ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Endoscopic retrograde cholangiopancreatography (ERCP) in patients with periampullary diverticula

VICTOR CĂTĂLIN SFARTI[1,2)], GHEORGHE BĂLAN JR.[1,2)], ANDREI ŞTEFAN CHIRIAC[1,2)], CAROL STANCIU[2)], GHEORGHE BĂLAN[2)], DUMITRIŢA GAFENCU-ŞAVLOVSCHI[2)], ANCA VICTORIŢA TRIFAN[1,2)]

[1)]*Department of Gastroenterology, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*
[2)]*Institute of Gastroenterology and Hepatology of Iaşi, Romania*

Abstract

Aim: The aim of our study was to compare baseline characteristics and clinical data as well as endoscopic retrograde cholangiopancreatography (ERCP) results in patients with and without periampullary diverticulum (PAD). *Patients, Materials and Methods*: A single center retrospective analysis was conducted from June 2016 to June 2017 and the patients that had undergone ERCP were divided into two groups, according to the presence (Group A, 43 patients) or absence (Group B, 55 patients) of PAD. *Results*: Mean age of patients with PAD was significantly higher than the ones in the control group (69.95 years *vs.* 55.35 years, $p<0.01$), but the two groups had a similar structure regarding the gender. The distribution of the PAD types identified 18.6% type 1 diverticula, 25.6% type 2 diverticula, and 55.8% type 3 diverticula, with a mean dimension of 12.7±4.63 mm. Higher rates of failed (11.6% *vs.* 0%) or difficult cannulation (25.6% *vs.* 16.3%) were observed in Group A, but the rate of peri-procedural complications was similar in patients with diverticula compared to the control group concerning bleeding, perforation and pancreatitis, with a greater incidence of infections in the group without diverticula. *Conclusions*: Our study confirms that PAD is a pathology occurring more frequently with increasing age and can increase the rate of difficult or failed cannulation, but even in this context, there is no increase in the peri-procedural complications even if in training endoscopists perform the procedure.

Keywords: endoscopic retrograde cholangiopancreatography (ERCP), periampullary diverticula (PAD), cannulation.

Introduction

Periampullary diverticula (PAD) are sacciform protrusions of the duodenal wall (duodenal outpunching), appearing through extraluminal evagination of the duodenal mucosa due to a defect in the muscular layer, in a context of increased intraduodenal pressure and some nonspecific motor disorders. Structurally, PAD have a wall containing only the mucosa and submucosa, without involving a muscular layer, and are located at a distance of up to 2–3 cm around the papillary orifice.

PAD prevalence ranges from 10% to 20% in patients in whom endoscopic retrograde cholangiopancreatography (ERCP) is performed, most commonly in women and increasing with age, reaching 65% in the elderly. Although, in general, PAD are asymptomatic and are incidentally found during ERCP, there are studies that associate the PAD with various pathologies: obstructions of the common bile duct (especially lithiasic), pancreatitis, perforations, papillary bleeding and, rarely with tumors of ampulla of Vater [1, 2]. The most common combination is described with biliary lithiasis and several hypotheses have been proposed to explain its increased incidence in patients with PAD. First, it was proposed that a possible dysfunction of the sphincter of Oddi would induce pancreatic and intestinal juice reflux into the biliary ducts, with the formation of calculi. Secondly, it was proposed that the PAD could lead to papillary spasm, increasing pressure in the biliary tract and promoting formation of gallstones. The third hypothesis was that the PAD would compress the distal portion of the common bile duct, with biliary stasis and association of pigment stones [3–5]. In terms of endoscopic examination, the standard classification of PAD includes three types: type 1, where the major papilla is located inside the diverticulum; type 2, with papilla located on the edge of the diverticulum; and type 3, with the papilla located outside the diverticulum.

One of the most important issues for the endoscopist represents the impact of PAD on the success of ERCP. According to most studies, the reported success rates of biliary cannulation in patients with PAD are between 61% and 95.4%, significantly lower values than those seen in patients without PAD [6]. Regarding the frequency of complications occurring post-ERCP in patients with PAD compared to those without PAD, generally, there seem to seem to be no significant differences [6, 7].

Aim

In this context, we evaluated in the present study the incidence and type of PAD identified during the ERCP examination, the success rate of ERCP performed by gastroenterologists in training, as well as the rate of complications post-ERCP in patients with or without PAD.

Patients, Materials and Methods

Patients

We have conducted a retrospective observational study from June 2016 to June 2017, in the Institute of Gastroenterology and Hepatology of Iaşi, Romania, including patients with biliary-pancreatic pathology, which had undergone ERCP. Participants were divided into two

groups according to the presence (Group A) or absence (Group B) of PAD.

Demographics, medical history, clinical and paraclinical examination results were obtained from patient observation sheets. In all patients, laboratory samples were taken [blood count, C-reactive protein (CRP), liver and renal function tests, pancreatic enzymes] before the procedure, then at 6 hours and 24 hours following ERCP. Bilio-pancreatic pathology diagnosis was suspected at ultrasonography and confirmed by computed tomography (CT) with contrast or by magnetic resonance (MR) cholangiography or intraoperative cholangiography.

The study was evaluated and approved by the Ethics Committee of the Institute of Gastroenterology and Hepatology of Iaşi.

