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Safety of endoscopic ultrasound-guided ethanol ablation for pancreatic cystic lesions: A single-center experience of 214 patients

Jin Ho Choi, Sang Hyub Lee*, Young Hoon Choi, Min Su You, Bang-Sup Shin, Woo Hyun Paik, Ji Kon Ryu, Yong-Tae Kim

Department of Internal Medicine, Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

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ABSTRACT

Background: Endoscopic ultrasound-guided ethanol ablation (EUS-EA) for pancreatic cystic lesions (PCLs) has been used in recent years as a feasible treatment modality for low malignant probability PCLs or patients considered high-risk for surgery. The present study aimed to confirm the safety of EUS-EA and to find predictive factors for adverse event (AE).

Methods: A retrospective review was performed from the prospectively maintained database of patients who underwent EUS-EA for PCLs from June 2006 to April 2018 at Seoul National University Hospital. The primary outcomes of the study were the rates of AEs and severe AEs by EUS-EA. The secondary outcome was the predictive factors of AEs including acute pancreatitis and abdominal pain.

Results: A total of 214 patients were evaluated and the diagnoses of PCLs according to cystic fluid analysis and clinical features were as follows: serous cystic neoplasm (32.2%), mucinous cystic neoplasm (26.6%), branch duct type intraductal papillary mucinous neoplasm (BD-IPMN) (29.4%), and pseudocyst (11.7%). Three patients (1.4%) experienced severe AEs. Overall, AEs occurred in 71 (33.2%) patients. BD-IPMN (OR: 2.87; 95% CI: 1.05–7.84; $P=0.040$), multilocular cysts (OR: 3.59; 95% CI: 1.09–11.85; $P=0.036$), suspected ethanol leakage during procedure (OR: 10.68; 95% CI: 1.98–57.53; $P=0.006$), and sticky cystic fluid (OR: 3.83; 95% CI: 1.20–12.24; $P=0.024$) were predictive factors for post-procedural acute pancreatitis. PCLs of uncinate process (OR: 2.99; 95% CI: 1.22–7.35; $P=0.017$) and PCLs with exophytic portion (OR: 3.70; 95% CI: 1.96–7.01; $P < 0.001$) were predictive factors for post-procedural abdominal pain.

Conclusions: EUS-EA is a safe procedure with a very low rate of severe AEs. It seems possible to predict the AEs according to the features of the procedure and PCLs.

Introduction

In recent years, management of incidentally found pancreatic cystic lesions (PCL) has gradually become more conservative [1–3], and treatments guided by endoscopic ultrasound (EUS) such as ablation [4–12] or thermocoagulation [13,14] have been attempted by several groups. The feasibility and safety of EUS-guided ablation have been confirmed through several studies, and it has been tried with ethanol [4,5,7,9,10], chemoagent with ethanol [6,8,11], and chemoagent without ethanol [12]. Also, previous studies have demonstrated the efficacy of EUS-guided ethanol-containing ablation (EUS-EA) with complete remission (CR) rates varying from 8.7% to 84.6% [4–11]. The long-term follow-up results indicate that the treatment effect of EUS-EA is well maintained [10,11], and one comparative study showed the possibility that EUS-EA could maintain quality of life (QOL) by preventing unnecessary surgery while providing a certain level of CR when compared to the surveillance strategy [15].

Safety and adverse events (AE) are very important in EUS-EA because it guarantees moderate level of CR despite the excellent cost-effectiveness of the procedure. According to previous studies, the most common AE was post-procedural abdominal pain and most AEs were reported to have mild severity and to be improved with conservative treatment. However, some severe AE occurred, such as severe acute pancreatitis (AP), chemical peritonitis, or portal vein thrombosis [8,9,11,12]. Severe AE of EUS-EA have been reported to occur in up to 4.3% of cases [9,11], which leads some critics to question whether the degree of AE for this procedure is acceptable [12,16]. The proposed mechanisms to explain post-procedural AE are a direct cytotoxic effect of the ethanol in the ductal epithelium, unintentional injection of the ablative agent into the pancreatic parenchyma, or inflammatory effects of

* Corresponding author.
E-mail address: gidoctor@snuh.org (S.H. Lee).

