

## ORIGINAL ARTICLE

# Risk of pancreatitis after endoscopic retrograde cholangiopancreatography and endoscopic biliary drainage

Hiroyuki Matsubayashi<sup>1</sup>, Akira Fukutomi<sup>2</sup>, Hideyuki Kanemoto<sup>3</sup>, Atsuyuki Maeda<sup>3</sup>, Kazuya Matsunaga<sup>3</sup>, Katsuhiko Uesaka<sup>3</sup>, Yosuke Otake<sup>1</sup>, Noriaki Hasuike<sup>1</sup>, Yuichiro Yamaguchi<sup>1</sup>, Hisatomo Ikehara<sup>1</sup>, Kohei Takizawa<sup>1</sup>, Kentaroh Yamazaki<sup>2</sup> & Hiroyuki Ono<sup>1</sup>

Divisions of <sup>1</sup>Endoscopy, <sup>2</sup>Gastrointestinal Oncology, and <sup>3</sup>Hepatopancreatobiliary Surgery, Shizuoka Cancer Centre, Nagaizumi, Suntogun, Shizuoka, Japan

## Abstract

**Background:** Pancreatitis is the most common and serious complication to occur after endoscopic retrograde cholangiopancreatography (ERCP). It is often associated with additional diagnostic modalities and/or treatment of obstructive jaundice. The aim of this study was to determine the risk of post-ERCP pancreatitis associated with pancreaticobiliary examination and endoscopic biliary drainage (EBD).

**Methods:** A total of 740 consecutive ERCP procedures performed in 477 patients were analysed for the occurrence of pancreatitis. These included 470 EBD procedures and 167 procedures to further evaluate the pancreaticobiliary tract using brush cytology and/or biopsy, intraductal ultrasound and/or peroral cholangioscopy or peroral pancreatoscopy. The occurrence of post-ERCP pancreatitis was analysed retrospectively.

**Results:** The overall incidence of post-ERCP pancreatitis was 3.9% (29 of 740 procedures). The risk factors for post-ERCP pancreatitis were: being female (6.5%; odds ratio [OR] 2.5,  $P = 0.02$ ); first EBD procedure without endoscopic sphincterotomy (ES) (6.9%; OR 3.0,  $P = 0.003$ ), and performing additional diagnostic procedures on the pancreaticobiliary duct (9.6%; OR 4.6,  $P < 0.0001$ ). Pancreatitis after subsequent draining procedures was rare (0.4%; OR for first-time drainage 16.6,  $P = 0.0003$ ). Furthermore, pancreatitis was not recognized in 59 patients who underwent ES. Seven patients with post-EBD pancreatitis were treated with additional ES.

**Conclusions:** Invasive diagnostic examinations of the pancreaticobiliary duct and first-time perampullary biliary drainage without ES were high-risk factors for post-ERCP pancreatitis. Endoscopic sphincterotomy may be of use to prevent post-EBD pancreatitis.

## Keywords

endoscopic retrograde cholangiopancreatography (ERCP), endoscopic biliary drainage (EBD), pancreatitis, endoscopic sphincterotomy (ES), pancreatic stent

Received 6 August 2008; accepted 25 October 2008

## Correspondence

Hiroyuki Matsubayashi, Division of Endoscopy, Shizuoka Cancer Centre, 1007 Nagaizumi, Suntogun, Shizuoka 411-8777, Japan. Tel: + 81 55 989 5222. Fax: + 81 55 989 5692. E-mail: h.matsubayashi@scchr.jp

## Introduction

Pancreatitis is the most common and serious complication of endoscopic retrograde cholangiopancreatography (ERCP), occurring in 2%<sup>1</sup> to 15%<sup>2</sup> of cases according to criteria defined by Cotton and others.<sup>3</sup> Several technical and patient-related risk factors for post-ERCP pancreatitis, which act independently or

**Grant support:** This study was partially supported by a grant from the Japanese Foundation for Research and Promotion of Endoscopy.

