 (0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Intra-abdominal abscess	7 (11.7%)	9 (13.4%)	.765
0–II	0 (0%)	0 (0%)	
IIIa	7 (11.7%)	9 (13.4%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	0 (0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Intra-abdominal hemorrhage	2 (3.4%)	5 (7.5%)	.309
0–II	0 (0%)	0 (0%)	
IIIa	1 (1.7%)	2 (3.0%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	2 (3.0%)	
Vb	0 (0%)	1 (1.5%)	
V	1 (1.7%)	0 (0%)	
Wound infection	2 (3.3%)	7 (10.4%)	.119
0–II	0 (0%)	0 (0%)	
IIIa	2 (3.3%)	7 (10.4%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	0 (0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Sepsis	1 (1.7%)	4 (6.0%)	.213
0–II	0 (0%)	0 (0%)	
IIIa	0 (0%)	0 (0%)	
IIIb	0 (0%)	0 (0%)	
IVa	1 (1.7%)	4 (6.0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Reoperation	0 (0%)	0 (0%)	.999
Mortality	1 (1.7%)	3 (4.5%)	.365

DGE = delayed gastric emptying.

*Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.

†Other complication except pancreatic fistula and DGE are classified based on Clavien classification.

‡Pancreatic fistula is classified based on the International Study Group on Pancreatic Fistula guideline.

§DGE is classified based on an International Study Group of Pancreatic Surgeons on DGE recommendation.

Table 4 Theassociation between preoperative cholangitis and postoperative complications

	Preoperative cholangitis*		
	+ (n = 16) (%)	− (n = 111) (%)	*P* value
All postoperative complications†	10 (62.5)	32 (28.8)	.007
0–II	0 (0)	4 (3.6)	
IIIa	9 (56.3)	19 (17.1)	
IIIb	0 (0)	0 (0)	
IVa	1 (6.3)	4 (3.6)	
IVb	0 (0)	1 (.9)	
V	0 (0)	4 (3.6)	
Severe complications (grade III or more)	10 (62.5)	28 (25.2)	.002
Infectious complications	5 (31.3)	20 (23.9)	.213
Pancreatic fistula‡	7 (43.8)	32 (28.8)	.226
Grade A	3 (18.7)	15 (13.5)	
Grade B	3 (18.7)	13 (11.7)	
Grade C	1 (6.3)	4 (3.6)	
Delayed gastric emptying§	5 (31.2)	6 (5.4)	.001
Grade A	1 (6.3)	4 (3.6)	
Grade B	3 (18.7)	1 (.9)	
Grade C	1 (6.3)	1 (.9)	
Bile leakage	0 (0)	2 (1.8)	.588
0–II	0 (0)	0 (0)	
IIIa	1 (6.3)	2 (1.8)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Intra-abdominal abscess	3 (18.8)	13 (11.7)	.428
0–II	0 (0)	0 (0)	
IIIa	3 (18.8)	13(11)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Intra-abdominal hemorrhage	1 (6.3)	6 (5.4)	.890
0–II	0 (0)	0 (0)	
IIIa	1 (6.3)	2 (1.8)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	2 (1.8)	
IVb	0 (0)	1 (.9)	
V	0 (0)	1 (.9)	
Wound infection	4 (25.0)	5 (4.5)	.003
0–II	0 (0)	0 (0)	
IIIa	4 (25.0)	5 (4.5)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Sepsis	1 (6.3)	4 (3.6)	.611
0–II	0 (0)	0 (0)	
IIIa	0 (0)	0 (0)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	1 (6.3)	4 (3.6)	
V	0 (0)	0 (0)	
Reoperation	0 (0)	0 (0)	.999
Mortality	0 (0)	4 (3.6)	.440

DGE = delayed gastric emptying.

*Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.

†Other complication except pancreatic fistula and DGE are classified based on Clavien classification.

‡Pancreatic fistula is classified based on the International Study Group on Pancreatic Fistula guideline.

§DGE is classified based on an international study group of pancreatic surgeons on DGE recommendation.

Table 5 Risk factors influencing severe complications after pancreaticoduodenectomy by univariate analysis

	Severe complications*		
	− (n = 89) (%)	+ (n = 38) (%)	*P* value
Age (y)			
≤75	64 (71.9)	26 (68.4)	
>75	25 (28.1)	12 (31.6)	.692
Gender			
Male	46 (51.7)	25 (65.8)	
Female	43 (48.3)	13 (34.2)	.143
Total bilirubin level (mg/dL)			
≤10	58 (65.2)	29 (76.3)	
>10	31 (34.8)	9 (23.7)	.216
Type of biliary drainage			
Internal drainage	41 (46.1)	26 (68.4)	
External drainage	48 (53.9)	12 (31.6)	.021
Preoperative cholangitis†			
Yes	6 (6.7)	10 (26.3)	
No	83 (93.3)	28 (73.7)	.002
Waiting periods for operation from drainage			
≤4 wk	65 (73.0)	22 (57.9)	
>4 wk	24 (27.0)	16 (42.1)	.093
Histology			
Pancreatic cancer	47 (52.8)	8 (21.1)	
Other disease	42 (47.2)	30 (78.9)	.001
Operative procedure			
PpPD	64 (71.9)	27 (71.1)	
PD/PrPD	25 (28.1)	11 (28.9)	.922
Operative time (min)			
≤420	66 (74.1)	26 (68.4)	
>420	23 (25.9)	12 (31.6)	.508
Intraoperative bleeding (mL)			
≤1000	64 (71.9)	25 (65.8)	
>1000	25 (28.1)	13 (34.2)	.490
Red blood cell transfusion			
Yes	31 (34.8)	10 (26.3)	
No	58 (65.2)	28 (73.7)	.347
Pancreatic texture			
Soft	38 (42.7)	28 (73.7)	
Hard	51 (57.3)	10 (26.3)	.001

PD = pancreaticoduodenectomy; PpPD = pylorus-preserving pancreaticoduodenectomy; PrPD = pylorus-resecting pancreaticoduodenectomy.
*"Severe complications" was defined in this study as a condition that was grade III or more based to the Clavien classification.
†Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.

All postoperative complications were significantly higher in the internal drainage group (41.8%) than in the external drainage group (23.3%; $P = .027$). Moreover, severe complications (grade III or more) were significantly higher in the internal drainage group (38.8%) than in the external drainage group (20.0%; $P = .021$). The overall incidence of pancreatic fistula was significantly higher in the internal drainage group (38.8% vs 21.7% in external drainage group; $P = .037$). Pancreatic fistula was classified into 3 categories by the International Study Group on Pancreatic Fistula (12). The proposed clinical grading of the 26 patients with pancreatic fistula in the internal drainage group were grade A, n = 12; grade B, n = 9; and grade C, n = 5. The 13 patients with pancreatic fistula in the external drainage group were grade A, n = 6; grade B, n = 7; and grade C, n = 0. Twenty-five of 127 patients with preoperative biliary drainage had infectious complications. There was no significant difference between internal drainage and external drainage (15% in external drainage group vs 23.9% in internal drainage group). There were no significant differences between the 2 groups concerning the incidence of other postoperative complications, such as DGE, bile leakage, intra-abdominal abscess, and intra-abdominal hemorrhage.

The mortality rate in this study was 3.1% (4 of 127 patients). Two patients died because of pancreatic fistula, 1 patient because of intra-abdominal hemorrhage, and 1 patient because of nonocclusive mesenteric ischemia.

Table 6 Risk factors influencing severe complications* after pancreaticoduodenectomy by multivariate analysis

Risk factor	*P* value	Odds ratio	95% CI
Internal drainage	.125	2.01	.8-4.9
Preoperative cholangitis†	.019	4.61	1.3-16.5
Soft pancreas	.846	1.79	.1-5.1
Other disease except pancreatic cancer	.141	4.22	.6-28.8

CI = confidence interval.

*"Severe complications" was defined in this study as a condition that was grade III or more based to the Clavien classification.

†Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013 (TG13).

The association between preoperative cholangitis and postoperative complications

Table 4 shows the association between preoperative cholangitis and postoperative complications. The incidence of preoperative cholangitis in this study was 12.6% (16 of 127 patients). Ten of 16 patients (62.5%) with preoperative cholangitis were given plastic stent exchange or change to ENBD and the administration of antibiotics.

All postoperative complications were significantly higher in patients with cholangitis (62.5%) than patients without it (22.8%; $P = .007$). Severe complications (grade III or more) were significantly higher in patients with cholangitis (62.5%) than patients without it (25.2%; $P = .002$). Likewise, the overall incidence of DGE was significantly higher in patients with cholangitis (31.2% vs 5.4% in patients without cholangitis; $P = .001$). DGE was classified into 3 categories by ISGPS.[13] The proposed clinical grading of 5 patients with DGE among those with cholangitis were grade A, n = 1; grade B, n = 3; and grade C, n = 1. The 6 patients with DGE among the 111 without cholangitis were grade A, n = 4; grade B, n = 1; and grade C, n = 1. The incidence of wound infection was significantly higher in patients with cholangitis (25%) than patients without it (4.5%; $P = .003$). There was no significant difference between patients with and without preoperative cholangitis (31.3% in patients with preoperative cholangitis vs 18.0% in patients without preoperative cholangitis). There were no significant differences between the 2 groups concerning the incidence of other postoperative complications, such as pancreatic fistula, bile leakage, intra-abdominal abscess, and intra-abdominal hemorrhage.

