Digestive and Liver Disease 55 (2023) 107–112

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Endoscopic pancreatic sphincterotomy in patients with IPMN-related recurrent pancreatitis: A single center experience

T. Schepis[a,b], A. Tringali[a,b,*], F. D'aversa[c], V. Perri[a,b], P. Familiari[a,b], I. Boškoski[a,b], E.C. Nista[d], G. Costamagna[a,b]

[a] Fondazione Policlinico Universitario A. Gemelli IRCCS, Digestive Endoscopy Unit, Rome, Italy
[b] Università Cattolica del Sacro Cuore, Centre for Endoscopic Research Therapeutics and Training (CERTT), Rome, Italy
[c] Pia Fondazione Cardinale Panico, Medicine Department, Tricase, Italy
[d] Fondazione Policlinico Universitario A. Gemelli IRCCS, Medical and Surgical Science Department, Rome, Italy

ARTICLE INFO

Article history:
Received 14 June 2022
Accepted 13 October 2022
Available online 8 November 2022

Keywords:
Acute pancreatitis
ERCP
Operative endoscopy

ABSTRACT

Background: Acute recurrent pancreatitis (ARP) is a rare manifestation of Intraductal Papillary Mucinous Neoplasms (IPMN) of the pancreas; ARP is a relative indication for pancreatic surgery in the setting of IPMN. Endoscopic pancreatic sphincterotomy (EPS) has been described as a minimal invasive treatment to reduce the episodes of ARP secondary to mucus migration in IPMN.
Methods: patients with IPMN-related ARP treated with ESP from January 2004 to December 2020 were retrospectively selected. Clinical and technical data were recorded. A clinical follow-up (minimum 12 months) was performed to assess the number of episodes of AP occurring after EPS.
Results: 25 patients were included. The mean follow-up after ESP was 93.4 months (SD± 56.6). The mean number of AP before and after EPS were respectively 3.29 (SD ± 1.04) and 0.51 (SD ± 0.71). A complete response (no further episodes of AP) and a partial response (>50% reduction of AP episodes) were obtained in 64% and 24% of the cases, respectively, with an overall response rate of 88%. One post-EPS bleeding and one minor-papilla stenosis were reported and were endoscopically managed. Two patients underwent pancreatic resection for the occurrence of high-risk stigmata for cancer progression.
Conclusions: EPS is a safe and effective treatment to reduce the number of episodes of AP in selected patients with IPMNs-related ARP. Prospective trials are needed to confirm these data.

1. Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are a mucin producing subtype of pancreatic cyst lesions arising from the pancreatic duct system and classified in main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN) and Mixed-type IPMN (MT-IPMN) depending on the involvement of the main duct and/or the lateral branches of the pancreatic ductal system [1]. IPMNs present a potential of malignant transformation, and account for 8% of pancreatic maligancies together with mucinous cystic neoplasm (MCN) [2]. The involvement of the main pancreatic duct (MPD), the pancreatobiliary or oncocytic histotype and the presence of worrisome features or high-risk stigmata (Table 1) are considered risk factors for malignancy [3]. The majority of patients with IPMNs are asymptomatic and the diagnosis is incidental, however in rare cases abdominal pain, weight loss, acute pancreatitis (AP), jaundice, palpable mass, and postprandial fullness may be present at the diagnosis [4]. According to the current literature, the prevalence of AP in IPMN patients is extremely variable ranging from 7 to 67% [5]. The production of thick mucus with consequent obstruction of the pancreatic ductal system and premature activation of pancreatic enzymes seems to be the physiopathological mechanism that leads to AP [6]. The prevalence of AP is higher in MD-IPMN when compared with BD-IPMN [5]. Acute recurrent pancreatitis (ARP), defined as two or more episodes of AP, occurs in 17–29% of patients following the first episode of AP of any etiology [7]. In IPMN the risk of ARP is even higher considering the persistence of mucus production believed to be the etiological mechanism of AP. ARP is considered a risk factor for the presence of high grade dysplasia or invasive cancer in IPMN, and can be considered a relative indication for surgery, even without other worrisome features or high-risk stigmata [8]. However, the level of evidence of the association between ARP and malignancy is low,