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alcohol on the surrounding tissues by pericystic leakage [5,6,17]. Recently, an ethanol-free regimen was attempted and similar levels of CR but superior safety were reported compared with an ethanol-containing regimen [12]. However, ethanol is still considered useful because it can provide a certain level of CR and maintain QOL by preventing unnecessary surgery. It is also cheaper than other chemoagents that are currently available only as an off-label for EUS-EA. The present study aimed to confirm the safety of EUS-EA and to find predictive factors for AE.

Methods

Study design and patients

This retrospective study investigated patients who visited Seoul National University Hospital with PCLs diagnosed by imaging tests. These patients underwent EUS-EA from June 2006 to April 2018. Patients' data including age, sex, follow-up duration, Adult Comorbidity Evaluation-27 [18], size of PCLs, characteristics of PCLs, periprocedural laboratory tests, total amount of ethanol used during the procedure, number of cyst punctures during the procedure, presence of suspicious ethanol leakage during the procedure, and the response to the procedure were collected.

The indications for EUS-EA were as follows: (1) cystic size over 2 cm; (2) PCLs had a plan of cystic fluid analysis; (3) patients with high operative risk or reluctance to undergo surgery. The exclusion criteria were as follows: (1) less than 20 years old; (2) PCLs associated with genetic disease; (3) PCLs with high-risk stigmata (obstructive jaundice, enhanced solid component, or main pancreatic duct dilatation more than 10 mm); (4) main duct type or mixed type intraductal papillary mucinous neoplasm (IPMN); (5) suspected pseudocyst before the procedure via imaging tests and clinical information; (6) cystic degeneration of solid tumors; (7) insufficient records of the procedure; (8) no results from cystic fluid analysis; (9) insufficient medical records or test results to evaluate AEs after the procedure; (10) post-procedural follow-up for less than 30 days.

Definitions and evaluation of PCL

Before the procedure, we categorized the PCLs as pseudocyst, serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), and branch duct type IPMN (BD-IPMN) on the basis of the clinical information and noninvasive imaging tests including abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), or EUS. We did not perform EUS-EA for clinically suspected pseudocyst. During the procedure, we acquired cystic fluid for further categorization of the PCLs and the PCLs were reclassified after the procedure based on cystic fluid analysis of carcinoembryonic antigen (CEA) and amylase level as follows: SCN (CEA $<$ 5 ng/mL, amylase $<$ 800 U/L), pseudocyst (CEA $<$ 5 ng/mL, amylase $>$ 800 U/L), IPMN (CEA $>$ 200 ng/mL, amylase $>$ 800 U/L), and MCN (CEA $>$ 200 ng/mL, amylase $<$ 800 U/L) [10]. The diagnosis which was classified prior to the procedure was maintained for the uncategorized cysts that did not meet these criteria (5 ng/mL $<$ CEA $<$ 200 ng/mL).

Exophytic feature of PCLs was defined as lesion growth outward from an epithelial surface in CT or MRI. The total amount of ethanol was calculated by the sum of ethanol during the EUS-EA. Suspected ethanol leakage referred to a leak into the pericystic lesion during the procedure. Sticky cystic fluid was defined as initial cystic fluid that was hard to aspirate due to high viscosity, or as a needle that was blocked several times by mucus.

Complete remission (CR) was defined as no visible PCLs on repeated imaging studies during the follow-up period. Partial response (PR) was a decrease of more than 30% in the longer diameter, progression disease (PD) was an increase of more than 20% in the longer diameter, and stable disease refers to a change between those of PR and PD [19]. The overall response rate was defined as the sum of PR and CR.

Procedure of EUS-EA

The patients received EUS-EA from four gastroenterologists (Lee SH, Kim YT, Ryu JK, Paik WH) who were experts in interventional EUS. Radial-scanning echoendoscope (GF-UM2000, GF-UE260; Olympus Optical Co., Tokyo, Japan) and curvilinear-array echoendoscope (GF-UCT2000, GF-UCT 240, GF-UCT 260; Olympus Optical Co.) with a 7.5-MHz transducer (EU-M 2000, Olympus Optical Co.; Aloka Alpha 5 and 10, Hitachi Aloka Medical, Ltd., Tokyo, Japan) were used. EUS-EA was conducted through transgastric or transduodenal puncture of the cysts using a curvilinear-array echoendoscope with a 19- or 22-gage needle (EchoTip Ultra; Cook Endoscopy, Winston-Salem, NC, EZ Shot 2 or 3^{TM}; Olympus Medical, Tokyo, Japan, Expect^{TM}; Boston Scientific, MA, USA).