together, have been identified.<sup>3-5</sup> To date, clinicians have attempted to minimize the incidence and severity of post-ERCP pancreatitis by identifying high-risk populations,<sup>5</sup> by making devices to reduce the trauma caused by endoscopic interventions, by administering pharmacological agents,<sup>6-8</sup> and by inserting pancreatic stents after ERCP.<sup>9-11</sup> Risk factors for the development of post-ERCP pancreatitis include patient factors (female gender,<sup>2,5</sup> younger age,<sup>1,2</sup> sphincter of Oddi dysfunction,<sup>2,5,12</sup> cannulation difficulty,<sup>2,12</sup> pancreatic divisum,<sup>2</sup> a history of post-ERCP

pancreatitis<sup>2,12</sup>), operator factors (inexperienced operator, prolonged procedure time,<sup>12</sup> repeated injection to pancreatic duct<sup>12</sup>) and the role of additional procedures such as endoscopic sphincterotomy (ES),<sup>2,12</sup> precut papillotomy,<sup>1</sup> endoscopic papillary balloon dilatation (EPBD) and biliary stone extraction.<sup>1</sup>

Regardless of ES, endoscopic (retrograde) biliary drainage (EBD), including EBD tube stent and endoscopic nasobiliary drainage (ENBD) catheter placement, have been thought of as safe and effective methods for treating acute cholangitis and obstructive jaundice<sup>13,14</sup> in both benign<sup>15,16</sup> and malignant disease.<sup>13</sup> At a recent international consensus conference of international pancreaticobiliary experts held in Tokyo, about 90% of panellists preferred endoscopic over percutaneous drainage approaches and 24% of panellists felt that ES was not necessary for biliary drainage.<sup>13</sup>

Thanks to the development of magnetic resonance cholangiopancreatography, the need for ERCP as a diagnostic procedure is declining. However, ERCP is still a powerful tool<sup>17-19</sup> for obtaining samples for cytology and pathology<sup>19,20</sup> and may help to determine the extent of the tumour prior to surgery using intraductal ultrasonography (IDUS)<sup>21,22</sup> and by placing a small cholangiopancreatroscope ('baby scope').<sup>23,24</sup> In this study, we retrospectively determined the risk for post-ERCP pancreatitis, focusing particularly on the incidence of pancreatitis after EBD insertion with or without ES and after other invasive diagnostic procedures.

## Materials and methods

### Patients

Between October 2002 and August 2007, 447 patients (male : female ratio 295 : 152, mean age 65.3 years) underwent 740 ERCP-associated procedures (male : female ratio 509:231) at Shizuoka Cancer Centre. Of these 740 ERCPs, 525 procedures were carried out in patients with invasive cancers (pancreatic ductal adenocarcinoma [296], biliary carcinoma [152; bile duct = 112, gallbladder = 40], metastatic tumour with biliary obstruction [56], hepatocellular carcinoma [12], ampullary carcinoma [9]), 68 were performed in patients with benign or intraductal neoplasms (intraductal papillary mucinous neoplasm [IPMN] [46], ampullary adenoma [15], pancreatic endocrine tumour [3], solid papillary tumour [2], mucinous cystic neoplasm [MCN] [1], serous cystadenoma [1]), and 147 were performed in patients with benign inflammatory diseases, which included 73 procedures carried out to remove bile duct stones. In the 12 cases with hepatocellular carcinoma, six ERCP procedures were performed for obstruction at the hepatic hilar bile duct, three for lower bile duct obstruction caused by lymph nodal metastases, two for suspected bile leak after hepatectomy, and one in a case with concurrent sphincter of Oddi dysfunction. The ERCP procedures were indicated for insertion or exchange of a plastic biliary stent in 470 cases (63.5%), and for invasive diagnostic examinations using at least one of brush cytology, biopsy from pancreaticobiliary tract, IDUS, peroral cholangioscopy (POCS) or peroral pancreatoscopy (POPS) in 167 (22.6%). Endoscopic retrograde cholangiopancre-

atography was performed using Olympus endoscopes (JF240, TJF240, JF260V), the PR109Q catheter for routine cannulation and the Clever Cut 3V for ES (Olympus Corp., Tokyo, Japan).

### Biliary drainage

Endoscopic biliary drainage was inserted or exchanged when the patient had at least one symptom of Charcot's triad (fever, jaundice, abdominal pain), but was rarely performed in cases with only mild hyperbilirubinaemia in order to maintain a constant level of chemotherapy (consisting of chemo-agents metabolized through the liver and biliary tract). The 470 biliary drainage procedures consisted of 404 EBD and 66 ENBD procedures. For EBD, we used a Tannenbaum plastic stent (8.5 and 10 Fr, 5 ~ 9 cm; Wilson-Cook Medical Inc., Winston-Salem, NC, USA) in 86% of cases, a Flexima® plastic stent (7.0 and 8.5 Fr, 10 ~ 12 cm; Boston Scientific Corp., Natick, MA, USA) in 5% and a Zimmon plastic stent (7 Fr, 7 ~ 10 cm; Wilson-Cook Medical Inc.) in the remaining 9% of cases. For ENBD, we used a pigtailed NB tube (6 and 7 Fr; Hanako Medical Co. Ltd, Saitama, Japan) in 97% of cases and a pigtailed Liguory tube (5 Fr; Wilson-Cook Medical Inc.) in 3%. We chose a thinner stent for the first insertion of a biliary drain ( $\leq 8.5$  Fr, 83% of procedures [203/245]), and a larger-diameter stent for second and subsequent procedures (10 Fr, 61% of procedures [137/225 procedures]).