* Corresponding author at: Dipartimento di Medicina e Chirurgia Traslazionale Fondazione Policlinico Universitario A. Gemelli IRCCS. Università Cattolica del Sacro Cuore, Roma, Italy. Largo Agostino Gemelli, 8, 00168 Roma, Italy.
E-mail address: andrea.tringali@unicatt.it (A. Tringali).

https://doi.org/10.1016/j.dld.2022.10.006
1590-8658/

Table 1
High-risk stigmata and worrisome features for IPMN according to the 2017 Fukuoka Consensus Guidelines.
CA 19.9 (Serum carbohydrate antigen 19–9), IPMN (Intraductal Papillary Mucinous Neoplasia).

High Risk Stigmata	Worrisome features
1. Obstructive jaundice in patients with cyst lesion of the head of the pancreas 2. Enhancing mural nodule ≥5 mm 3. Main pancreatic duct diameter ≥10 mm	1. Increased levels of CA 19.9 (>37 U/ml) 2. Main pancreatic duct diameter 5–9.9 mm 3. Cyst diameter >30 mm 4. Enhancing mural nodules <5 mm 5. IPMN related acute pancreatitis 6. Thickened/enhancing cyst walls 7. Cyst grow-rate >5 mm/2year 8. Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy 9. Lymphadenopathy

and pancreatic surgery is still today burdened by high mortality and morbidity rate [8,9]. Endoscopic pancreatic sphincterotomy (EPS) has been described as an alternative minimal invasive procedure to decompress the pancreatic ductal system and reduce the recurrence of acute pancreatitis [10].

The aim of this study is to assess the safety, technical success, and long-term clinical efficacy of EPS in reducing the recurrence of AP in patients with IPMN.

2. Materials and methods

2.1. Patients' selection and follow-up

All patients with a confirmed diagnosis of IPMN and ARP treated with EPS from January 2004 to December 2020 were retrospectively identified from the prospectively maintained ERCP database of our Endoscopic Digestive Unit. Patients' charts were reviewed to exclude other causes of AP and to confirm the diagnosis of IPMN and ARP. Demographic data (gender and age at the time of procedure), clinical data (type, size and location of IPMN, number of episodes of AP prior the EPS), technical data (type of EPS, technical success, prophylactic placement of stents or nasopancreatic drainage, reinterventions) and adverse events were recorded. Inclusion criteria were patients' age ≥18 years old, confirmed diagnosis of IPMN, confirmed diagnosis of ARP. Exclusion criteria were the presence of other etiologies of AP, uncertain diagnosis of IPMN, diagnosis of chronic pancreatitis, the presence of absolute indications for surgery in patients fit for surgery, patients not eligible to endoscopic treatments.

All patients underwent a clinical follow-up (last contact December 2021) to assess the occurrence of delayed adverse events, the recurrence and the number of AP after EPS, the need for reinterventions, the evolution of IPMN (occurrence of worrisome features or high-risk stigmata), and the need for surgery. In all cases clinical and radiological follow-up was performed [3]. Magnetic resonance cholangio-pancreatography (MRCP) and/or Endoscopic Ultrasound (EUS) were used for radiological follow-up, as suggested from international guidelines [3]. Patients lost to follow-up or those with a follow-up shorter than 12 months after EPS, were excluded from the study.

The ethical committee of the Catholic University of Rome approved data collection and follow-up of patients undergoing endoscopic therapy of pancreatic diseases at our Institution (protocol #0026801/17).

2.2. Definitions

IPMN was defined as patients with typical radiological features at cross sectional imaging (Magnetic Resonance Imaging, Magnetic resonance cholangiopancreagraphy, Computed tomography) or at Endoscopic Ultrasound, and patients with spontaneous extruding mucus from the papilla ("fish-eye sign") [11].