Risk factors influencing severe complications after PD

Univariate and multivariate analyses were used to reveal risk factors influencing severe complications (grade III or more) after PD. Table 5 shows the results of 12 parameters univariately examined as potential risk factors for 38 patients with severe complications (grade III or more) vs 89 patients without severe complications after PD. Four factors were extracted as being useful for discriminating between patients with and without severe complications after PD: internal drainage ($P = .021$), preoperative cholangitis ($P = .002$), soft pancreas ($P = .001$), and other disease except pancreatic cancer ($P = .001$) were identified. A multivariate logistic regression analysis revealed that preoperative cholangitis (odds ratio 4.61, 95% confidence interval 1.3 to 16.5; $P = .019$) was the significant risk factor for morbidity after PD (Table 6).

Comments

Routine preoperative biliary drainage for jaundiced patients with PD remains still controversial for occurrence of biliary drainage–related complications. However, preoperative biliary drainage for jaundiced patients is generally accepted in Japan. Because period for the expected waiting time until surgery in Japan generally requires a few weeks. All 127 jaundiced patients with PD in the present study underwent preoperative biliary drainage. Therefore, the present study focused on the advantage or disadvantage by various types of preoperative biliary drainage. This is the first study to compare whether internal drainage or external drainage is better for preoperative biliary drainage in patients with PD. Moreover, it remains controversial how biliary drainage–related complications affect the incidence of postoperative complications after PD. In the present study, we evaluated the associations between biliary drainage–related complications and postoperative complications after PD between internal drainage and external drainage.

The occurrence of preoperative cholangitis during biliary drainage was clarified to be the independent risk factor of severe complications after PD. Two previous studies reported that occurrence of preoperative cholangitis significantly increased postoperative complications including pancreatic fistula or DGE.[16,17] Preoperative cholangitis significantly increased DGE and wound infection in the present study. Many pancreatic surgeons believe that DGE after PD is secondary caused by pancreatic fistula or intra-abdominal abscess. However, in the present study, there was no significant difference between patients with and without intra-abdominal abscess according to the incidence of DGE (18.7% in patients with intra-abdominal abscess vs 7.2% in patients without

intra-abdominal abscess, $P = .144$). This study demonstrates that there was no significant association between intra-abdominal abscess and DGE.

Stent occlusion was reported to cause more than half the incidence of preoperative cholangitis, and cholangitis occurred in 26% of patients who underwent internal drainage.[6] The cause of cholangitis because of internal drainage may be stent occlusion or ascent of microorganisms from the open passage to the duodenum and subsequent reflux of duodenal contents.[18,19] In this study, patients undergoing internal drainage had significantly higher incidence of cholangitis because of biliary drainage (22.4% vs 1.7% in external drainage group). As a result, internal drainage, which was associated with more preoperative cholangitis, significantly increased the incidence of morbidity compared with external drainage (41.8% vs 22.3%). Biliary drainage was shown to increase infectious complications such as wound infection after PD.[20] On the other hand, Jagannath et al[21] reported that a positive intraoperative bile culture was associated with higher morbidity rates after PD, and biliary drainage was not associated with increased morbidity. In addition, biliary drainage with complications such as cholangitis was reported to increase significantly the incidence of positive bile culture.[21] Therefore, clinicians have to take special care not to initiate preoperative cholangitis because of biliary drainage.

Preoperative internal biliary drainage may increase postoperative complications after PD compared with external drainage. However, there are some disadvantages in external drainage such as PTBD or ENBD. Drains for external drainage may be dislodged or pulled out by patients at the unconscious level. Other drawbacks of PTBD are the invasiveness of the technique or seeding risk. Other drawbacks of ENBD are patient discomfort or cosmetic problems because of the presence of the tube through nasopharynx. In contrast, compared with external drainage, internal drainage allows normal bile flow, which is important from the viewpoint of intestinal immunity and the prevention of bacterial translocation.[22–24] One problem with internal drainage is cholangitis because of stent occlusion. In this study, plastic stents in all cases were used as internal drainage. Metallic stents in patients with unresectable pancreatic cancer were reported to provide large caliber, longer patency, and lower incidence of acute cholangitis compared with plastic stents.[25] A few studies reported that metallic stents have more advantages compared with plastic stents as preoperative internal biliary drainage in patients awaiting PD, such as those undergoing neoadjuvant therapy for pancreatic cancer.[26–28] Moreover, covered metallic stents may be possible not only to protect against tumor ingrowth but also to minimize bacterial adherence and sludge formation that cause biliary infections.[29,30] Additional studies are required to evaluate how the use of metallic stents as preoperative biliary drainage affects surgical technique or perioperative course.

There are several limitations to this study for the retrospective study. First, external drainage by PTBD was performed by choice in the early period. One might consider that there is a bias because of the increasing experience between the early period in this study and the latter period concerning the operative time, intraoperative bleeding, and red blood cell transfusion. Second, in our institution, we have performed pylorus PrPD instead of PpPD by the result of clinical trial since February 2009.[9] A bias for the period affects a significant difference between drainage type and operative procedure. However, we checked that there was no significant difference between patients with and without severe complications concerning operative procedures.

In conclusion, preoperative cholangitis during biliary drainage significantly increases the incidence of postoperative complications after PD. In particular, plastic stents as internal biliary drainage may increase preoperative cholangitis related to stent occlusion during the waiting period for PD. Therefore, management of biliary drainage to prevent preoperative cholangitis should be standardized for patients who require preoperative biliary drainage for PD.

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J Hepatobiliary Pancreat Sci (2014) ••:••–••
DOI: 10.1002/jhbp.94

TECHNICAL VIEW

Endoscopic removal technique of migrated pancreatic plastic stents

Kazuyuki Matsumoto · Akio Katanuma · Hiroyuki Maguchi

Abstract Endoscopic pancreatic stenting (EPS) is used for various pancreatic conditions. With the increasing use of pancreatic stents, many complications have been observed. Especially, proximal stent migration presents a more serious condition because of the possibility of pancreatic duct (PD) damage. However, the removal of proximally migrated stents is technically challenging because of the small PD diameter, the bended PD course, the presence of PD strictures, and the lack of suitable devices for stent removal. Thus, few cases of surgical intervention have been encountered. In this study, we review the endoscopic treatment of proximally migrated pancreatic plastic stents. We classify migrated stent conditions into four types according to stent and PD conditions. In Type A, the main pancreatic duct (MPD) has no stricture. In Type B, the stent is positioned across the stricture on the MPD. In Type C, the stent is positioned further away from the stricture on the MPD. The tip of the proximal stent is located in the MPD in types A thru C. In Type D, the tip of the proximal stent is located in a branch duct. We introduced the strategy of endoscopic removal technique of each type of migrated plastic stents.

Keywords Endoscopic retrograde cholangiopancreatography · Pancreatic plastic stent · Stent migration

Introduction

Endoscopic pancreatic stenting (EPS) is used for various pancreatic conditions, including ductal obstruction due to benign strictures, stones, or tumors, drainage of pancreatic pseudocysts, recurrent pancreatitis associated with pancreas divisum, and prophylaxis against post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis [1–7].

K. Matsumoto (✉) · A. Katanuma · H. Maguchi
Center for Gastroenterology, Teine-Keijinkai Hospital, 1-jo 12-chome, Maeda, Teine-ku, Sapporo 006-8555, Japan
e-mail: matsumotokazuyuki0227@yahoo.co.jp

With the increasing use of pancreatic stents, many complications have been observed, including infection, stent occlusion, duodenal erosions, ductal perforation, and either proximal (upstream) or distal (downstream) stent migration. A previous meta-analysis indicated a distal stent migration rate of 7.5% [8]. Distal stent migration is rarely harmful as the stent passes into the duodenum and is then excreted. On the other hand, proximal stent migration further into the pancreatic duct (PD) has been shown to occur at a rate of about 5.2% [8] and results in pancreatitis. This type of migration presents a more serious condition because of the possibility of PD damage. The removal of proximally migrated stents is technically challenging, because of the small PD diameter, the bended PD course, the presence of PD strictures, and the lack of suitable devices for stent removal. Thus, few cases of surgical intervention have been encountered [9–11].

Despite these concerns, little is known about the management and treatment of proximally migrated pancreatic stents. In this study, we initially review the endoscopic treatment of proximally migrated pancreatic plastic stents. We then introduce the strategy of endoscopic removal of these plastic stents. Thereafter, we report the case of proximal migration of a single pig tail pancreatic plastic stent successfully removed by endoscopy.

Migrated stent conditions

The removal of proximally migrated stents is technically challenging. One of the reasons for this is the presence of PD strictures. This implies the importance of understanding the relations of the locations of the PD strictures and the positions of the migrated stents. These relations are classified into four types of migrated stent conditions: Types A, B, C, and D (Fig. 1).

In Type A, the tip of the proximal stent is located in the main pancreatic duct (MPD) and the MPD has no stricture. In Type B, the tip of the proximal stent is located in the MPD and the stent is positioned across the stricture on the

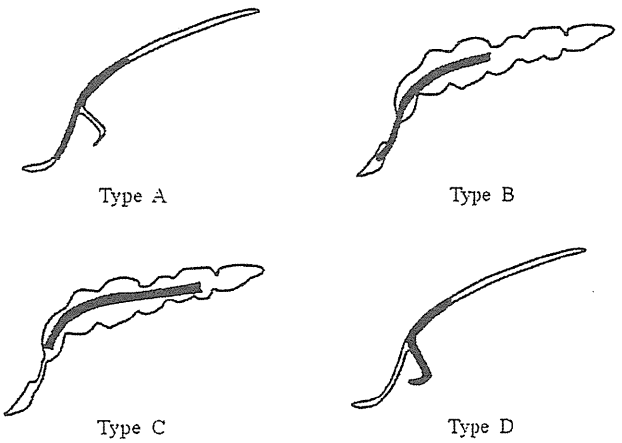

Fig. 1 Type A: the tip of the proximal stent is located in the normal main pancreatic duct (MPD). Type B: the stent is located across the MPD stricture. Type C: the stent is located further away from the MPD stricture. Type D: the tip of the proximal stent is located in a branch duct

MPD. In Type C, the tip of the proximal stent is located in the MPD and the stent is positioned further away from the stricture on the MPD. In Type D, the tip of the proximal stent is located in a branch duct.