### Diagnostic examination of the pancreaticobiliary tract

We categorized a procedure as a 'diagnostic examination' when the ERCP procedure included at least one of the following modalities: endoscopic biopsy; brush cytology; IDUS; POCS, or POPS. The indication for these invasive diagnostic examinations generally referred to the need to establish a diagnosis of malignancy before surgical operation. We used an FB44U-1 biopsy forceps (Olympus Corp.) for duct biopsy, a BC-24Q (Olympus Corp.) endoscopic brush catheter for brush cytology, a UM-G20-29R (Olympus Corp.) for IDUS, a CHF-B260 (Olympus Corp.) for POCS, and a PF Type 8P (Olympus Corp.) for POPS. When POCS was performed, ES was always added. We did not include simple aspiration cytology from the pancreaticobiliary duct because of the low rate of pancreatitis. Of 167 procedures, 80 were biliary duct procedures, 69 involved the pancreatic duct and 18 involved both the pancreatic and biliary tracts.

### Criteria for the diagnosis of post-ERCP pancreatitis

Post-ERCP pancreatitis was diagnosed according to the generally accepted criteria defined by Cotton *et al.*,<sup>3</sup> (i.e. patients who had upper abdominal pain 24 hours after an ERCP procedure and a serum amylase level [U/l] more than three times the upper limit of normal).

### Data analysis

First, we examined 11 factors for the development of post-ERCP pancreatitis, including seven factors identified in previous reports (gender, age, biliary stone removal, performance of ES, EPBD,

biliary metallic stent insertion and pancreatic plastic stent insertion) and new factors (ERCP-associated diagnostic procedure, EBD insertion [first-time and subsequent] and disease type). These were analysed using chi-square test<sup>2</sup> or Fisher's test. Multivariate analysis using multiple logistic regression analysis was added on the factors revealed to be significant by a single-variate analysis to identify factors that were independently significant for post-ERCP pancreatitis. Then, combinations of three significant risk factors including initial EBD insertion, additional diagnostic procedures and disease type were analysed by chi-square test<sup>2</sup> or Fisher's test. A *P*-value of < 0.05 was considered as statistically significant.

## Results

### Risk factors of post-ERCP pancreatitis

Post-ERCP pancreatitis occurred in 29 of 740 (3.9%) ERCP procedures. Ten risk factors for the development of post-ERCP pancreatitis are summarized in Table 1. Invasive diagnostic examination (biopsy, brush cytology, IDUS and baby scope observation), first-time biliary drainage, being female and the presence of particular disease types (pancreatic tumour other than pancreatic carcinoma including IPMN, MCN, solid-cystic tumour) were evaluated as statistically significant by single-variate analysis. The odds ratio (OR) for developing post-ERCP pancreatitis as a result of pancreaticobiliary invasive examination was 4.6, of first-time biliary drainage 3.0, of pancreatic tumour other than pancreatic carcinoma 2.9 and of female gender 2.5. Although the *P*-value was 0.0502, the group with non-neoplastic pancreaticobiliary disease without bile duct stone removal showed a higher trend of post-ERCP pancreatitis (OR 2.5) (Table 1). The six risk factors listed above were further analysed by multivariate analysis and the result showed independent risk for post-ERCP pancreatitis for first-time EBD ( $r = 3.44$ ), diagnostic examination ( $r = 2.98$ ), being female ( $r = 2.47$ ) and benign pancreatic tumour ( $r = 2.15$ ) (Table 2). Most ERCP procedures were performed by two experienced endoscopists (HM and AF had each carried out >1000 ERCP-associated procedures) and the incidence of post-ERCP pancreatitis did not differ by operator. All pancreatitis cases were graded as mild and recovery required only a couple of days of hospitalization with i.v. analgesia and i.v. fluids.