EUS-EA for PCLs was accomplished using the previously described protocol [10,15] from our center: (1) the longest diameter was measured; (2) 80% of the cystic fluid was aspirated, after which 99% ethanol was injected and stored in the cyst for 3 to 5 min; (3) step 2 was repeated two or more times; (4) all injected ethanol and remnant cystic fluid was aspirated.

Outcomes

The primary outcomes of the study were the rates of AEs and severe AEs by EUS-EA. The secondary outcome was the predictive factors of AEs including AP and abdominal pain.

In this study, we evaluated the AEs that occurred within 30 days after the procedure. The category and severity of AEs were classified and evaluated with reference to the lexicon for endoscopic AEs by the American Society for Gastrointestinal Endoscopy [20]. We defined AP as typical abdominal pain with elevated pancreatic enzyme (serum amylase or lipase $>$3 folds of upper normal limit), bleeding as hematemesis and/or melena or hemoglobin drop of more than 2 g/dL, cholangitis as fever $>$38 °C for over 24 h with cholestasis, and duodenal stricture as complete or partial obstruction of the duodenum on duodenography or imaging tests in patients who had dietary difficulties. Any patient who complained of pain of 1 point or more on a numeric rating scale in the nursing record was recognized as having abdominal pain. Multiple AEs that occurred in one patient were analyzed regardless of the severity.

Estimation of sample size

The sample size does not necessarily have to be computed in this study, but we calculated the sample size to ensure the validity of the study. To make an appropriate estimate of the sample size for the patients who undergo severe AE, we applied finite population correction to the sample size formula [21]. We calculated it based on the expected severe AE of 10%, which was over the maximal value among the previous studies [12]. The margin of error and confidence level in this estimation was 5% and 95%, respectively. The calculated sample size is 139, and it was calculated to be 151 in consideration of 10% dropout. Therefore, we conclude that the validation in this study will be sufficient with more than 151 patients.

Statistical analysis

Continuous variables were analyzed by Student's *t* test and categorical variables were analyzed using the Chi-square test or

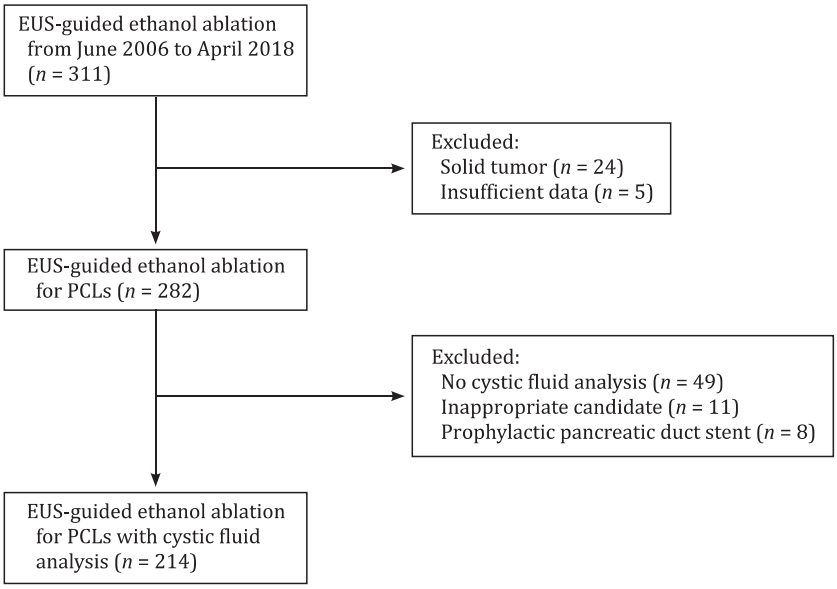

Fig. 1. Flow-chart of this study. EUS: endoscopic ultrasound; PCL: pancreatic cystic lesion.