AP was defined according to the Revised Atlanta Classification as the presence of two of the following three features: 1) abdominal pain consistent with pancreatic origin; 2) amylase or lipase ≥3 times the normal cut-off; 3) abdominal imaging consistent with AP. ARP was defined as 2 or more episodes of AP, each one fulfilling the previous reported diagnostic criteria for AP.

Complete clinical response was defined as no further episodes of AP after the EPS at the clinical follow-up. Partial clinical response was defined as a reduction of the number of episodes of AP after EPS ≥50% compared with the number of episodes of AP occurred before EPS.

2.3. Endoscopic procedure

EPS was performed in all cases with a pull-type sphincterotome over a 0.035 fully hydrophylic guidewire with angled tip (Terumo, Radiofocus, Japan). Endocut-type current (ERBE, Tubingen, Germany) was used to perform the sphincterotomy (*Video 1*). When EPS was completed, a prophylactic 5 or 6 french nasopancreatic drainage or a 5 french pancreatic plastic stent without proximal flaps were inserted into the main pancreatic duct.

2.4. Outcomes

The primary outcome of the study was to assess the clinical efficacy of EPS in resolving the occurrence of AP or in reducing the number of AP episodes ≥50%.

The secondary outcomes were the occurrence of ERCP related adverse events, the need for reinterventions, the evolution of IPMN (occurrence of worrisome features or high-risk stigmata), and the need for surgery.

2.5. Statistics

Descriptive data are reported as mean/median ± standard deviation and range, or percentage, wherever suitable. Statistical analysis was performed with SPSS 16. Mean values between the different groups were compared using the student *t*-test for continuous variables with normal distribution and using Mann Whitney U test for non-normal distribution. Categorical data were compared using the χ_2 test. All reported p values were two-tailed, and p values less than 0.05 were considered statistically significant.

3. Results

Between January 2004 and December 2020 30 patients with IPMN related ARP underwent ERCP at our Endoscopy Unit in order to perform EPS. Of these 5 patients were excluded from the study: 3 were lost at follow-up, 1 underwent pancreaticoduodenectomy for the evidence malignancy within 2 months (a minimum of 12 months of follow-up was needed to avoid an underestimation of AP rate after EPS), 1 presented a concomitant etiology

Table 2
Demographic and technical data of endoscopic pancreatic sphincterotomy in 25 patients with IPMNs induced RAP.

Demographics:	
No. of patients treated, n	25
Age (years), mean ± SD	62.6 ± 19
Sex (men), n (%)	9 (45%)
Type of IPMN:	
Main duct-IPMN, n (%)	6 (24%)
Side Branches-IPMN, n (%)	17 (68%)
Mixed type-IPMN, n (%)	2 (8%)
IPMN location	
Pancreatic head, n (%)	16 (64%)
Pancreatic Body, n (%)	4 (16%)
Multifocal, n (%)	5 (20%)
Endoscopic procedure:	
Major Papilla Sphincterotomy, n (%)	
Minor Papilla Sphincterotomy, n (%)	20 (80%)
Naso-Pancreatic Drainage, n (%)	5 (20%)
Pancreatic stent, n (%)	4 (16%)
Procedure related adverse events:	2 (8%)
Minor papilla sphincterotomy stenosis (treated with re-sphincterotomy, no further episodes of AP)	1
Post-sphincterotomy bleeding (treated with adrenaline injection and endoclip)	1

IPMNs: Intraductal Papillary Mucinous Neoplasms; MD-IPMN: Main Duct-Intraductal Papillary Mucinous Neoplasm; BD-IPMN: Side Branches-Intraductal Papillary Mucinous Neoplasm; MT-IPMN: Mixed-Type-Intraductal Papillary Mucinous Neoplasm; AP: acute pancreatitis; SD: standard deviation.

of AP (biliary lithiasis). Twenty-five patients were finally included in the study (55% female, mean age 62.0 ± 19 years, range 43–77) (Table 2). The majority of patients presented a BD-IPMN (17, 68%), while MD-IPMN and MT-IPMN were diagnosed respectively in 6 (24%) and 2 (8%) patients (Table 2). According to the Fukuoka consensus, no high-risk stigmata or worrisome features were documented in patients with BD-IPMN. Among patients diagnosed with MD/MT-IPMN four patients were considered unfit for surgery and two patients refused surgery. In the other two cases, a multidisciplinary team proposed EPS because of comorbidities precluding surgery and patient preference.