### Risk for pancreatitis after endoscopic biliary drainage

Post-EBD pancreatitis occurred in 17 of 246 (6.9%) patients undergoing biliary drainage for the first time, despite the fact that most stents were small-bore ( $\leq 8.5$  Fr in 83% of cases). There was a trend for post-ERCP pancreatitis to be more common when larger-bore ( $\geq 8.5$  Fr) stents were used (7.4% [14/189] of cases, including 7.3% [3/41] of 10-Fr cases and 7.4% [11/148] of 8.5-Fr cases) than when stents <8.5 Fr were used (5.3% [3/57] of cases). As Table 3 shows, performing additional invasive examinations on first-time drainage increased the incidence up to three times (15.2% vs. 5.0%; OR 3.4, *P* = 0.01). However, pancreatitis did not occur after sphincterotomy (none of 17 cases). Post-EBD pancre-

atitis often occurred in cases with small papilla or narrow papilla apertures that impeded the smooth insertion of the drainage tube.

### Risk of pancreatitis after ERCP-associated diagnostic examination

We recognized pancreatitis in 9.6% of subjects who underwent ERCP-associated diagnostic examination using at least one additional diagnostic modality (biopsy, brush cytology, IDUS, POCS or POPS) with an OR of 4.6 (*P* < 0.0001) (Table 1). As shown in Table 4, when the first EBD was added after these diagnostic examinations, the risk of pancreatitis increased 2.2 times (*P* = 0.13). When we applied multiple modalities, the incidence of pancreatitis increased modestly but not significantly. The incidence of post-ERCP pancreatitis did not differ by site of lesion or diagnostic modality (Table 4).

### Risk of post-ERCP pancreatitis by disease type

As Table 5 shows, the incidence of post-ERCP pancreatitis varied by disease type.

The incidence of post-ERCP pancreatitis was high in patients with benign pancreatic tumours other than pancreatic carcinoma (9.4%, five of 53 cases), those with benign pancreaticobiliary disease except for bile duct stone (8.1%, six of 74 cases) and biliary carcinoma (5.9%, nine of 152 cases), and lower than average in patients with pancreatic adenocarcinoma (2.4%, seven of 296 cases) and those with metastatic cancers with biliary obstruction (3.6%, two of 56 cases). There was a significant difference in the incidence of pancreatitis in patients with pancreatic tumours other than pancreatic carcinoma compared with those with pancreatic adenocarcinoma (*P* = 0.009) and between patients with benign pancreaticobiliary disease and those with pancreatic adenocarcinoma (*P* = 0.016). In cases of first-time EBD insertion, subjects with biliary carcinoma (17.0%) showed a higher incidence of post-EBD pancreatitis than those with pancreatic adenocarcinoma (4.2%) (*P* = 0.005). Similarly, by adding other risk factors, the incidence of post-ERCP pancreatitis increased, for instance, up to 27.3% (six of 22) in biliary carcinoma cases with first-time EBD and diagnostic examination (Table 5).

### Post-ERCP pancreatitis after ES and ES for post-EBD pancreatitis

As Table 1 shows, whether with or without EBD, none of the 59 patients who underwent ES procedures and none of 17 cases with pancreatic stent insertion developed pancreatitis. In cases of initial EBD without ES, seven patients who developed post-EBD pancreatitis were treated with additional ES to facilitate pancreatic drainage, including one subject who was treated further with the placement of a smaller EBD instrument and another with the placement of a pancreatic stent. These procedures were associated with a decrease in abdominal pain and improved serum amylase levels.

**Table 1** Incidence and risk level of post-endoscopic retrograde cholangiopancreatography pancreatitis (*n* = 740 procedures)