Fisher's exact test. The logistic regression analysis was used to analyze the predictive factors for AEs. *P* values less than 0.05 were considered significant. Statistical analyses were performed using SPSS v.23.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

Among 311 patients who underwent EUS-EA, 24 patients with solid tumor and 5 patients who had limited medical records were excluded. Forty-nine patients without cystic fluid analysis, 8 patients with prophylactic pancreatic duct stent, and 11 patients with inappropriate indication were also excluded. Finally, 214 patients were included in the study (Fig. 1). The baseline characteristics for study patients are shown in Table 1. The mean age of the patients was 55.61 ± 14.66 years and the mean follow-up period was 51.02 ± 39.68 months. A total of 52.8% patients had no comorbidity and 3.7% had severe comorbidities. The mean ablative cystic size was 32.20 ± 9.56 mm. Diagnosis of PCLs by combined diagnosis criteria were as follows: SCN 32.2%, MCN 26.6%, BD-IPMN 29.4%, and pseudocyst 11.7%.

Procedure-related outcome

The total amount of ethanol for each procedure was 18.7 ± 17.29 mL. Multiple punctures were performed in 23.8% (51 of 214) of patients. Sticky cystic fluid was observed in 10.8% (23 of 213) of patients. Suspected ethanol leakage occurred in 3.3% (7 of 214) of cases and there was no difference in mean amount of ethanol between the 7 patients with suspected leakage and the others (13.76 ± 6.26 mL vs. 18.89 ± 17.52 mL, $P = 0.441$). Multiple puncture was performed more often in multiseptated PCLs (OR: 5.23; 95% CI: 2.13–12.84; $P < 0.001$), and in PCLs with sticky fluid (OR: 2.81; 95% CI: 1.15–6.87; $P = 0.019$). Response to the procedure including short-term follow-up was assessed in 190 patients as follows: overall response rate 69.0%, CR 24.7%, PR 44.3%, SD 22.6%, and PD 8.4%. Among them, the response rate according to the diagnosis after fluid analysis was 75.0% (36 of 48) of MCN, 73.8% (48 of 65) of SCN, 77.3% of pseudocyst (17 of 22) and 54.5% of IPMN (30 of 55), respectively.

Table 1
Baseline characteristics ($n = 214$).

Characteristics	Value
Sex	
Male	74 (34.6%)
Female	140 (65.4%)
Age (yr)	55.61 ± 14.66
Comorbidity (ACE-27)	
No	113 (52.8%)
Mild	71 (33.2%)
Moderate	22 (10.3%)
Severe	8 (3.7%)
Follow-up duration (mon)	51.02 ± 39.68
Location	
Uncinate	25 (11.7%)
Head/Neck	64 (29.9%)
Body	69 (32.2%)
Tail	56 (26.2%)
Size at ablation (mm)	32.20 ± 9.56
20.0–29.9	89 (41.6%)
30.0–39.9	74 (34.6%)
≥40.0	51 (23.8%)
Diagnosis	
SCN	69 (32.2%)
MCN	57 (26.6%)
BD-IPMN	63 (29.4%)
Pseudocyst	25 (11.7%)
Loculation	
Unilocular	116 (54.2%)
Oligolocular	75 (35.0%)
Multilocular	23 (10.7%)
Exophytic portion	
Yes	114 (53.3%)
No	100 (46.7%)

Data were expressed as *n* (%) or mean ± SD. ACE-27: Adult Comorbidity Evaluation-27 [18]; SCN: serous cystic neoplasm; MCN: mucinous cystic neoplasm; BD-IPMN: branch duct type intraductal papillary mucinous neoplasm.

Post-procedural AEs and severe AEs

A total of 33.2% (71 of 214) patients experienced AEs after the procedure and severe AEs occurred in 1.4% (3 of 214) (Table 2). The onset of the AE was all within 30 days. AP occurred in 9.8% (21 of 214) patients, of which 2 experienced severe AE. Duodenal stricture

Table 2
Details and severity of post-procedural adverse events ($n=214$).