Devices for stent removal and retrieval techniques

Each device for removing migrated stents has some advantages and disadvantages, thus it is important to properly select the device depending on the migrated stent condition. Three different techniques for stent retrieval were previously described [9, 12]: (i) indirect traction with an inflating extraction and/or dilatation balloon catheter; (ii) direct traction of the stent using various devices; and (iii) retrieval after cannulating the stent lumen. Direct traction involved grasping the stent using various devices (e.g., forceps, basket, or snare) and pulling the stent distally. Retrieval after cannulating the stent lumen involved passing a guidewire (GW) through the stent lumen and pulling the stent distally using different devices (e.g., Sohendra stent retriever: SSR, basket, balloon or snare).

a. Retrieval technique using a balloon catheter

The retrieval technique using an extraction balloon (Extractor Pro RX; Boston Scientific, Natick, MA, USA) involves positioning the balloon above or alongside the stent, followed by pulling the inflated balloon down towards the duodenum. The stent can be removed either by balloon traction alone or by changing the stent position so that it can be removed using other devices. Another retrieval method using an extraction balloon is possible. After cannulation of the stent lumen with a 0.025-inch GW (VisiGlide; Olympus Medical Systems, Tokyo, Japan), part of the balloon catheter is inserted into the stent lumen. The balloon is then inflated inside the stent and pulled down towards the duodenum.

The retrieval method using a dilatation balloon (Hurricane RX, 6-mm-wide dilatation, 4-cm long; Boston Scientific) is similar to that using an extraction balloon (Fig. 2a–c). The advantage of the dilatation balloon is the larger adhesion area between the balloon and the migrated stent than in the case of the extraction balloon. Moreover, the dilatation balloon can be used to create a space by dilating the stricture or the distal side of the MPD. After dilatation of the stricture, many devices can be introduced to the migrated stent. Moreover, dilatation balloons can be easily pulled out from the PD without resistance of the stricture.

However, it is difficult to use a balloon technique if the balloon cannot pass through the MPD stricture (particularly in Types B and C) or if the balloon fails to adhere to the migrated stent completely because of MPD dilatation (Type C).

b. Retrieval technique by direct grasping using a forceps, basket or snare

The retrieval technique using a forceps is carried out by directly grasping the end or side of the stent, or a flap of the stent. The forceps can provide a secure grasp; however, the jaws of the forceps cannot be opened when there is insufficient space (Types A, B, and D). Moreover, in cases in which the migrated stent is located further away from the stricture (Type C), it is difficult to pass the forceps across the stricture.

The retrieval technique using a basket (TetraCatchV Wire-guided; Olympus Medical Systems) or snare (Crescent type; Boston Scientific) is performed by directly grasping the distal end of the stent. The basket has multiple wires, making it easier to capture the stent. If there is a restriction at the MPD stricture and it is difficult to guide the device up to the proximal end of the stent, a ropeway type of basket may be used after initially advancing the GW. A half-moon snare or a snare that has a manually created flexure can easily capture the stent. However, extending the basket or snare may also be difficult when there is limited space, just as with the direct forceps grasp.

c. Retrieval technique using a stent retriever

The stent retriever (Cook Medical, Bloomington, IN, USA) is a wire-guided, hollow, spring-coil catheter with a threaded metal screw-like tip. After the stent lumen has been cannulated with a GW, the stent retriever is then screwed into the distal end of the stent by clockwise rotation of the device (Fig. 3a–c). The stent retriever makes it easier to remove the stent; however, this device cannot be used when the GW cannot pass through the lumen of the migrated stent.

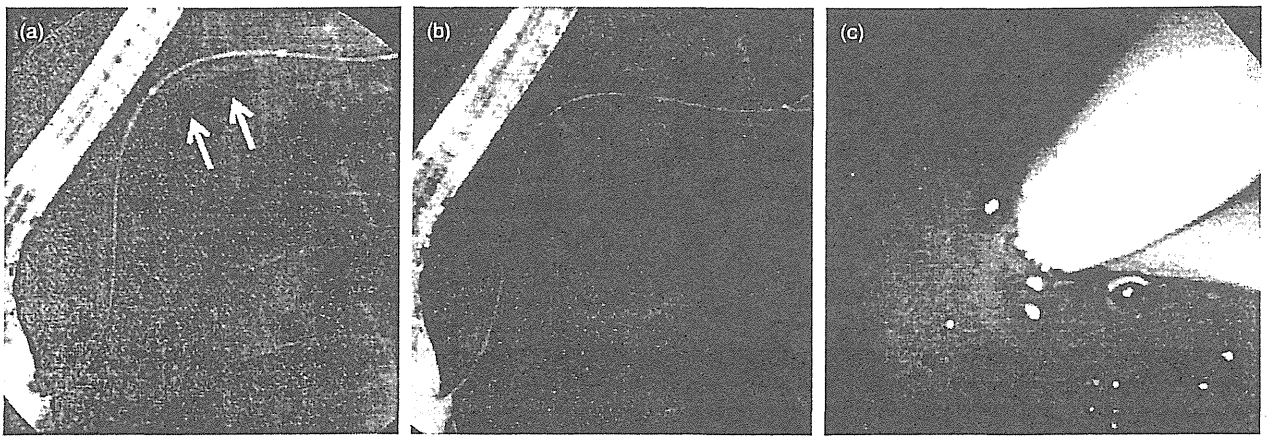

Fig. 2 (a) The balloon was positioned alongside the stent and then inflated. (b) The inflated balloon was pulled down towards the duodenum. (c) The stent was pulled up with a balloon catheter via the ampulla of Vater

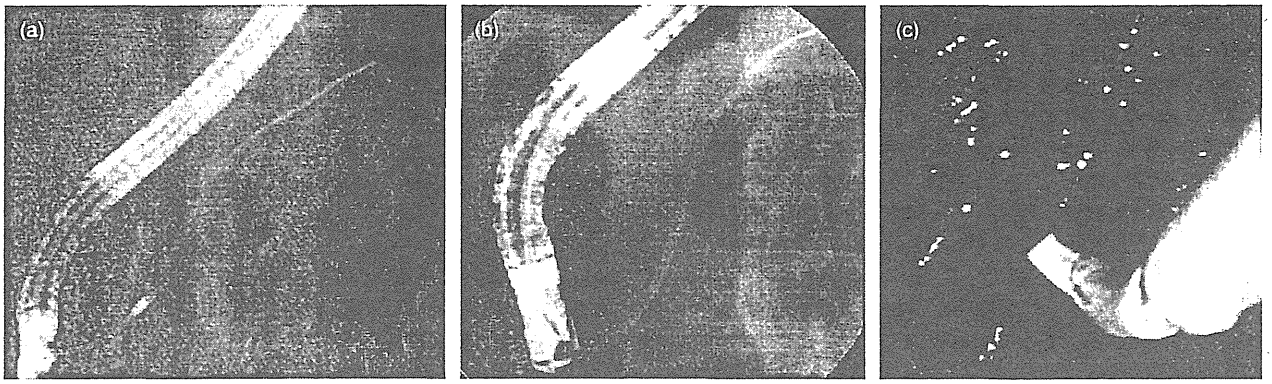

Fig. 3 (a) After the stent lumen has been cannulated with a GW, the stent retriever was screwed into the distal end of the stent. (b) The stent retriever was pulled down towards the duodenum in consideration of the PD axis. (c) The stent was removed with a stent retriever via the ampulla of Vater

Moreover, if the tips of the proximal stent are located in a branch duct (Type D), this device cannot be used.

Procedural steps for removing stents according to their type of migration

In all types of stent migration, the migrated stent is removed using both endoscopic force, in which the endoscope is pushed into the anal side of the duodenum, and device pulling force. It is very important to consider the PD axis. The most effective method of removing the migrated stent is to apply force in the axial direction of the PD. When the migrated stent is removed only by device pulling force, stent fragmentation or PD disruption might occur. After the migrated stent is moved downstream by endoscopic force, the stent should be collected in the channel using the appropriate device.

a. Type A: the stent is located in the MPD without a stricture

In Type A stent migration, the stent is usually easy to remove when the stent can be caught by direct grasping devices. However, in some cases, these grasping devices cannot be opened in the MPD because the MPD diameter is usually small. In this case, the following procedural steps are undertaken in this sequence:

1. The MPD is cannulated with a catheter, and a 0.025-inch or 0.035-inch GW is led into the MPD tail or passed through the stent lumen.
2. The stent is removed by direct traction using various devices such as a forceps, basket, or snare. For cases in which the GW can pass through the stent lumen, stent cannulation techniques using an SSR, balloon, basket, or snare are useful for stent removal.