Factor		Frequency of post-ERCP pancreatitis ( <i>n</i> )	Odds ratio	<i>P</i> -value <sup>a</sup>
Significant				
Diagnostic examination <sup>b</sup>	(+)	9.6% (16/167)	<b>4.6</b>	< <b>0.0001</b>
	(-)	2.3% (13/573)		
First EBD	(+)	6.9% (17/246)	<b>3.0</b>	<b>0.003</b>
	(-)	2.4% (12/494)		
Gender	Female	6.5% (15/231)	<b>2.5</b>	<b>0.02</b>
	Male	2.8% (14/509)		
Disease	Neoplasm	3.9% (23/593)	0.9	0.95
	Non-neoplasm	4.1% (6/147)		
	Pancreatic carcinoma	2.4% (7/296)	0.5	0.08
	Biliary carcinoma <sup>c</sup>	5.9% (9/152)	1.8	0.15
	Obstructive jaundice by distant metastasis	3.6% (2/56)	0.9	0.89
	HCC	0% (0/12)	-	0.48
	Pancreatic tumour other than pancreatic carcinoma	9.4% (5/53) <sup>d</sup>	<b>2.9</b>	<b>0.03</b>
	Ampullary tumour <sup>e</sup>	0% (0/24)	-	0.31
	Bile duct stone	0% (0/73)	-	0.07
Non-neoplastic pancreaticobiliary disease <sup>f</sup>	8.1% (6/74)	2.5	0.0502	
Not significant				
ES	(+)	0% (0/59)	-	0.11
	(-)	4.3% (29/681)		
Stone removal	(+)	0% (0/44)	-	0.17
	(-)	4.2% (29/696)		
EPBD	(+)	0% (0/24)	-	0.31
	(-)	4.1% (29/716)		
Pancreatic stent	(+)	0% (0/17)	-	0.40
	(-)	4.0% (29/723)		
Biliary metallic stent	(+)	0% (0/14)	-	0.45
	(-)	4.0% (29/726)		
Overall EBD	(+)	3.8% (18/470)	0.9	0.90
	(-)	4.1% (11/270)		
Age, years	>65	4.0% (15/378)	1.0	0.94
	≤65	3.9% (14/362)		
Overall		3.9% (29/740)		

<sup>a</sup>Chi-square test, Fisher's test

<sup>b</sup>Diagnostic examination of pancreaticobiliary duct included at least one of biopsy, brush cytology, intraductal ultrasound, peroral cholangioscopy and peroral pancreatoscopy

<sup>c</sup>Biliary carcinomas included 42 cases of bile duct carcinoma and 11 cases of gallbladder carcinoma

<sup>d</sup>Post-ERCP pancreatitis was recognized in 6.5% (6/46) of cases with intraductal papillary mucinous neoplasm, one of two cases with solid-cystic tumour, one case of serous cyst adenoma and none of three pancreatic endocrine tumours and one mucinous cystic neoplasm

<sup>e</sup>Ampullary tumours included nine cases of carcinoma and 15 cases of adenoma

<sup>f</sup>Benign pancreaticobiliary inflammatory disease included benign biliary and pancreatic duct stricture, pancreatic cyst, chronic pancreatitis, cholecystitis and gallstone, except for cases with bile duct stone

ERCP, endoscopic retrograde cholangiopancreatography; EBD, endoscopic biliary drainage; HCC, hepatocellular carcinoma; ES, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation

## Discussion

We have identified four risk factors for the development of post-ERCP pancreatitis: being female; first-time EBD com-

pared with subsequent EBD procedures; the performance of additional invasive diagnostic examinations associated with ERCP, and the underlying disease (benign pancreatic tumours).

**Table 2** Risk for post-endoscopic retrograde cholangiopancreatography pancreatitis by multivariate analysis ( $n = 740$  procedures)

Factor	R	P-value	95% CI
First EBD	<b>3.44</b>	<b>0.0006</b>	1.98 ~ 12.16
Diagnostic examination, $n$	<b>2.98</b>	<b>0.003</b>	1.56 ~ 8.63
Female	<b>2.47</b>	<b>0.013</b>	1.23 ~ 5.90
Benign pancreatic tumour other than pancreatic cancer	<b>2.15</b>	<b>0.032</b>	1.13 ~ 15.46
Non-neoplastic pancreaticobiliary disease <sup>a</sup>	1.82	0.069	0.93 ~ 7.88

<sup>a</sup>Non-neoplastic pancreaticobiliary disease except for 73 cases of biliary stone  
95% CI, 95% confidence interval; EBD, endoscopic biliary drainage

**Table 3** Risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in cases of first-time endoscopic biliary drainage ( $n = 246$  cases)

Factor		Frequency of post-ERCP pancreatitis ( $n$ )	Odds ratio	P-value <sup>a</sup>
Diagnostic examination	(+)	15.2% (7/46)	<b>3.4</b>	<b>0.01</b>
	(-)	5.0% (10/200)		
Endoscopic sphincterotomy	(+)	0% (0/17)	-	0.24
	(-)	7.4% (17/229)		
Size of drain	$\geq 8.5$ Fr	7.4% (14/189)	1.4	0.58
	$< 8.5$ Fr	5.3% (3/57)		

<sup>a</sup>Chi-square test, Fisher's test

**Table 4** Risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in cases with pancreaticobiliary diagnostic examination ( $n = 167$  procedures)