Major papilla-EPS was performed in 20 patients (80%), while minor papilla-EPS was performed in 5 patients with concomitant diagnosis of complete pancreas divisum (PD). EPS was performed successfully in all patients. A short-term prophylactic pancreatic drainage following EPS was always performed in order to prevent post-ERCP pancreatitis: 21 (84%) naso-pancreatic drainage removed 24 h later and 4 (16%) a 5 Fr pancreatic plastic stent without proximal flaps (an abdominal X-ray was performed after 2 weeks confirming spontaneous stent displacement in all). In 24% of cases the "fish-eye" sign was detected during duodenoscopy, while in all the cases mucus extrusion through the papilla was documented after EPS.

ERCP related adverse events occurred in 2 patients (8%): 1 case of delayed post-sphincterotomy bleeding successfully managed endoscopically with submucosal injection of diluted epinephrine (1:10.000) and placement of one endoclip, and 1 case of minor papilla sphincterotomy stenosis leading to AP recurrence 10 years after minor papilla EPS in a patient with BD-IPMN; this case was managed by re-sphincterotomy without further pancreatitis during subsequent follow-up.

Long-term follow-up was available for all the 25 patients included in the study. The mean follow-up from ESP was 93.4 months (SD± 56.6), ranging from 1 to 16 years. The mean number of AP episodes occurred before and after EPS were respectively 3.29 (SD ± 1.04) and 0.51 (SD ± 0.71) ($p < .00001$) (Fig. 1). A complete response was reported in 16 patients (64%) and a partial response was obtained in 6 patients (24%) with an overall response rate of 88% (Table 3).

At subgroup analysis, the clinical response in patients with pancreas divisum (PD) and IPMN undergoing minor papilla EPS and patients with IPMN only undergoing major papilla EPS were compared. No statistically significant difference was found in the mean number of AP after EPS in both groups (0.61 vs 0.40, p 0.31). Moreover, excluding patients with PD from the statistical analysis, the mean number of AP occurred before and after EPS were respectively 3.47 (SD ± 1.04) and 0.63 (SD ± 0.69) ($p < .00001$).

The clinical response in patients with BD-IPMN and patients with MD-IPMN or MT-IPMN was also compared. The mean number of AP before and after EPS in BD-IPMN group were respectively 3.34 (SD ± 1.07) and 0.76 (SD ± 0.82) ($p < .00001$), while in the MD\MT-IPMN group were respectively 3.38 (SD ± 1.12) and 0.12 (SD ± 0.12) ($p < .00001$) (Fig. 2). Although no statistically significant difference was found in the mean number of AP episodes before and after the endoscopic treatment, the mean number of AP after EPS was significantly lower in MD\MT-IPMN group when compared with BD-IPMN group, 0.12 (SD ± 0.12) vs 0.76 (SD ± 0.82) (p 0.033).

Two patients underwent pancreatic surgery for IPMN progression. In one case BD-IPMN presented an increase in the major cyst size (30 mm x 20 mm vs. 22 mm x 17 mm) and pancreaticoduodenectomy was performed with a histopathological diagnosis of IPMN with high grade dysplasia. The second patient presented a MD-IPMN with high-risk stigmata (MD size >10 mm) underwent pancreaticoduodenctomy with a final diagnosis of IPMN with high-grade dysplasia.