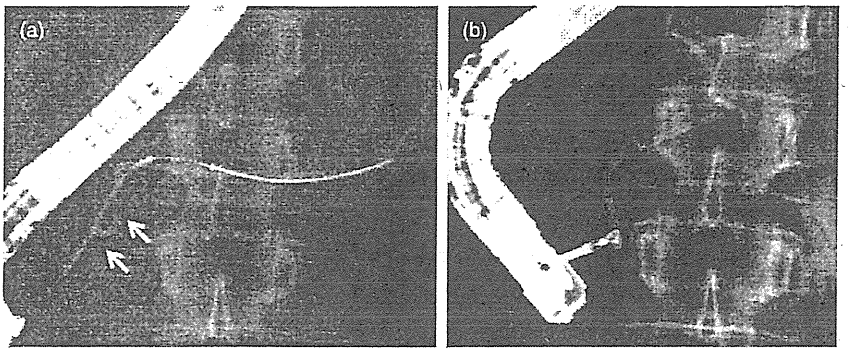

Fig. 4 (a) The pig tail part of the stent migrated into a branch duct in the pancreatic head, as shown on this endoscopic retrograde pancreatography image (white arrow). (b) A part of the pig tail stent was caught using a direct forceps grasp and the stent was removed successfully

b. Type B: the stent is located across the MPD stricture

Direct traction is useful for stent retrieval in Type B stent migration. In this type of migration, there is insufficient space for using the device similarly to Type A stent migration. Moreover, stent fragmentation can occur when the stent is fixed by a severe stricture. Therefore, the stent is removed using both endoscopic force and device pulling force in consideration of the PD axis. The procedural steps are basically the same as those for Type A stent migration.

c. Type C: the stent is located further away from the MPD stricture

In Type C stent migration, a combination of indirect and direct tractions is required for stent retrieval. The stent is grasped using direct traction devices such as a forceps or basket, after which the stent is pulled down distally by indirect traction using a balloon catheter. The procedure for Type C is that balloon dilation is needed to be able to pass the device or remove the migrated stent when the proximal stricture of the MPD is severe. The indirect traction technique using a balloon is not effective when the balloon does not adhere to the migrated stent completely because of MPD dilatation. In this case, the following procedural steps are undertaken in this sequence:

1. The MPD is cannulated with a catheter, and a 0.025-inch or 0.035-inch GW is led into the MPD tail or passed through the stent lumen.
2. Indirect traction with a balloon is used. The balloon is positioned above or alongside the stent and is inflated until the stent and balloon adhere to each other. If the proximal stricture of the MPD is severe, balloon dilatation is performed.
3. The balloon is pulled carefully. The stent is removed either by indirect balloon traction alone or by changing the stent position distally.
4. The stent is removed by direct traction using various devices such as a forceps grasp, basket, or snare. For cases in which the GW can pass through the stent lumen, the stent cannulation technique is useful for stent removal.

d. Type D: the stent tip is located in a branch duct

Type D stent migration is the most difficult type. In this type of migration, the proximal stent tip is migrated and hooked into a branch duct. Therefore, a basket, snare, or SSR cannot basically be used. In this case, the following procedural steps are undertaken in this sequence:

1. The MPD is cannulated with a catheter, and a 0.025-inch or 0.035-inch GW is led into the MPD tail.
2. Indirect traction with a balloon is used. The balloon is positioned above or alongside the stent and is inflated until the stent and balloon adhere to each other.
3. The balloon is pushed into the tail side of the pancreas to dislodge the hooked part of the stent.
4. The head side of the MPD is dilated to create a space using the balloon.
5. Direct traction using a direct forceps grasp is useful for catching part of the stent and removing the stent.

Clinical case of Type D stent migration

The patient was a 35-year-old woman who had undergone ERCP for a common bile duct stone. A 5F 3-cm single pig tail pancreatic stent was placed for the prevention of post-ERCP pancreatitis. About 1 month later, the patient experienced abdominal pain and pancreatic stent migration was detected by abdominal CT. The stent at the pig tail side completely migrated into the pancreas. In addition, the proximal stent tip migrated into a branch duct in the pancreatic head (Fig. 1; Type D), as observed on an endoscopic retrograde pancreatography image (Fig. 4a). We cannulated the MPD with a catheter, and a 0.025-inch GW (VisiGlide; Olympus Medical Systems) was led into the MPD tail. First, we attempted to use a direct forceps grasp (Radial Jaw 4 Biospy Forceps; Boston Scientific); however, the forceps could not be passed through the MPD head, and the stent could not be moved. Subsequently, we passed a 6-mm balloon (Hurricane RX, 6-mm-wide dilatation, 4-cm long; Boston Scientific) alongside the stent, and then carefully inflated the balloon under radiographic guidance until the

stent and balloon adhered to each other. Thereafter, we pushed the balloon into the pancreatic tail side to dislodge the hooked part of the stent. We also dilated the head side of the MPD to create space. Finally, we used a direct forceps grasp to catch part of the pig tail stent and we could remove the stent successfully (Fig. 4b and Video S1).

Additional management after stent removal

Stent removal procedures have potential risk of damage to the pancreatic duct, which may lead to post-procedure pancreatitis. The indication for endoscopic nasopancreatic drainage (ENPD) after stent removal is still not clearly defined. Theoretically, the PD might be severely injured by the removal of the migrated stent in cases of the presence of pancreatic duct strictures and complicated types of stent migration. After pancreatic stent removal, ENPD placement would be ideal to prevent post-procedure pancreatitis.

Price et al. [10] reported that post-procedure pancreatitis may be minimized by carrying out ENPD. They performed ENPD after the removal of pancreatic stents in 15 of 22 (68%) cases and reported only two cases (9.1%) of post-procedure complications (i.e., PD disruption with subsequent leakage and pancreatitis). In our study, ENPD was performed in 4 of 5 (80%) cases. Post-procedure pancreatitis occurred in only one (20%) case (i.e., mild pancreatitis).

Pancreatic and extra-pancreatic infections are determining factors leading to severe pancreatitis. Therefore, antibiotic prophylaxis has been recommended to prevent infectious complications after stent removal. The serum amylase level should be followed up the next day. The indicators for starting the meal are a serum amylase level that is three times lower than the upper normal limits and the absence of abdominal pain.

Technical and treatment outcomes

Three reports have described the endoscopic removal of proximally migrated pancreatic plastic stents [9, 10, 13] (Table 1). Including the present study, there were 56 cases of proximally migrated stents reported. The overall successful endoscopic retrieval rate was 80%. In 14 of 45 (31%) cases, the stent could be removed by indirect balloon extraction. Direct traction was used in 25 (56%) cases, including forceps in nine, basket in 11, and snare in five. Retrieval technique after stent lumen cannulation was used in six (13%) cases, including balloon in two, snare in two, basket in one, and SSR in one. Of the 56 cases, seven (13%) required surgical stent removal, including pancreatectomy in four, pancreaticojejunostomy in one, and unknown in two. Excluding the surgical stent removal cases, the stents in

Table 1 Summary of published data on endoscopic removal of proximally migrated pancreatic duct (PD) stents

Reference	No. cases	No. retrieved stents	Technical success rate (%)	Successful techniques								No. surgeries required	No. not retrieved stents	Complication(s) (no. cases)
				Indirect	Direct			Stent lumen cannulation						
				Balloon extraction	Forceps	Basket	Snare	Balloon	Basket	Snare	SSR			
Laholi et al. [9]	26	20	77	5	1	9	2	2	1	0	0	3	3	NA
Prince et al. [10]	23	18	78	8	5	1	2[a]	0	0	2	0	4	1	PD disruption (1) Stent fragmentation (1) Pancreatitis (1)
Sakai et al. [13]	2	2	100	0	1	0	1	0	0	0	0	0	0	Pancreatitis (1)
Present study	5	5	100	1	2	1	0	0	0	0	1	0	0	Pancreatitis (1)

NA not available, *PD* pancreatic duct, *SSR* Sohendra stent retriever

[a] One case was retrieved by interventional radiology loop snare

four patients could not be retrieved. All of them were asymptomatic patients, and they have been followed for 2–5 years (the follow-up period for one patient was unknown) without stent removal. They showed no complications from the remaining migrated stents. Procedure-related complications were observed in five cases (9%): pancreatitis in three, PD disruption in one, and stent fragmentation in one.

Of the 56 cases, 12 (21%) were symptomatic and presented with abdominal pain. The indications for EPS included relapsing pancreatitis with divisum ($n = 18$), relapsing pancreatitis with chronic pancreatitis ($n = 17$), relapsing pancreatitis with idiopathy ($n = 5$), pseudocysts ($n = 3$), PD leak ($n = 3$), ampullary adenoma ($n = 3$), papillary stenosis ($n = 3$), prophylaxis of post-ERCP pancreatitis ($n = 3$), and unknown ($n = 1$). The lengths of the migrated pancreatic stents were 3 cm ($n = 11$), 5 cm ($n = 13$), 7 cm ($n = 8$), 8 cm ($n = 2$), 9 cm ($n = 10$), 10 cm ($n = 6$), and unknown ($n = 6$). The sizes of the pancreatic stents were 3F ($n = 2$), 5F ($n = 29$), 6F ($n = 3$), 7F ($n = 15$), 8.5F ($n = 2$), 10F ($n = 1$), and unknown ($n = 4$). The shapes of the pancreatic stents were straight ($n = 26$), single pig tail ($n = 3$), and unknown ($n = 27$). The median time interval from stent placement to migration detection was 2.3 (1–3.3) months.

Endoscopic ultrasound (EUS)-guided PD interventions are useful for salvage therapies to decompress the PD pressure in cases of non-candidates for surgery and failed removal of the stent by ERCP [14, 15]. There are two major EUS-guided PD interventions, namely, the rendezvous technique and pancreaticogastrostomy. Pancreaticogastrostomy is performed for stenting between the PD and the gastrointestinal tract (i.e., stomach, duodenum, or jejunum). On the other hand, the rendezvous technique is performed using a guidewire across the papilla or anastomotic site for retrograde stent insertion. Although EUS-guided PD interventions are useful for salvage therapies, the procedure is not always successful even with skilled endosonographers. Thus, this procedure should be performed in selected patients such as in cases of failed standard ERCP.

Surgical intervention is another option for failed cases of removal of the migrated stent; however, this method is more invasive for patients particularly for benign cases.