Factor		Frequency of post-ERCP pancreatitis ( $n$ )	Odds ratio	P-value <sup>a</sup>
First-time biliary drainage	(+)	15.2% (7/46)	<b>2.2</b>	<b>0.13</b>
	(-)	7.4% (9/121)		
Target region	Biliary duct	10.0% (8/80)	-	0.83
	Pancreatic duct	10.1% (7/69)		
	Both	5.6% (1/18)		
Number of modalities per case	1	8.2% (4/49)	-	0.88
	2	8.9% (5/56)		
	3	9.8% (4/41)		
	4	14.3% (3/21)		
Modality	Biopsy	10.1% (11/109)	-	0.90
	Brush cytology	9.0% (10/111)		
	IDUS	11.9% (12/101)		
	POCS or POPS	12.0% (3/25)		

<sup>a</sup>Chi-square test, Fisher's test

ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasound; POCS, peroral cholangioscopy; POPS, peroral pancreatoscopy

Our results suggest that the first EBD procedure is riskier than subsequent procedures, especially when the drainage instrument is thicker ( $\geq 8.5$  Fr); by contrast, no pancreatitis was observed and post-EBD pancreatitis recovered when biliary ES was added. To date, the first EBD procedure has not been reported as a risk for post-ERCP pancreatitis.<sup>1,15</sup> Hui *et al.*<sup>15</sup> reported that the risk of pancreatitis did not depend on whether or not an ES was performed before EBD insertion; however, these authors used a small (7 Fr) stent. Multicentre analysis in Italy also showed no difference

in occurrences of pancreatitis with and without EBD insertion ( $P = 0.12$ ). Of note, more than two-thirds of ERCP procedures for biliary drainage in this study (1662 of 2444) were carried out with ES. At a consensus meeting in Tokyo in 2006,<sup>13</sup> more than two-thirds of international experts agreed on the necessity of ES for EBD insertion in certain situations despite the known complications of ES, which include haemorrhage and pancreatitis.<sup>25-27</sup> In our experience of initial EBD insertion, post-EBD pancreatitis is frequently observed when there is resistance against stent inser-

**Table 5** Risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis by disease type ( $n = 740$  procedures)

Disease	Frequency of post-ERCP pancreatitis ( $n$ )			
	Overall	With first EBD	With diagnostic examination	With diagnostic examination and first EBD
Pancreatic carcinoma	2.4% (7/296) <sup>A</sup>	4.2% (5/118) <sup>D</sup>	3.3% (1/30)	0% (0/10)
Biliary carcinoma <sup>a</sup>	5.9% (9/152)	17.0% (9/53) <sup>E</sup>	13.6% (6/44)	27.3% (6/22)
Obstructive jaundice by distant metastasis	3.6% (2/56)	7.4% (2/27)	0% (0/3)	0% (0/1)
HCC	0% (0/12)	0% (0/8)	–	–
Pancreatic tumour other than pancreatic carcinoma	9.4% (5/53) <sup>AB</sup>	0% (0/1)	9.1% (4/44)	–
Ampullary tumour <sup>b</sup>	0% (0/24)	0% (0/6)	0% (0/8)	0% (0/1)
Bile duct stone	0% (0/73)	0% (0/13)	0% (0/4)	0% (0/2)
Non-neoplastic pancreaticobiliary disease <sup>c</sup>	8.1% (6/74) <sup>C</sup>	5.0% (1/20)	14.7% (5/34)	10.0% (1/10)
Total	3.9% (29/740)	6.9% (17/246)	9.6% (16/167)	15.2% (7/46)

<sup>a</sup>Biliary carcinomas included 42 cases of bile duct carcinoma and 11 cases of gallbladder carcinoma

<sup>b</sup>Ampullary tumours included nine cases of carcinoma and 15 of adenoma

<sup>c</sup>Benign pancreaticobiliary disease included benign biliary and pancreatic duct stricture, pancreatic cyst, chronic pancreatitis, cholecystitis, gallstone

<sup>d</sup>Post-ERCP pancreatitis was found in 6.5% (6/46) of cases with intraductal papillary mucinous neoplasm, one of two cases with solid-cystic tumour, one case of serous cyst adenoma and none of three pancreatic endocrine tumours and one mucinous cystic neoplasm

A vs. B:  $P = 0.009$ ; A vs. C:  $P = 0.016$ ; D vs. E:  $P = 0.005$

ERCP, endoscopic retrograde cholangiopancreatography; EBD, endoscopic biliary drainage; HCC, hepatocellular carcinoma

tion through a relatively small papillary orifice (data not shown), presumably because of the tight obstruction of the ampullary pancreatic duct by the biliary drainage. This impression is supported by data showing that the incidence of post-ERCP pancreatitis was significantly higher after a first drainage procedure (6.9%, 17 of 246 procedures) than after the second (0.5%, one of 224 procedures). More than 80% of EBD procedures were performed using stents of  $\leq 8.5$  Fr for initial drainage. These data thus highlight the fact that pancreatitis is not uncommon after EBD, even when small-bore stents ( $< 8.5$  Fr) are used.