4. Discussion

AP is considered a global burden with a pooled incidence of 34 cases per 100,000 general population per year representing one of the most frequent gastrointestinal causes of hospital admission [12]. IPMN is a rare cause of AP. Although the exact mechanism of IPMN-related AP is not well known, obstruction of the pancreatic ductal system by hypersecretion of thick mucus seems to be the most plausible mechanism (Video 1) [13]; in fact the intestinal subtype of IPMN that strongly express MUC2, a glycoprotein that composes the high viscous intestinal mucus, is reported to be most commonly associated with AP [14]. The correlation between IPMN-related AP and an increased risk of high-grade dysplasia or invasive carcinoma is controversial [15]. Interestingly, Muniraj et al. reported in a retrospective study involving 172 patients that malignancy was not increased in patients with pancreatic cystic neoplasms with ARP compared with those without ARP [16]. Other authors conversely reported that ARP was an independent predictor of malignancy [17]. According to the major international guidelines, IPMN related AP is considered a relative indication for pancreatic surgery [4,11,18]. However, pancreatic resection is still today burdened by high morbidity and mortality and endoscopy may represent a less invasive approach to manage the recurrence of AP. Few studies evaluated the role of ERCP in IPMN-related ARP (Table 4) [10,19–21]. Bernardoni et al. reported their experience in 16 patients [10]: after a mean follow-up of 27.4 months, a significant reduction in AP episodes after EPS (3.5 ± 2.32 vs. 0.56 ± 1.03, $P < .0001$) without IPMN progression and only moderate adverse events were reported. Gonzalez et al. in a multicenter retrospective study involving 21 patients with symptomatic BD-IPMN (including both ARP and pancreas related abdominal pain) treated with EPS reported a complete response in 71% of the cases and a partial response in 81% [19]; at subgroup analysis patients with ARP presented a better response than patients with pancreas related abdominal pain (90% vs 50%).

The present experience confirms that EPS is safe and effective in the management of IPMN related ARP including BD-IPMN, MD-IPMN and MT-IPMN. After a long-term follow-up (mean 93.4

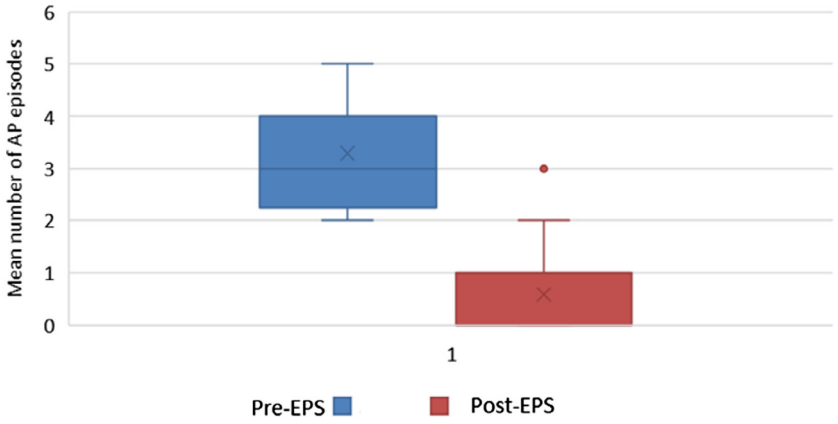

Fig. 1. Mean number of AP episodes before EPS (3.29 ± 1.04 SD) and after EPS (0.51 ± 0.71 SD) (*p 0.00001 paired samples t-test*).
AP: acute pancreatitis; EPS: endoscopic pancreatic sphincterotomy; SD: standard deviation.