A few reports have described the successful retrieval of proximally migrated pancreatic stents, including the use of indirect traction using a balloon positioned above or alongside the stent, direct traction using various devices (forceps, basket, or snare), and stent retrieval after stent lumen cannulation (stent retriever) [9, 10, 13, 16]. These reports suggest that stent retrieval should be approached by indirect balloon extraction, followed by direct traction such as that applied using a forceps, basket, or snare. Details of our experience of removal of proximally migrated pancreatic stents are shown in Table 2. Our most common stent removal technique was balloon extraction. In 4 of 5 (80%)

Table 2 Characteristics of patients and proximally migrated pancreatic duct (PD) stents, including endoscopic retrieval techniques in our study

No.	Disease	Indication	Stent size (F)	Stent length (cm)	Stent shape	Duration of placement (days)	Stricture location	Type of stent migration	MPD diameter (mm)	Attempted removal techniques (use turn order)	Successful techniques	Procedure time (min)
1	Bile duct stone	Prophylaxis of PEP	5	3	Single pig tail	37	None	Type D	3	Direct forceps/ Balloon extraction/ Direct forceps	Balloon extraction → Direct forceps	50
2	Chronic pancreatitis	Stone and stricture	5	7	Straight	5	Head	Type C	5	Balloon extraction	Balloon extraction	36
3	Chronic pancreatitis	Stricture	7	9	Straight	98	Head	Type B	4	Direct forceps	Direct forceps	10
4	Chronic pancreatitis	Stricture	7	9	Straight	30	Head	Type B	6	SSR/ Balloon extraction / Basket	Balloon extraction → Basket	47
5	Chronic pancreatitis	Stricture	7	9	Straight	30	Head and Tail	Type C	6	Balloon extraction / Direct forceps/ SSR	Balloon extraction → SSR	35

PEP post-ERCP pancreatitis, *SSR* Sohendra stent retriever

cases, the stent was removed using either the balloon alone or a combination of the balloon with a forceps, basket, or stent retriever. We suggest a combination of the balloon with other devices as the basis of techniques for the removal of proximally migrated stents. In addition, a retrieval strategy should be considered depending on the anatomical relations of the MPD stricture and the migrated stents.

Technical limitations

Some limitations with the endoscopic removal of PD stents according to the techniques used are as follows: (i) direct traction technique—opening of devices (forceps, basket, or snare) is difficult when there is insufficient space in the MPD (Types A, B, and D); (ii) both indirect and direct traction techniques—in cases in which the migrated stents are located further away from the stricture (Type C), it is difficult to pass the device (forceps, basket, balloon, or snare) across the stricture; (iii) retrieval after stent lumen cannulation technique—if the GW cannot pass through the migrated stent lumen, this technique cannot be used.

Acknowledgments The authors are indebted to Dr Edward Barroga, Associate Professor and Senior Medical Editor of the Department of International Medical Communications of Tokyo Medical University for reviewing and editing the English manuscript.

Conflict of interest None declared.

Author contributions Study design: Matsumoto K and Katanuma A. Acquisition of data: Matsumoto K and Katanuma A. Analysis and interpretation: Matsumoto K and Katanuma A. Manuscript drafted by: Matsumoto K and Katanuma A. Revision: Maguchi H.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1 The case was one in which a 5F 3-cm single pig tail stent completely migrated into the pancreatic branch duct. First, we attempted to use a direct forceps grasp, however the forceps could not be passed through the head of MPD. Subsequently, we passed a 6-mm balloon alongside the stent, and then carefully inflated the balloon. Thereafter we pushed the balloon into the pancreas tail side to dislodge the hooked part of the stent. We also dilated the head side of the MPD to create space. Finally, we used a direct forceps grasp to catch a part of the pig tail stent and could remove the stent successfully.

Clinical Characteristics of Adenosquamous Carcinoma of the Pancreas

A Matched Case-Control Study

Hiroshi Imaoka, MD, Yasuhiro Shimizu, MD,† Nobumasa Mizuno, MD,* Kazuo Hara, MD,* Susumu Hijioka, MD,* Masahiro Tajika, MD,* Shinya Kondo, MD,* Tsutomu Tanaka, MD,* Takeshi Ogura, MD,* Tomohiko Obayashi, MD,* Toshiyuki Hasegawa, MD,‡ Yasumasa Niwa, MD,* and Kenji Yamao, MD**

Objectives: Adenosquamous carcinoma of the pancreas (ASC) is a variant of pancreatic ductal adenocarcinoma (PDAC), but the prognosis remains unclear. The purpose of this study was to clarify the prognosis of ASC using a matched case-control design.

Methods: We evaluated clinical characteristics of ASC treated between 2001 and 2011 in our institution. As controls, PDAC cases matched with ASC cases for sex, age, pretreatment Eastern Cooperative Oncology Group performance status, location, initial therapy and American Joint Committee on Cancer TNM staging for pancreatic cancer were also evaluated.

Results: Of the 914 cases of pancreatic neoplasm, 28 cases (3.06%) of ASC were identified, and 56 cases of PDAC were matched as controls. Median overall survival (OS) was significantly worse for ASC (8.38 months) than for PDAC (15.75 months; hazard ratio [HR], 1.94; 95% confidence interval, 1.07–3.51; $P = 0.026$). Of the 22 unresected cases, median OS was again significantly worse for ASC (4.67 months) than for PDAC (12.36 months; HR, 2.39; 95% confidence interval, 1.27–4.51; $P = 0.007$).

Conclusion: These results demonstrate that ASC is more aggressive than PDAC.

Key Words: adenosquamous carcinoma of the pancreas (ASC), pancreatic ductal adenocarcinoma (PDAC), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), matched case-control study, pancreatic cancer

(*Pancreas* 2014;43: 287–290)

Pancreatic neoplasms may exhibit more than one line of cellular differentiation.[1–3] Adenosquamous carcinoma of the pancreas (ASC) is one such mixed neoplasm, exhibiting both glandular and squamous differentiation.[4–6] Herxheimer[7] reported the first case of ASC in 1907, but despite the accumulation of reports, most descriptions have been from case studies[8] and small surgical series.[9] Adenosquamous carcinoma of the pancreas has anecdotally been considered aggressive and has shown poor prognosis compared with pancreatic ductal adenocarcinoma (PDAC). However, as 2 recent population-based analyses reported,[10,11] whether ASC is actually more aggressive than PDAC remains unclear. Furthermore, many clinical trials have treated both PDAC and ASC equally. The purpose of this study was therefore to clarify the clinical features and prognosis of ASC using a matched case-control design.

From the Departments of *Gastroenterology, †Gastroenterological Surgery, and ‡Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Japan.

Received for publication October 11, 2012; accepted July 26, 2013.

Reprints: Kenji Yamao, MD, Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan (e-mail: kyamao@aichi-cc.jp).

The authors declare no conflict of interest.

MATERIALS AND METHODS

We evaluated the pathological and clinical records of ASC and PDAC treated in our institution between 2001 and 2011. All cases were diagnosed based on cytological or histological confirmation from a surgical specimen or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Pathological diagnosis of ASC was made based on the following criteria for surgical and EUS-FNA specimens. In the surgical specimen, the tumor exhibits both glandular and squamous differentiation, with the squamous component accounting for at least 30% of the neoplasm.[4,5] In the EUS-FNA specimen, aspirate shows both glandular and squamous differentiation characterized by an infiltrating sheetlike arrangement of polygonal cells with keratinization, confirmed by cytological or histological examination (Fig. 1).[12] To distinguish between primary ASC and metastasis from another site,[13] patients with any history of squamous cell carcinoma or other cancers were excluded from this analysis.

The procedure for EUS-FNA has been described previously.[14] After the procedure, one slide was air-dried and examined immediately with a rapid staining method (Diff-Quik stain; International Reagents, Kobe, Japan) to verify adequacy of the specimen and provide a presumptive diagnosis, if possible. Multiple passes were made in each case to provide specimens for cytological studies with Papanicolaou stain. Samples were also exposed to 10% formalin and then processed as a tissue block for histopathological evaluation using hematoxylin-eosin staining.

As controls, PDAC cases matched in a 2:1 ratio to ASC cases for pretreatment Eastern Cooperative Oncology Group performance status (0–1 or ≥2), initial therapy and tumor staging were also included in this study. Data were abstracted from medical records by 2 reviewers (T.O. and T.O.) who were blinded to case-control status. Two reviewers independently assessed these data, and disagreements were resolved by discussion with a third reviewer (K.Y.). In surgical cases, tumor staging was made based on pathological findings. In unresectable cases, staging was made based on computed tomographic results. In both situations, staging was performed in accordance with the American Joint Committee on Cancer staging system for pancreatic cancer. Tumor response and lymph node status were determined according to the Response Evaluation Criteria in Solid Tumor.[15]

Statistical Analysis

All values represent mean ± standard deviation. Bivariate analysis was performed using the Student *t* test for continuous