Adverse events	Number of patients	Severity grade		
		Mild	Moderate	Severe
Total[a]	71 (33.2%)	59	9	3
Acute pancreatitis	21 (9.8%)	11	8	2
Duodenal stricture	2 (0.9%)	0	0	2
Bleeding	1 (0.5%)	0	1	0
Cholangitis	1 (0.5%)	0	1	0
Abdominal pain	70 (32.7%)[b]/49(22.9%)[c]	59	8	3
Analgesic needed cases	30 (42.9%)[d]	20	7	3

[a] Each category includes multiple adverse events in one patient. Severity was determined by the most severe adverse event.
[b] Patients of acute pancreatitis were also included.
[c] Number and ratio of patients with abdominal pain except acute pancreatitis patients.
[d] Ratio of analgesic needed cases among the patients suffered from abdominal pain.

Table 3
Detailed information of patients with post-procedural severe adverse events.

Characteristics	Patient A	Patient B	Patient C
Baseline characteristics			
Age (yr)/Sex	60/Male	62/Female	45/Female
Past medical history	Previous healthy No symptom	Breast cancer No symptom	Previous healthy No symptom
Diagnosis modality	Incidentally by CT	Incidentally by CT	Incidentally by CT
Total follow-up (mon)	88.4	95.9	18.1
Post-procedural follow-up (mon)	9.5	9.2	7.4
Indication of procedure	Growing cyst Patient wish	Growing cyst	Growing cyst Patient wish
Cystic feature			
Diagnosis	BD-IPMN	MCN	MCN
Initial size (mm)	20	15	17
Ablative size (mm)	35	52	26
Location	Uncinate process	Head	Neck
Loculation	Unilocular cyst	Oligolocular cyst	Unilocular cyst
Exophytic portion	Yes	No	No
High-risk stigmata	No	No	No
Worrisome features	Size >30 mm Rapid growing	Size > 30 mm Rapid growing	Rapid growing
Procedure details			
Needle (G)	22	19	19
Ethanol volume (mL)	15	48	16
Puncture number	2	2	1
Suspected leakage	Yes	No	No
Sticky cystic fluid	No	No	No
Final response	Complete remission	Partial response	Complete remission
Adverse events and management			
Adverse event (onset, day)	Acute pancreatitis (1) Duodenal stricture (20)	Duodenal stricture (4)	Acute pancreatitis (1)
Management other than conservative management	Five sessions of endoscopic balloon dilatation for duodenum	Endoscopic duodenal stent insertion	Endoscopic retrograde pancreatic duct drainage with plastic stent
Additional hospitalization	2 months	3 weeks	12 days

CT: computed tomography; BD-IPMN: branch duct type intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm.

occurred in 0.9% (2 of 214) patients, and both were evaluated as severe AE. Bleeding and cholangitis occurred in 1 patient each and both were of moderate grade severity. Abdominal pain occurred in 32.7% (70 of 214) patients and 30 needed pain killers.

A review of three patients with SAE is described in Table 3. A 60-year-old male patient with rapidly growing asymptomatic BD-IPMN at uncinate process experienced necrotizing pancreatitis with duodenal stricture due to suspected pericystic leakage by uncooperative patient movement during the procedure. It was improved after several sessions of endoscopic balloon dilatation with hospitalization for two months. Another 62-year-old female patient underwent EUS-EA for a rapidly growing MCN of the pancreatic head. We decided to endoscopically insert a duodenal stent for unsolved gastrointestinal obstructive symptoms due to duodenal stricture that developed 4 days after the procedure. The stent was spontaneously removed as the stricture improved after 3 weeks. The third patient was a 45-year-old female who underwent EUS-EA for a rapidly growing MCN of the pancreatic neck. Endoscopic retrograde pancreatic drainage with a plastic stent was performed and the patient was hospitalized for an additional 12 days with conservative management for post-procedural AP.