Another risk factor for the development of post-ERCP pancreatitis is the performance of additional 'invasive diagnostic procedures' including biopsy, brush cytology, IDUS and the use of a baby scope. In our series, the incidence of pancreatitis was higher in patients who underwent many diagnostic procedures, especially when a procedure followed EBD insertion. It is noteworthy that post-ERCP pancreatitis was higher in patients with biliary adenocarcinoma, benign pancreatic tumours and non-neoplastic pancreaticobiliary diseases than in those with pancreatic adenocarcinoma. This trend was remarkable when initial biliary drainage was added (Table 4) and in cases of biliary carcinoma or benign non-neoplastic pancreaticobiliary disease (Table 5). Many pancreatic cancers have already caused obstruction of the main pancreatic duct and accompanying chronic pancreatitis of the upstream pancreas at the time of clinical presentation. It is quite possible that acute pancreatitis after ERCP is less likely in a chronically scarred gland that has severe fibrosis and atrophy. As many pancreaticobiliary duct neoplasms are accompanied by obstructed jaundice, one of the techniques by which post-EBD pancreatitis can be avoided involves improving pancreatic juice drainage by performing a biliary sphincterotomy when the papillary orifice is small.

To date, many risk factors for post-ERCP pancreatitis have been reported from high-volume centres, such as being female,<sup>2,5</sup> being of younger age,<sup>1,2</sup> sphincter of Oddi dysfunction,<sup>2,5,12</sup> cannulation difficulty,<sup>2,12</sup> prolonged procedure time,<sup>12</sup> repeated injection to the pancreatic duct,<sup>12</sup> precut papillotomy,<sup>1</sup> EPBD and biliary stone extraction.<sup>1</sup> Our result was not fully consistent with these, however, and we must remember that not many of these factors were analysed in our study and that the major proportion of our study population consisted of cases with neoplasm. Further prospective study is needed to confirm the current postulations.

Endoscopists should be aware of the risk of pancreatitis when they perform additional invasive diagnostic examinations and/or first-time perampullary biliary drainage associated with ERCP, depending on the disease type. Recent reports have demonstrated the effects of guidewire cannulation<sup>28,29</sup> and pancreatic stent insertion<sup>9,10</sup> in the prevention of post-ERCP pancreatitis. Given the current results, minimizing the number of invasive diagnostic modalities and adding ES may also be effective in preventing post-ERCP and post-EBD pancreatitis.

#### Acknowledgements

The authors are grateful to Dr Michael Goggins of the Department of Gastrointestinal Pathology and Medicine, Johns Hopkins University, for his English review of this manuscript.

#### Conflicts of interest

None declared.

#### References

- Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, *et al.* (2001) Complications of diagnostic and therapeutic ERCP: a prospective multi-centre study. *Am J Gastroenterol* 96:417–423.

2. Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, *et al.* (2006) Risk factors for post-ERCP pancreatitis: a prospective multicentre study. *Am J Gastroenterol* 101:139–147.
3. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, *et al.* (1991) Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 37:383–393.
4. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, *et al.* (2001) Risk factors for post-ERCP pancreatitis: a prospective, multicentre study. *Gastrointest Endosc* 54:425–434.
5. Masci E, Mariani A, Curioni S, Testoni PA. (2003) Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. *Endoscopy* 35:830–834.
6. Katsinelos P, Kountouras J, Chatzis J, Christodoulou K, Paroutoglou G, Mimidis K, *et al.* (2005) High-dose allopurinol for prevention of post-ERCP pancreatitis: a prospective randomized double-blind controlled trial. *Gastrointest Endosc* 61:407–415.
7. Murray B, Carter R, Imrie C, Evans S, O'Suilleabhain C. (2003) Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 124:1786–1791.
8. Manes G, Ardizzone S, Lombardi G, Uomo G, Pieramico O, Porro GB. (2007) Efficacy of post-procedure administration of gabexate mesylate in the prevention of post-ERCP pancreatitis: a randomized, controlled, multicentre study. *Gastrointest Endosc* 65:982–987.
9. Ito K, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Takazawa O, *et al.* (2007) Efficacy and safety of prophylactic pancreatic duct stent (Pit-stent) placement in patients at high risk of post-ERCP pancreatitis. *Dig Endosc* 19:130–133.
10. Sofuni A, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, *et al.* (2007) Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. *Clin Gastroenterol Hepatol* 5:1339–1346.
11. Singh P, Das A, Isenberg G, Wong RC, Sivak MV, Jr, Agrawal D, *et al.* (2004) Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. *Gastrointest Endosc* 60:544–550.
12. Friedland S, Soetikno RM, Vandervoort J, Montes H, Tham T, Carr-Locke DL. (2002) Bedside scoring system to predict the risk of developing pancreatitis following ERCP. *Endoscopy* 34:483–488.
13. Nagino M, Takada T, Kawarada Y, Nimura Y, Yamashita Y, Tsuyuguchi T, *et al.* (2007) Methods and timing of biliary drainage for acute cholangitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 14:68–77.
14. Sharma BC, Kumar R, Agarwal N, Sarin SK. (2005) Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. *Endoscopy* 37:439–443.
15. Hui CK, Lai KC, Yuen MF, Ng M, Chan CK, Hu W, *et al.* (2003) Does the addition of endoscopic sphincterotomy to stent insertion improve drainage of the bile duct in acute suppurative cholangitis?. *Gastrointest Endosc* 58:500–504.
16. Sugiyama M, Atomi Y. (1998) The benefits of endoscopic nasobiliary drainage without sphincterotomy for acute cholangitis. *Am J Gastroenterol* 93:2065–2068.
17. Fujita N, Noda Y, Kobayashi G, Kimura K, Ito K. (2004) Endoscopic approach to early diagnosis of pancreatic cancer. *Pancreas* 28:279–281.
18. Tanaka M. (2005) Important clues to the diagnosis of pancreatic cancer. *Rocz Akad Med Bialymst* 50:69–72.
19. Hawes RH. (2002) Diagnostic and therapeutic uses of ERCP in pancreatic and biliary tract malignancies. *Gastrointest Endosc* 56:S201–S205.
20. Sheehan MM, Fraser A, Ravindran R, McAteer D. (2007) Bile duct brushings cytology – improving sensitivity of diagnosis using the ThinPrep technique: a review of 113 cases. *Cytopathology* 18:225–233.
21. Fujita N, Noda Y, Kobayashi G, Kimura K, Yago A. (1998) Staging of bile duct carcinoma by EUS and IDUS. *Endoscopy* 30 (Suppl. 1):A132–A134.
22. Yamao K, Okubo K, Sawaka A, Hara K, Nakamura T, Suzuki T, *et al.* (2003) Endolumenal ultrasonography in the diagnosis of pancreatic diseases. *Abdom Imaging* 28:545–555.
23. Fukuda Y, Tsuyuguchi T, Sakai Y, Tsuchiya S, Saisyo H. (2005) Diagnostic utility of peroral cholangioscopy for various bile duct lesions. *Gastrointest Endosc* 62:374–382.
24. Yamao K, Ohashi K, Nakamura T, Suzuki T, Sawaki A, Hara K, *et al.* (2003) Efficacy of peroral pancreatoscopy in the diagnosis of pancreatic diseases. *Gastrointest Endosc* 57:205–209.
25. Chen YK, Foliente RL, Santoro MJ, Walter MH, Collen MJ. (1994) Endoscopic sphincterotomy-induced pancreatitis: increased risk associated with non-dilated bile ducts and sphincter of Oddi dysfunction. *Am J Gastroenterol* 89:327–333.
26. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, *et al.* (1996) Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 335:909–918.
27. Rabenstein T, Roggenbuck S, Framke B, Martus P, Fischer B, Nusko G, *et al.* (2002) Complications of endoscopic sphincterotomy: can heparin prevent acute pancreatitis after ERCP? *Gastrointest Endosc* 55:476–483.
28. Lella F, Bagnolo F, Colombo E, Bonassi U. (2004) A simple way of avoiding post-ERCP pancreatitis. *Gastrointest Endosc* 59:830–834.
29. Artifon EL, Sakai P, Cunha JE, Halwan B, Ishioka S, Kumar A. (2007) Guidewire cannulation reduces risk of post-ERCP pancreatitis and facilitates bile duct cannulation. *Am J Gastroenterol* 102:2147–2153.