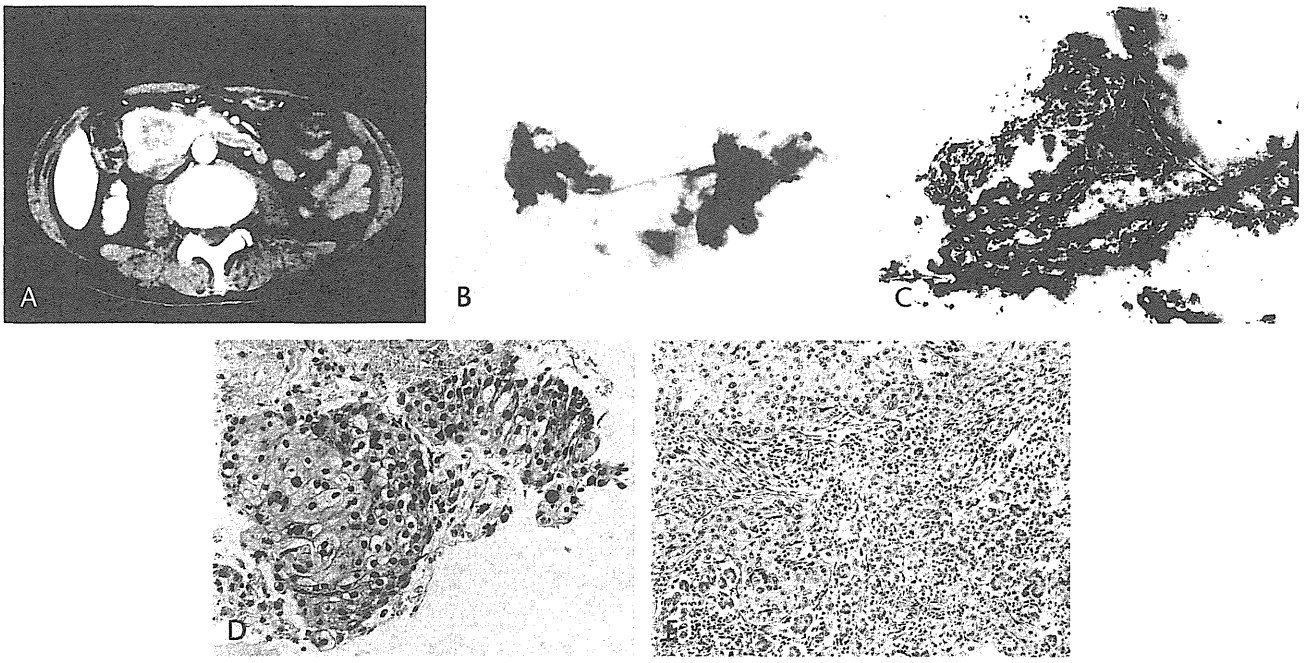

FIGURE 1. Representative images of ASC pathology. A, Computed tomography shows a large heterogeneous mass in the head of the pancreas. In the EUS-FNA specimen, aspirates show atypical keratinized cells with hyperchromatic nucleus and cytoplasmic orangeophilia (Papanicolaou stain, original magnification ×400; B), tissue fragments of neoplastic cells with cytoplasmic opacity and glandular differentiation against a necrotic background (Diff-Quik stain, original magnification ×200; C), and prominent squamous differentiation (hematoxylin and eosin stain, original magnification ×400; D). E, In the surgical specimen, both glandular and squamous differentiation are present (hematoxylin and eosin stain, original magnification ×200).

variables, and using the χ^2 test or the Fisher exact test for categorical variables. Survival was evaluated using the Kaplan-Meier method, and hazard ratios (HRs) were calculated using Cox proportional hazards model. $P < 0.05$ was considered statistically significant, and all P values are 2 sided. Data were analyzed using STATA version 11.1 statistical software (StataCorp, College Station, Tex).

RESULTS

First, we examined clinical characteristics of ASC based on our diagnostic criteria. Of the 914 cases of the pancreatic neoplasms treated between 2001 and 2011, a total of 28 cases (3.0%) of ASC were identified. Patients' characteristics are summarized in Table 1. Median age at diagnosis was 64.0 years (range, 44–79 years). The American Joint Committee on Cancer tumor staging was IIA in 5 patients (17.8%), IIB in 2 patients (7.1%), III in 5 (17.8%), and IV in 16 patients (57.1%). Adenosquamous carcinoma of the pancreas was slightly more common in the body-tail of the pancreas (57.1%). The initial treatment for ASC was curative resection in 6 patients, palliative chemotherapy using gemcitabine (Gem) in 16 cases, Gem plus S-1 in 1 case, 5-fluorouracil-based chemoradiotherapy in 1 case, S-1-based chemoradiotherapy in 1 case, and best supportive care in 3 cases. For the 6 cases of patients (21.4%) who underwent curative resection, pathological tumor staging was IIA in 4 cases and IIB in 2 cases. Three of these cases were located in the pancreatic head, and the others were in the pancreatic body-tail. Five of these cases showed no recurrence, with only 1 case showing recurrence 13.5 months postoperatively (median observation period, 36.6 months [range, 7–90.7 months]).

Next, we clarified the clinical features and prognosis of ASC using a matched case-control study. Characteristics of the control group in the matched case-control study are also shown in Table 1. Demographic and baseline disease characteristics of patients were similar in both ASC and PDAC groups. However, fewer measurable target lymph nodes metastases were seen in the ASC group than in the PDAC group (42.8% vs. 17.8%, $P = 0.014$). In the stage IV patients with ASC, the most common metastatic sites were the liver (81.2%) and lymph nodes (75%). In patients with PDAC, the most common sites were the same, but with different proportions (liver, 59.3%; and lymph nodes, 31.2%). Median duration of follow-up was 14.9 months (95% confidence interval [CI], 11.6–18.1). Median overall survival (OS) was 8.3 months (95% CI, 3.8–16.6 months) in the ASC group, compared to 15.7 months (95% CI, 12.3–32.7 months) in the PDAC group (HR for death, 1.94; 95% CI, 1.07–3.51) (Fig. 2). Overall survival rates at 6, 12, and 24 months were 53.3%, 38.7%, and 12.1%, respectively, in the ASC group compared with 86.9%, 65.3%, and 42.0%, respectively, in the PDAC group.

In unresected patients, the median OS was 4.6 months (95% CI, 3.8–11.8 months) in the ASC group and 12.3 months (95% CI, 8.9–16.0 months) in the PDAC group (HR for death, 2.39; 95% CI, 1.27–4.51) (Fig. 3). Overall survival rates at 6, 12, and 24 months were 43.2%, 24.7%, and 0.0%, respectively, in the ASC group, compared with 83.1%, 55.0%, and 26.9%, respectively, in the PDAC group. Among patients receiving either chemoradiotherapy or chemotherapy, the objective response rate was 10.5% in the ASC group and 13.5% in the PDAC group ($P = 1.000$). On the other hand, among patients receiving palliative chemotherapy using Gem, the objective response rate was 6.25% in the ASC group and 12.5% in the PDAC group ($P = 0.652$). In patients with stage IV disease, the median OS was 3.9 months (95% CI, 3.1–8.3 months) in the ASC group and 9.3 months (95% CI, 6.9–14.8 months) in the PDAC group (HR for death, 2.27; 95% CI, 1.07–4.83). In patients with liver

TABLE 1. Patient Characteristics

	ASC (n = 28)	PDAC (n = 56)	*P*
ECOG performance status score, %			
0–1	27 (96.4)	54 (96.4)	
≥2	1 (3.5)	2 (3.5)	1.000
Initial treatment			
Curative resection	6	12	
Chemoradiation	2	4	
Gem	16	32	
Gem+S-1	1	2	
BSC	3	6	1.000
Tumor stage (AJCC)			
IIA	5	10	
IIB	2	4	
III	5	10	
IV	16	32	1.000
Age, mean ± SD, yr	64.5 ± 9.1	63.8 ± 8.7	0.639
Sex, %			
Male	19 (67.8)	38 (67.8)	
Female	9 (32.1)	18 (32.1)	1.000
Location, %			
Head	12 (42.8)	24 (42.8)	
Body-Tail	16 (57.1)	32 (57.1)	1.000
Measurable metastatic sites, %			
Liver	13 (46.4)	19 (33.9)	0.266
Lymph node	12 (42.8)	10 (17.8)	0.014
Lung	1 (3.5)	6 (10.7)	0.416
Peritoneal	5 (17.8)	12 (21.4)	0.780
Size, mean ± SD, mm	40.6 ± 13.6	35.1 ± 16.3	0.929

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; SD, standard deviation.

metastasis, the median OS was 3.9 months (95% CI, 2.4–8.3 months) in the ASC group and 10.4 months (95% CI, 7.4–14.8 months) in the PDAC group (HR for death, 3.03; 95% CI, 1.26–7.28).

DISCUSSION

Adenosquamous carcinoma of the pancreas is a variant of PDAC that accounts for 3% to 4% of malignant neoplasms of the pancreas.[16–18] Adenosquamous carcinoma of the pancreas has been considered to show poor prognosis owing to its aggressive behavior,[19–21] but the clinical features of ASC have been based primarily on case studies[8] and small surgical series with early-stage cancers.[9] Thus, whether ASC is actually more aggressive than PDAC has remained controversial. Two population-based analyses of ASC have recently been reported.[10,11] Boyd et al[10] described OS after surgical resection of ASC as significantly worse compared to that after resection of PDAC. On the other hand, Katz et al[11] reported that median OS for ASC was 4 months, similar to that for PDAC. They also mentioned that treatment of patients with ASC by surgical resection was associated with a favorable prognosis.[11] These reports about the prognosis of ASC have shown several problems. One is the prejudiced staging of disease. Although ASC has been regarded as a more progressive malignancy, reports have mainly mentioned locoregional disease, not metastatic disease. The other drawback is a

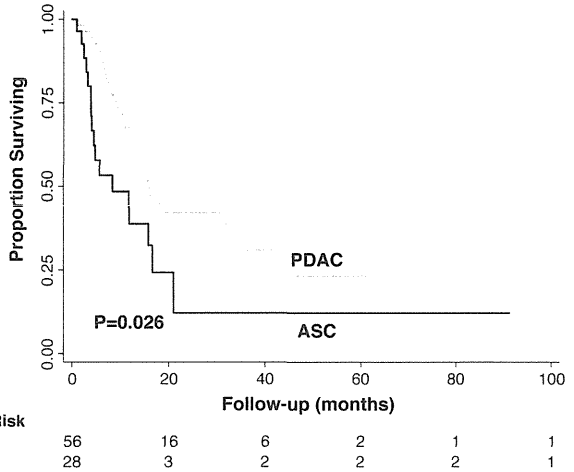

FIGURE 2. Kaplan-Meier curve comparing ASC with PDAC. Kaplan-Meier estimates show overall survival, with median values of 8.3 months in the ASC group and 15.7 months in the PDAC group.

lack of specific information about treatment. Based on registry data, they did not mention detailed palliative treatments in unresectable cases. This information seems essential to clarify the real clinical characteristics and behaviors of ASC. This study therefore examined the clinical characteristics and prognosis of ASC in a matched case-control study.