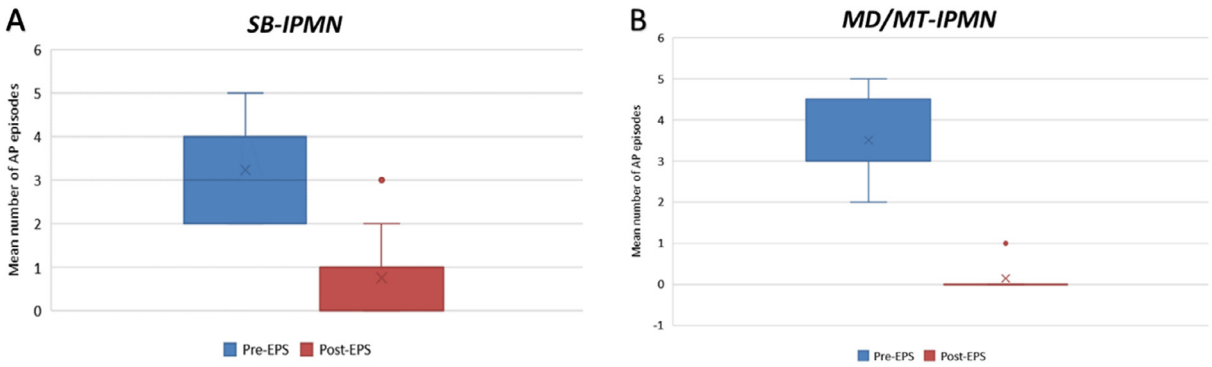

Fig. 2. Mean number of AP before and after EPS in BD-IPMN group and MD/MT-IPMN group.
The mean number of AP before and after EPS in BD-IPMN group were respectively 3.34 (SD ± 1.07) and 0.76 (SD ± 0.82) ($p < .00001$ paired samples *t*-test) (A). The mean number of AP before and after EPS in the MD\MT-IPMN group were respectively 3.38 (SD ± 1.12) and 0.12 (SD ± 0.12) ($p < .00001$ paired samples *t*-test) (B). (AP: acute pancreatitis, IPMN: Intraductal Papillary Mucinous Neoplasm; MD-IPMN: Main Duct-Intraductal Papillary Mucinous Neoplasm; BD-IPMN: Branch duct-Intraductal Papillary Mucinous Neoplasm; MT-IPMN: Mixed Type-Intraductal Papillary Mucinous Neoplasm; EPS: endoscopic pancreatic sphincterotomy.

Table 3
Clinical success of EPS in the 25 patients evaluated at follow-up.

Clinical success	Patients achieving clinical success after EPS n (%)
Complete response (no further episodes of AP)	16 (64%)
Partial response (≥50% reduction in the number of AP episodes)	6 (24%)
Total response (complete and partial response)	22 (88%)

EPS: endoscopic pancreatic sphincterotomy; AP: acute pancreatitis.

months), a statistically significant reduction of AP episodes was documented with a complete response, a partial response and an overall response in 64%, 24% and 88% of the cases respectively. EPS has a decompressive effect and facilitates mucus extrusion, with a possible reduction for the risk of obstructive acute pancreatitis in patients with IPMN. Only moderate adverse events were related to ERCP, all managed endoscopically; no cases of post-ERCP pancreatitis occurred possibly due to the systematic prophylactic drainage after EPS (naso-pancreatic drain or stent). In our institution, the placement of naso-pancreatic drainage is generally preferred over pancreatic stents, due to the high risk for stents occlusion from the thick mucus in the setting of IPMN. No differences in term of clinical efficacy were reported between patients undergoing major papilla sphincterotomy and minor papilla sphincterotomy and those with and without PD. Comparing the clinical response in patients with different types of IPMN, those with MD/MT-IPMN presented a better response at follow-up with a significant lower recurrence of AP (0.12 ± 0.12 vs 0.76 ± 0.82). The best outcomes described in patients with MD/MT-IPMN is not univocally explained. Possibly EPS decompresses the main pancreatic duct allowing the extrusion of mucus plugs that may be more commonly present into the MPD in patients with MD/MT-IPMN. However, the small sample size limits a deeper evaluation of clinical response in the different groups of patients.