Predictive factor for adverse events

We analyzed the predictive factors of procedure-related AEs, focusing on AP and abdominal pain (Tables 4 and 5). AP was more likely to occur in PCLs of uncinate process (28.6% vs. 9.8%, $P=0.022$), BD-IPMN (52.4% vs. 26.9%, $P=0.022$), multilocular cysts (28.6% vs. 8.8%, $P=0.015$), suspected ethanol leakage (19.0% vs. 1.6%, $P<0.001$), and sticky cystic fluid (33.3% vs. 8.3%, $P<0.001$) in univariate analysis. Among these factors, BD-IPMN (OR: 2.87, 95% CI: 1.05–7.84; $P=0.040$), multilocular cysts (OR: 3.59, 95%

Table 4
Analysis of predictive factors for post-procedural acute pancreatitis.

Variables	AP ($n=21$)	No AP ($n=193$)	Univariate		Multivariate	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male sex	10 (47.6%)	64 (33.2%)	0.55 (0.22–1.35)	0.228		
Age (yr)	58.19 ± 11.27	55.33 ± 14.98	1.01 (0.98–1.05)	0.397		
Comorbidity (ACE-27)			0.28 (0.04–2.19)	0.322		
No or mild	20 (95.2%)	164 (85.0%)				
Moderate to severe	1 (4.8%)	29 (15.0%)				
Location			3.66 (1.27–10.56)	**0.022**		NS
Uncinate	6 (28.6%)	19 (9.8%)				
Non-uncinate	15 (71.4%)	174 (90.2%)				
Ablative size (mm)			0.40 (0.16–1.01)	0.062		
<30	13 (61.9%)	76 (39.4%)				
≥30	8 (38.1%)	117 (60.6%)				
Diagnosis			2.98 (1.20–7.44)	**0.022**	2.87 (1.05–7.84)	**0.040**
BD-IPMN	11 (52.4%)	52 (26.9%)				
Non-BD-IPMN	10 (47.6%)	141 (73.1%)				
Loculation			4.14 (1.42–12.07)	**0.015**	3.59 (1.09–11.85)	**0.036**
Non-multilocular	15 (71.4%)	176 (91.2%)				
Multilocular	6 (28.6%)	17 (8.8%)				
Exophytic feature	14 (66.7%)	100 (51.8%)	1.86 (0.72–4.81)	0.251		
Needle (G)			1.16 (0.46–2.93)	0.811		
19	8 (38.1%)	67 (34.7%)				
22	13 (61.9%)	126 (65.3%)				
Number of puncture			1.32 (0.48–3.59)	0.594		
1	15 (71.4%)	148 (76.7%)				
≥2	6 (28.6%)	45 (23.3%)				
Suspected ethanol leakage	4 (19.0%)	3 (1.6%)	14.90 (3.08–72.13)	**<0.001**	10.68 (1.98–57.53)	**0.006**
Sticky cystic fluid	7 (33.3%)	16 (8.3%)	5.53 (1.95–15.67)	**<0.001**	3.83 (1.20–12.24)	**0.024**

OR: odds ratio; 95% CI: 95% confidence interval; NS: not significant; AP: acute pancreatitis; ACE-27: Adult Comorbidity Evaluation-27 [18]; BD-IPMN: branch duct intraductal papillary mucinous neoplasm.

Table 5
Analysis of predictive factors for post-procedural abdominal pain.

Variables	Abdominal pain ($n=70$)	No abdominal pain ($n=144$)	Univariate		Multivariate	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male sex	24 (34.3%)	50 (34.7%)	1.02 (0.56–1.86)	1.000		
Age (yr)	54.94 ± 14.10	55.93 ± 14.97	0.99 (0.98–1.02)	0.638		
Comorbidity (ACE-27)			0.86 (0.37–2.00)	0.835		
No or mild	61 (87.1%)	123 (85.4%)				
Moderate to severe	9 (12.9%)	21 (14.6%)				
Location			2.51 (1.08–5.83)	**0.040**	2.99 (1.22–7.35)	**0.017**
Uncinate	13 (18.6%)	12 (8.3%)				
Non-uncinate	57 (81.4%)	132 (91.7%)				
Ablative size (mm)			1.58 (0.87–2.85)	0.142		
<30	24 (34.3%)	65 (45.1%)				
≥30	46 (65.7%)	79 (54.9%)				
Diagnosis			1.41 (0.76–2.60)	0.338		
BD-IPMN	24 (34.3%)	39 (27.1%)				
Non-BD-IPMN	46 (65.7%)	105 (72.9%)				
Loculation			2.05 (0.86–4.91)	0.156		
Non-multilocular	59 (84.3%)	132 (91.7%)				
Multilocular	11 (15.7%)	12 (8.3%)				
Exophytic feature	51 (72.9%)	63 (43.8%)	3.45 (1.85–6.42)	**<0.001**	3.70 (1.96–7.01)	**<0.001**
Needle (G)			1.65 (0.92–2.98)	0.126		
19	30 (42.9%)	45 (31.3%)				
22	40 (57.1%)	99 (68.8%)				
Number of puncture			1.30 (0.68–2.52)	0.494		
1	51 (72.9%)	112 (77.8%)				
≥ 2	19 (27.1%)	32 (22.2%)				
Suspected ethanol leakage	5 (7.1%)	2 (1.4%)	5.46 (1.03–28.89)	**0.039**		NS
Sticky cystic fluid	11 (15.7%)	12 (8.3%)	2.05 (0.86–4.91)	0.156		