The present study examined the clinical characteristics and prognosis of ASC. Among all pancreatic neoplasms, 28 cases (3.06%) of ASC were identified. Adenosquamous carcinoma of the pancreas predominantly affected males (67.8%), and the mean age at diagnosis was 64.5 years. These findings resemble the results from other reports for ASC[17,22] and shared clinical characteristics with conventional PDAC. On the other hand, our matched case-control study showed that ASC metastasizes to lymph nodes more frequently than PDAC. Although the difference was not significant, tumors also tended to be larger in ASC than PDAC. Boyd et al[10] reported in a population-based analysis that ASC was more likely to be larger and node

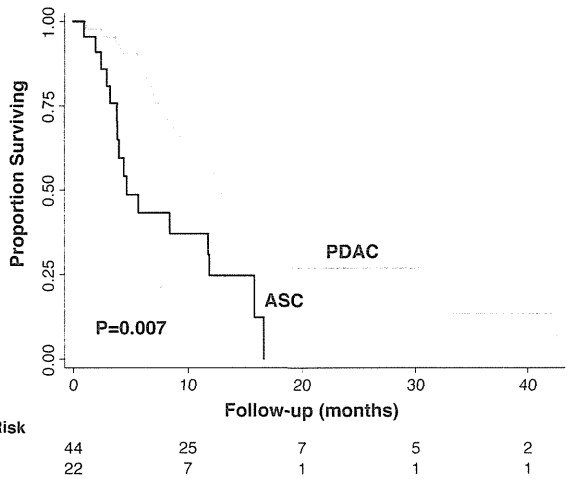

FIGURE 3. Kaplan-Meier curve comparing ASC with PDAC in unresected patients. Kaplan-Meier estimates show overall survival, with median values of 4.6 months in the ASC group and 12.3 months in the PDAC group.

positive compared with PDAC. Results from our matched case-control study support their findings. Because we used cancer stage as a matching valuable, we could not examine the frequency of distant metastases in patients with ASC compared with PDAC. However, ASC being more likely to be larger and node-positive may indicate more aggressive behavior of ASC compared with PDAC.

Our results clearly show that ASC was more progressive than conventional PDAC. The median OS was significantly worse for ASC (8.38 months) than for PDAC (15.75 months). Of the 22 unresected cases, OS was significantly worse for ASC than for PDAC, with an HR of 2.39 (95% CI, 1.27–4.51; $P = 0.007$; median, 4.67 months vs 12.36 months). This seems attributable to the aggressive behavior of ASC. As previously mentioned, ASC tends to metastasize to lymph nodes more frequently than PDAC, even within the same cancer stage. Furthermore, in patients with stage IV disease, simultaneous metastases to the liver and lymph nodes were seen more frequently in the ASC group (43.7%) than in the PDAC group (3.1%, $P = 0.001$). This aggressiveness may contribute to the poor prognosis. We suppose that stronger chemotherapy is one promising option for patients with ASC. In this study, Gem was the most frequently administered agent as palliative chemotherapy. However, Gem shows modest survival benefit in patients with pancreatic cancer. Other newer combination chemotherapeutic regimens, such as GEM+erlotinib[23] and FOLFIRINOX,[24] may thus offer promising therapies for ASC.

In summary, we investigated the clinical characteristics and prognosis of ASC using a matched case-control study. The present results show that ASC was more progressive than conventional PDAC. Conversely, in resectable cases, surgical resection can provide a better prognosis for these patients.

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Can Long-Term Follow-Up Strategies Be Determined Using a Nomogram-Based Prediction Model of Malignancy Among Intraductal Papillary Mucinous Neoplasms of the Pancreas?

Susumu Hijioka, MD, Yasuhiro Shimizu, MD,† Nobumasa Mizuno, MD,* Kazuo Hara, MD,* Hiroshi Imaoka, MD,* Mohamed A. Mekky, MD,‡ Vikram Bhatia, MD,§ Yoshikuni Nagashio, MD,* Toshiyuki Hasegawa, MD,* Akihide Shinagawa, MD,* Masanari Sekine, MD,* Masahiro Tajika, MD,|| Tsutomu Tanaka, MD,|| Makoto Ishihara, MD,|| Yasumasa Niwa, MD,|| and Kenji Yamao, MD**

Objectives: This study investigated whether a risk assessment nomogram can predict the malignant potential of intraductal papillary mucinous neoplasms (IPMNs) and provide valuable information for the follow-up and counseling strategies of such patients.

Methods: We studied 126 of 589 patients with IPMN who were followed up for at least 36 months with annual endoscopic ultrasonography. We analyzed scores derived from our nomogram, incorporating the parameters of sex, lesion type, mural nodule height, and pancreatic juice cytology determined at the initial IPMN evaluation.

Results: The rate of malignant IPMNs was 5.5% (7/126). The initial average nomogram score was 19.8 (range, 0–55), and the final follow-up average was 23.8 (range, 0–109). When a cutoff score was set at 35 points, the sensitivity, specificity, and accuracy of the nomogram to assess malignancy risk were 87.5%, 96.6%, and 96%, respectively. The area under the receiver operating characteristic curve of malignant IPMN prediction during follow-up was 0.865.

Conclusions: The ability of the nomogram to predict malignancy in patients with IPMN was validated. Our findings can suggest that a follow-up for patients at high and low risk for cancer progression could be scheduled every 3 to 6 and 12 months, respectively.

Key Words: IPMN, risk scoring model, treatment, nomogram

(*Pancreas* 2014;43: 367–372)

Ohashi et al[1] originally described intraductal papillary mucinous neoplasms (IPMNs) of the pancreas as mucin-secreting tumors in 1982. The number of individuals diagnosed with IPMN based on the 2005 International Consensus Guidelines for the Management of IPMNs[2] revised in 2012 is increasing.[3] Although IPMNs are considered malignant, clear data that can guide follow-up protocols are not available. The 2012 guidelines recommend a follow-up schedule based on cyst size, namely, annually, every 6 to 12 months, and every 3 to 6 months for cysts that are less than 10 mm, 10 to 20 mm, and more than 20 mm.[3] However, several reports have shown that cyst size alone is not a suitable morphological parameter for evaluating malignancy potential.[4–7] Moreover, a single variable such as cyst size is insufficiently reliable for planning individualized follow-up strategies. Hence, a new risk scoring model is needed to predict the likelihood of carcinoma occurrence and to establish follow-up protocols.

Nomograms are predictive mathematical models that calculate the overall probability based on several factors and are thus more accurate than other models.[8] Treatment and follow-up strategies for various neoplasms such as prostate and colorectal cancers have often been developed based on nomograms.[8–12]

Here, we validate a nomogram that we originally constructed to predict malignancy in 81 patients who had undergone an IPMN resection.[13] The nomogram predicted malignancy with an area under receiver operating characteristic curve (AUC) of 0.903 in that patient set.

In our previous study, multivariate analysis with 81 patients who had undergone IPMN resection demonstrated that pancreatic carcinoma was associated with the female sex, main pancreatic duct (MPD) IPMN, nodule size, and pancreatic juice cytology grade in patients. Thus, the present study performed a retrospective evaluation of whether a scoring system incorporating these variables was a good reflection of the risk for pancreatic carcinoma.

MATERIALS AND METHODS

Patients' Selection

A retrospective study was designed to evaluate our database registry system of endoscopic ultrasonography (EUS) procedures, which revealed 18,000 that were performed between September 1988 and April 2013 at Aichi Cancer Center Hospital (Nagoya, Japan). Of them, we identified 589 patients with IPMN. Among these 589 patients, 126 patients who fulfilled our inclusion criteria were included in the study.

Inclusion Criteria

- Patients had to be followed up for at least 3 years after diagnosis.
- Available data on sex, lesion type, mural nodule (MN) height measured by EUS, and pancreatic juice cytology findings obtained by endoscopic retrograde pancreatography (ERP).
- Patients had to be free of concomitant pancreatic ductal adenocarcinoma development.

The remaining 460 were excluded from the analysis because of the short follow up period (<3 years, n = 372), missing pancreatic juice cytology data (n = 83), or pancreatic ductal adenocarcinoma developing during the study period (n = 3). To avoid a potential for selection bias, 2 patients were also excluded because they were duplicated in our formal study of the original nomogram.

This study was approved by our institutional review board.

From the Departments of *Gastroenterology, and †Gastrointestinal Surgery, Aichi Cancer Center Hospital, Nagoya, Japan; ‡Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut, Egypt; §Department of Medical Hepatology, Institute of Liver and Biliary Sciences, Delhi, India; and ||Department of Endoscopy, Aichi Cancer Center Hospital, Nagoya, Japan.

Received for publication December 26, 2012; accepted August 6, 2013.

Reprints: Susumu Hijioka, MD, Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan (e-mail: rizasusu@aichi-cc.jp).

The authors declare no conflict of interest.