Endoscopic treatment is effective only in the reduction of AP episodes, without effects on the progression of IPMN and on the presence of any grade of dysplasia. In our series, 2 patient presented disease progression and underwent pancreatic resection; one patient was not included in the cohort because received pancreaticoduodenectomy for malignancy within 2 months from EPS. Patients with IPMN-related ARP undergoing EPS should continue the scheduled follow-up in order to detect the occurrence of high-risk stigmata or worrisome features. Moreover, considering AP as a worrisome feature and given the non-reducible risk for malig-

Table 4
Studies available on EPS in patients with IPMN related ARP.

Author, year	N° of patients	Type of IPMN	Complete response	Partial response	Mean number of AP before EPS	Mean number of AP after EPS	Adverse events	IPMN progression	Need for surgery
Present series	25	BD-IPMN 68%MD-IPMN 24%MT-IPMN 8%	64%	88%	3.29 (SD ± 1.04)	0.51 (SD ± 0.71)	1 minor papilla EPS stenosis1 post-EPS bleeding	1	2
Gonzalez et al., 2019 [19]	21 (19 with ARP)	BD-IPMN 71%MT-IPMN 29%	71%	81%	NA	NA	4 post-ERCP pancreatitis	4 patients	5 (4 for IPMN progression; 1 for endoscopic treatment failure)
Bernardoni et al., 2017 [10]	16	BD-IPMN 56%MD-IPMN 44%	68.7%	18.7%	3.50 ± 2.32	0.56 ± 1.03	1 post-ERCP pancreatitis	1	2 (1 for IPMN progression; 1 for endoscopic treatment failure)
Oh et al., 2011 [20]	2	BD-IPMN 50%MD-IPMN 50%	50%	50%	NA	NA	None	None	None
Elton et al., 1998[21]	3	NA	100%	0%	NA	NA	NA	NA	NA

IPMNs: Intraductal Papillary Mucinous Neoplasms; MD-IPMN: Main Duct-Intraductal Papillary Mucinous Neoplasm; BD-IPMN: Side Branches-Intraductal Papillary Mucinous Neoplasm; AP: acute pancreatitis; EPS: endoscopic pancreatic sphincterotomy.

nancy, even a shorter radiological and clinical follow-up may be offered to early detect any disease progression.

The main limitations of the present study are the retrospective design, the limited number of patients enrolled, the absence of a control group, and the impossibility to evaluate the clinical response as an incidence, due to the retrospective nature of the study. Notwithstanding these limitations, this is the largest cohort on the use of EPS in patients with IPMN related ARP so far. Moreover, the "a priori" minimum follow-up of 12 months, the long-term follow-up (mean 93.4 months), the high rate of complete response (64% of cases), and the low rate of adverse events highlight the efficacy and safety of EPS in selected patients with IPMN-related ARP that might be offered to avoid an early pancreatic surgery. However, given the non-reducible risk for malignancy, this procedure should be reserved only to patients with low risk for disease progression and for those unfit for surgery or refusing surgery. Further studies are required to confirm our findings and to deeply evaluate the relation between AP and dysplasia in IPMN.

Declaration of Competing Interest

Andrea Tringali is a consultant for Boston Scientific and Olympus.

Ivo Boškoski is a consultant for Apollo Endosurgery, Cook Medical, and Boston Scientific Corp., he holds a research grant from Apollo Endosurgery, and is on the scientific board of EndoTools. Guido Costamagna is on the advisory board for Cook Medical, Olympus, and Ethicon, and holds a research grant from Boston Scientific Corp. and Apollo Endosurgery.

The other authors have no financial relationships with a commercial entity producing health-care related products and/or services relevant to this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.10.006.