OR: odds ratio; 95% CI: 95% confidence interval; NS: not significant; ACE-27: Adult Comorbidity Evaluation-27 [18]; BD-IPMN: branch duct intraductal papillary mucinous neoplasm.

CI: 1.09–11.85; $P=0.036$), suspected ethanol leakage during procedure (OR: 10.68, 95%CI: 1.98–57.53; $P=0.006$), and sticky cystic fluid (OR: 3.83, 95% CI: 1.20–12.24; $P=0.024$) were independent predictive factors for post-procedural AP. Abdominal pain was more likely to occur in PCLs of uncinate process (18.6% vs. 8.3%; $P=0.040$), PCLs with exophytic portion (72.9% vs. 43.8%; $P < 0.001$), and suspected ethanol leakage (7.1% vs. 1.4%; $P=0.039$) in univariate analysis. Among these factors, PCLs of uncinate process (OR: 2.99, 95% CI: 1.22–7.35; $P=0.017$) and exophytic PCLs (OR: 3.70, 95% CI: 1.96–7.01; $P < 0.001$) were

independent predictive factors for abdominal pain in multivariate analysis.

Discussion

The traditional treatment strategy for PCLs has been either wait-and-see or surgery, and treatments such as the minimally invasive EUS-EA have been attempted recently since there have been unmet needs of real practice in treating PCLs with lower malignant risk or patients at high-risk in surgery. However, there has still been a safety concern for EUS-EA, and we performed this large-scale study to evaluate AEs and their predictive factors to suggest more appropriate indications for the procedure. Discussion of this safety issue would be important where EUS-EA is attempting various indications such as ethanol ablation of tumor combined with celiac plexus neurolysis in patients with pancreatic adenocarcinoma [22].

This study was conducted on the largest number of patients yet, and high safety was confirmed with a very low rate of severe AE, which was consistent with several previous studies [6,10,11]. It was impossible to analyze predictors for severe AE because of the small number of cases. Overall AE seems slightly high (33.2%), but most were mild grade (83.1%) and most were temporary abdominal pain. Several predictive factors were identified in this study, and the most critical prediction is that of post-procedural pancreatitis through proven factors during the peri-procedural period. Ethanol is thought to flow directly into the pancreatic duct and cause direct chemical injury in IPMN. Ethanol leakage can induce abdominal pain or AP by causing chemical damage to pancreatic tissue and peripancreatic tissue. In addition, traces of pericystic ethanol leakage are believed to be more likely in multipuncture cases, which seem to be triggered by multilocular cyst and sticky fluid.

Recently, Moyer and colleagues evaluated the efficacy and safety of ethanol-free EUS-guided ablation because ethanol was blamed as the main cause of pancreatitis and EUS-EA was found to be more efficacious when it was supplemented by addition of chemoagent [12]. They reported that similar levels of CR after 12 months were assured regardless of the presence of ethanol (61% in ethanol group, 67% in ethanol-free group), but AEs were more likely to occur when ethanol was used (28% of AE in ethanol group, 0 in ethanol free group, $P = 0.01$). Major AE of AP occurred in 1 patient in the ethanol group but was not classified as severe AE under the criteria of their study. Four other minor AEs in the ethanol group were comprised entirely of abdominal pain that required unscheduled clinical evaluation and treatment for pain control. It is unreasonable to suggest that the ethanol-based regimen has a lethal safety problem because reported AEs were not severe in substance. Some limitations of their study are expected to be covered by the CHARM-II trial [23].