TABLE 1. Clinical Characteristics of Patients

Factors	Patients (n = 126)
Male/female	70/56
Age, median (range), y	62.3 (33–77)
Period, median (range), mo	89 (36–269)
EUS times, median (range)	6.1 (2–15)
Symptomatic/asymptomatic, n (%)	14/112 (9)
MPD type-BD type ratio	6:120
Nodules, n (%)	Yes, 19 (14.%); no, 107 (89.1)
Nodule size, median (range), mm	3.5 (2–5)
Cytological classification (I/II/III/IV/V)	48/62/16/0/0

Evaluation of IPMN Size

The maximal diameter of MNs as well as the sizes of cysts and the MPD were measured by EUS along with computed to mography (CT) and/or magnetic resonance cholangiopancreatography (MRCP).

Follow-Up Protocol

This is composed of at least an annual evaluation with EUS and laboratory tests plus CT and/or MRCP examination every 12 months.

Indications for Surgery

These included MPDs 10 mm or greater, MNs 5 mm or greater, short-term disease progression with a high likelihood of malignancy, cytological detection of malignant cells in pancreatic juice, and significant symptoms such as acute pancreatitis.

Diagnosis of IPMN

Others have characterized IPMN based on the patulous appearance of the ampulla of Vater, filling defects in the pancreatic duct on ERCP, or cystic lesions connecting with the MPD, as determined by EUS, MRCP, and/or CT imaging. Lesions that predominantly involved the MPD and caused a dilatation 10 mm or greater were classified as MPD-IPMN, whereas those that mainly involved a branch pancreatic duct were classified as branch duct (BD)–IPMN.

Cytopathological Evaluation

Two experienced pathologists (Y.Y. and W.H.) reviewed all resected lesions. Based on the degree of cytoarchitectural atypia and the arrangement of the intraductal components, tumors were classified as IPMN adenoma, borderline IPMN, IPMN carcinoma in situ (noninvasive intraductal papillary mucinous carcinoma [IPMC]), or invasive IPMC in accordance with the World Health Organization classification system.[14]

Nomogram

The nomogram incorporated the following risk factors: sex, lesion type, MN height, and pancreatic juice cytology data according to the logistic regression model. Each predictor was scored between 0 and 100, and the scores were totaled. The sum of all scores was represented on a vertical axis that was used to estimate malignancy risk (Fig. 1). The ability of the nomogram to predict malignancy potential had an AUC of 0.903 in the original patient cohort.[13]

Statistical Analysis

Continuous variables are described as mean (SD), and dichotomous variables are expressed as simple proportions. The χ^2 test was used for comparative analyses. Data were statistically analyzed using the SPSS software for Windows, release 11 (SPSS Inc, Chicago, Ill). Significance was achieved when P is less than 0.05. The optimal cutoff levels for nomogram point were determined by receiver operating characteristic (ROC) curves to differentiate the low-risk group from the high-risk group of developing cancer and identify the point which showed equal sensitivity and specificity, which were also calculated.

RESULTS

Patients' Characteristics

A total of 108 patients with IPMN (male, n = 70; mean age, 62.3 years at the time of diagnosis) were followed up for a

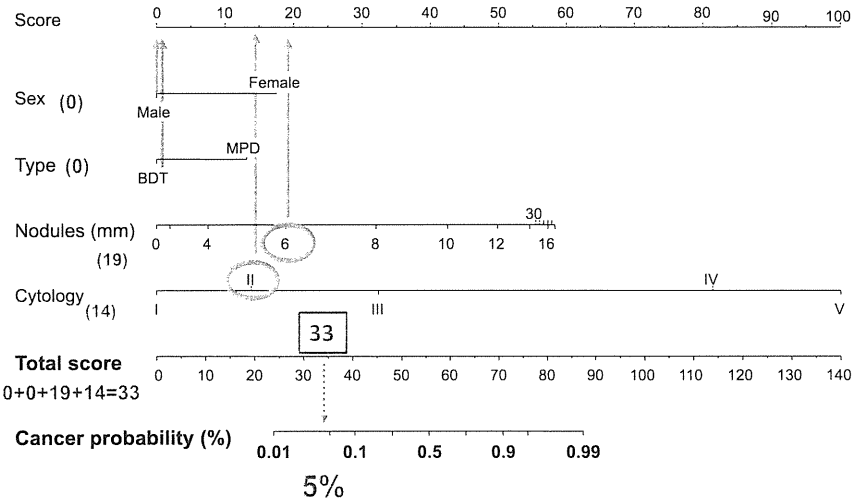

FIGURE 1. How to use the nomogram. Find the position of each variable on the corresponding axis, draw a line to the "points" axis for the number of points, add the points from all variables, and draw a line from the "total points" axis to determine cancer probability at the bottom. For example, for BD-IPMN in men, the nodule height was 6 mm, the cytological classification of the pancreatic juice was class II, men had 0 point, branch duct type was 0 point, 6-mm nodule height corresponds to 19 points, and cytological class II corresponds to 14 points. The total score was 0 + 0 + 19 + 14 = 33, where cancer probability was calculated as approximately 5%. BDT, branch duct type.

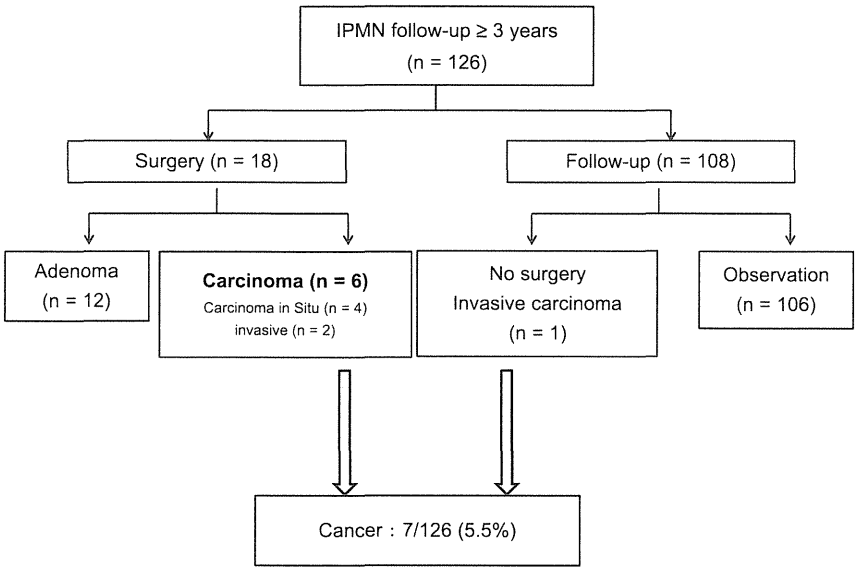

FIGURE 2. Clinical course of IPMN followed up for 3 years or more. Only 5.6% (6/108) of patients developed malignancies, assuming that the entire follow-up group had only benign lesions at the start of study.

median of 89 months (range, 36–269 months). Each patient underwent an average of 6.1 EUS procedures (range, 2–15 procedures) throughout the follow-up period. Six and 120 patients had MPD-IPMN and BD-IPMN, respectively. The median diameters of the cysts and MPDs were 18.6 mm (range, 0–60 mm) and 2.7 mm (range, 1–10 mm), respectively. Nineteen patients (14.9%) had MNs with a median size of 3.5 mm (range, 2–5 mm). Pancreatic juice cytology was classified as I, II, and III in 48, 62, and 16 patients, respectively, among whom 18 (14.2%) underwent surgery. Table 1 summarizes the clinical characteristics of the patients.

Follow-Up Results

Patients were assigned to either a group that was followed up for at least 3 years (follow-up group) or an operation group throughout the follow-up period. The follow-up group included 1 patient who developed carcinoma. This patient was managed with a best supportive care regimen because of having a poor performance status and was excluded thereafter from the analysis. The operation group (n = 18) was composed of patients who had undergone surgery to treat MPD dilation (n = 5), large MNs (n = 9), or acute pancreatitis (n = 4). Among them, 12 had adenoma and 6 had carcinoma (in situ, n = 4; minimally invasive,

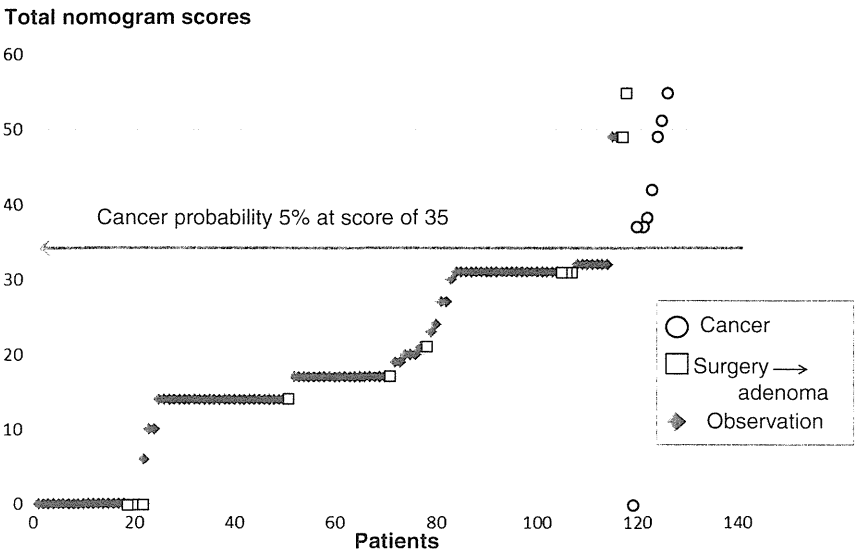

FIGURE 3. Initial nomogram total scores for all patients in order. Diamonds, squares, and circles indicate patients who were observed, underwent surgery to treat adenoma and patients with cancer respectively. A score of 35 indicates a 5% probability of developing cancer.