References

[1] Furukawa T, Klöppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Arch 2005 Published online. doi:10.1007/s00428-005-0039-7.
[2] Le H, Ziogas A, Rhee JM, Lee JG, Lipkin SM, Zell JA. A population-based, descriptive analysis of malignant intraductal papillary mucinous neoplasms of the pancreas. Cancer Epidemiol Biomarkers Prev 2008 Published online. doi:10.1158/1055-9965.EPI-08-0417.
[3] Tanaka M, Fernández-del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017 Published online. doi:10.1016/j.pan.2017.07.007.
[4] Fernández-Del Castillo C, Targarona J, Thayer SP, et al. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg 2003. doi:10.1001/archsurg.138.4.427.
[5] Jang JW, Kim MH, Jeong SU, et al. Clinical characteristics of intraductal papillary mucinous neoplasm manifesting as acute pancreatitis or acute recurrent pancreatitis. J Gastroenterol Hepatol 2013 Published online. doi:10.1111/jgh.12121.
[6] Retter J, Dinter D, Bersch C, Singer MV, Löhr M. Acute recurrent pancreatitis curtaining an intraductal papillary mucinous tumor of the pancreas. J Gastrointest Liver Dis 2007 Published online.
[7] Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol 2016 Published online. doi:10.1016/j.cgh.2015.12.040.
[8] Del Chiaro M, Besselink MG, Scholten L, et al. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018 Published online. doi:10.1136/gutjnl-2018-316027.
[9] Simon R. Complications after pancreaticoduodenectomy. Surg Clin N Am 2021 Published online. doi:10.1016/j.suc.2021.06.011.
[10] Bernardoni L, Crinò S, De Conti G, et al. Preliminary experience with pancreatic sphincterotomy as treatment for intraductal papillary mucinous neoplasm-associated recurrent pancreatitis. Endosc Int Open 2017 Published online. doi:10.1055/s-0043-119753.
[11] Rodrigues JP, Fernandes S, Proença L, Carvalho J. Fish-eye ampulla: a rare pathognomonic sign. GE Port J Gastroenterol 2019 Published online. doi:10.1159/000494570.
[12] Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol 2019 Published online. doi:10.1038/s41575-018-0087-5.
[13] Tanaka M, Kobayashi K, Mizumoto K, Yamaguchi K. Clinical aspects of intraductal papillary mucinous neoplasm of the pancreas. J Gastroenterol 2005 Published online. doi:10.1007/s00535-005-1646-4.
[14] Yonezawa S, Goto M, Yamada N, Higashi M, Nomoto M. Expression profiles of MUC1, MUC2, and MUC4 mucins in human neoplasms and their relationship with biological behavior. Proteomics 2008 Published online. doi:10.1002/pmic.200800040.
[15] Tanaka M, Fernández-Del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012. doi:10.1016/j.pan.2012.04.004.
[16] Muniraj T, Aslanian HR, Laine L, et al. Resection of pancreatic cystic neoplasms in recurrent acute pancreatitis prevents recurrent pancreatitis but does not identify more malignancies. World J Gastroenterol 2021;27(15):1630–42. doi:10.3748/wjg.v27.i15.1630.
[17] Morales-Oyarvide V, Mino-Kenudson M, Ferrone CR, et al. Acute pancreatitis in intraductal papillary mucinous neoplasms: a common predictor of malignant intestinal subtype. Surgical 2015 Published online. doi:10.1016/j.surg.2015.04.029.

[18] Vege SS, Ziring B, Jain R, Moayyedi P. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015 Published online. doi:10.1053/j.gastro.2015.01.015.
[19] Gonzalez J-M, Lorenzo D, Ratone J-P, et al. Pancreatic sphincterotomy improves pain symptoms due to branch-duct intrapapillary mucinous neoplasia without worrisome features: a multicenter study. Endosc Int Open 2019 Published online. doi:10.1055/a-0841-3385.
[20] Oh YS, Dua K. Pancreatic sphincterotomy for pancreatitis associated with main duct intraductal papillary mucinous neoplasm. Endoscopy 2011 Published online. doi:10.1055/s-0030-1255915.
[21] Elton E, Howell DA, Parsons WG, Qaseem T, Hanson BL. Endoscopic pancreatic sphincterotomy: indications, outcome, and a safe stentless technique. Gastrointest Endosc 1998 Published online. doi:10.1016/S0016-5107(98)70320-7.