Also, there has still been the efficacy concern for this procedure such as true effect for inhibition of malignant transformation by EUS-EA, or guarantee of effective epithelial ablation by reaching radiologic CR [24]. In the previous studies, the range of effective ablated cystic epithelium showed a variable amount in the resected specimens up to complete epithelial ablation [4,6], but it was hard to find the records of epithelial ablation because it was not routinely described in pathologic reports of our institution and there are few patients who have undergone surgery after the procedure. If the epithelium is not ablated enough, the cyst will grow again during the follow-up period, and re-ablation or surgical resection would be needed. The practical meaning of EUS-EA was discussed in the previous study of our group [15], which revealed EUS-EA for PCLs with low-risk of malignancy might not be able to obtain a survival benefit, but prevent unnecessary surgery, and a certain level of CR was achieved when compared to the wait-and-see strategy. Although EUS-EA is not an alternative treatment for surgery, it is evaluated as an possible option that can be selected for the appropriate indication. The most obvious answer would be to assess the effectiveness of the procedure through long-term, large scale randomized controlled trail in the future.

It is difficult to determine definite indications for EUS-EA, but PCLs with high-risk stigmata are considered contraindications of EUS-EA except in some inevitable situations involving a patient's wishes or inoperable status due to poor performance or severe comorbidities. Based on the results of this study, we will discuss the appropriate indications for EUS-EA considering AEs. First, PCLs with predictive factors for AP may be one of the most inappropriate indications for EUS-EA. Some physicians were reluctant to enforce EUS-EA for IPMN due to controversial ablative effect and the tendency for AEs according to long-term follow-up data [6,10,11]. It seems to be better to consider IPMN a relative indication for EUS-EA because post-procedural AP is prone to occur with IPMN according to the current study. In the same context, multilocular PCLs should also be used as a relative indication because pancreatitis is more likely to occur after EUS-EA. Second, PCLs at uncinate process or PCLs with exophytic portion are also considered relative indications for EUS-EA because these features are prone to post-procedural abdominal pain. It is not necessary to treat them as a contraindication because most of the abdominal pain is mild. Third, ablative cystic size over 2 cm was considered a proper criterion because there were no significant differences according to the ablative cystic size in this study. Cystic size of 2.0–3.5 cm has also been suggested as a proper size criterion because ablative size less than 3.5 cm had predictive value for CR in a recent study [11]. In addition, EUS-EA may be performed in one-step for patients who require cystic fluid analysis by EUS, endoscopic biopsy through EUS, or repeated EUS due to ambiguous diagnosis or treatment plan. We can expect a certain level of CR and avoidance of unnecessary surgery to help maintain QOL in these patients [15].

This study has limitations. First, it is a retrospective, single-center study. However, it is considered sufficient to confirm the safety of EUS-EA because it involved the largest number of patients to date. Second, we analyzed a few factors based on the procedural results and the nursing records, although AEs were also affected by various factors during the time of the procedure in addition to the characteristics of PCLs. Sticky fluid or suspected leakage during the procedure affected AEs in this study, but it should be noted that the presence of these features were not required for entry in the test results in our institution.

In conclusion, EUS-EA is a safe procedure with rare occurrence of severe AE. It is possible to predict the post-procedural AEs by the predictive factors and it is desirable to perform the EUS-EA for the proper indication with meticulous consideration of the benefits and loss by the procedure.

Contributors

CJH and LSH conceived and designed the study. CJH, CYH, YMS and SBS participated in the data acquisition, analysis and interpretation. CJH and LSH drafted the manuscript. PWH, RJK and KYT contributed to the administrative, technical, or material support, study supervision, and critical revision of the manuscript for important intellectual content. All authors approved the final version. LSH is the guarantor.

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Ethical approval

This study was approved by the institutional review board of Seoul National University Hospital, Korea (IRB No. H-1606-049-770).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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