Method

The examinations were performed by classical techniques of ERCP, using the Olympus duodenoscopes. The procedures were performed by gastroenterologists in training supervised by an expert, all patients being sedated with Midazolam/Propofol/Ketamine under the supervision of an anesthesia care team. A PAD was defined as a depressed lesion of 5 mm or more located within a range of 2.5 cm of the papilla of Vater. The success of cannulation procedure was defined as evidence of free and deep passage of biliary duct by sphincterotome/ standard catheter. Cannulation attempt was considered after at least 5 seconds of continuous contact of cannulation device with papilla or papillary orifice. Cannulation was defined as easy, difficult or impossible. A cannulation was considered difficult in the following circumstances:

▪ over five failed attempts to cannulate or cannulation attempts that have lasted more than 5 minutes;

▪ more than two unintended passages in the Wirsung's duct;

▪ cases where it was considered appropriate the early use of needle knife due to papillary;

▪ loco-regional anatomy indicating a high probability of impossible cannulation by standard method (early access needle knife sphincterotomy).

Post-ERCP complications under observation included pancreatitis, bleeding, infection and perforation.

The data were analyzed statistically using the Statistical Package for the Social Sciences (SPSS) 20.0 software. Statistical significance was considered for a value of $p<0.05$.

Results

During this period, 382 procedures were performed in 356 patients, while PAD were described in 43 cases (12.07% of the total number of cases) (Group A). Of the remaining patients, we selected a control group of 55 subjects without PAD (Group B) with similar demographic and clinical characteristics with Group A.

Age values were normally distributed, therefore we used Student's *t*-test in order to compare the two groups with and without PAD. Thus, we found that the patients included in the active group were older than those from the control group, respectively, as presented in Table 1. The mean age was significantly higher in the group with PAD compared to the group without diverticula, 69.95±13.438 years as opposed to 55.35±15.95 years ($p=0.000005$), respectively, which proves once again the increased risk of occurrence of diverticula with the advance in age. The two groups had a similar structure with regard to patients' gender (Table 2). We also carried out a risk assessment, in order to determine whether patients' gender was as a possible risk factor for diagnosis of diverticula. The odds ratio (OR) for women was 1.099, thus the female gender associated a weak positive risk (Table 3).

Table 1 – *Age distribution of patients*

		Levene test for equality of variances		Student's *t*-test for equality of means – independent samples						
		F	*Sig.*	*t*	*df*	*p*	*Difference of the means*	*Standard error of difference*	*95% CI for the difference*	
									Inf. L.	*Sup. L.*
Age [years]	Equal variances	3.246	0.075, *NS*	4.815	96	0	14.608	3.034	8.586	20.63
	Unequal variances			4.917	95.43	0	14.608	2.971	8.711	20.505

CI: Confidence interval; *NS*: Not significant.

Table 2 – *Gender distribution of patients*

Pearson's *chi*-square: 0.052, *p*=0.819, *NS* Contingency coefficient: 0.023			Diverticulum		Total
			Present	*Absent*	
Gender	Female	*N*	26	32	58
		Percent	60.5%	58.2%	59.2%
	Male	*N*	17	23	40
		Percent	39.5%	41.8%	40.8%
Total		*N*	43	55	98
		Percent	100%	100%	100%

NS: Not significant; *N*: No. of cases.

Table 3 – *Risk assessment for gender involvement*

Risk assessment	Value	95% CI	
		Inf. L.	*Sup. L.*
Odds ratio for gender (females/males)	1.099	0.488	2.478
For cohort diverticulum – present	1.055	0.666	1.671
For cohort diverticulum – absent	0.96	0.674	1.366
No. of valid cases	98		

CI: Confidence interval.

Diagnostic indications for ERCP in the active group were represented by lithiasic pathology in 35 (81.4%) cases, hepato-bilio-pancreatic tumor lesions in four (9.3%) cases and other etiologies (postoperative stenosis, hydatid cyst) in four (9.3%) cases, while in the control group, 45 (81.8%) patients had calculi, one patient (1.8%) had

cholangiocarcinoma (16.4%) and nine cases presented other etiologies (Table 4).

Of the total of 43 patients with diverticula, in five cases small diverticula (<5 mm) were identified, in 21 cases medium-size diverticula (5–15 mm) were found and 17 patients had voluminous diverticula (>15 mm) (Table 5). The dimensions of diverticula varied between 3 mm and 35 mm, with a mean dimension of 12.7± 4.63 mm. Regarding the location of the different types of diverticula, eight (18.6%) patients had type 1 diverticula, 11 (25.6%) patients type 2 diverticula, and 24 (55.8%) cases type 3 diverticula (Table 6).

Table 4 – ***Diagnostics indications for ERCP procedure***

Pearson's *chi*-square: 12.6, *p*=0.32 Contingency coefficient: 0.023			**Diagnostic**						**Total**
			Benign bile duct structures	***Choledocian lithiasis***	***Cholecystitis with postoperative calculus migration***	***Cholangio-carcinoma***	***Hydatid cyst***	***Pancreatic neoplasm***	
Diverticulum	Present	*N*	3	33	2	2	1	2	43
		Percent	7%	76.75%	4.62%	4.65%	2.3%	4.65%	100%
	Absent	*N*	6	38	7	1	3	0	55
		Percent	10.9%	69.1%	12.7%	1.8%	5.5%	0%	100%
Total		*N*	9	71	9	3	4	2	98
		Percent	9.2%	72.4%	9.2%	3.1%	4.1%	2%	100%

ERCP: Endoscopic retrograde cholangiopancreatography; *N*: No. of cases.

Table 5 – ***Size of diverticula***

		Frequency	**Valid percent**
Valid	Small	5	11.6%
	Medium	21	48.8%
	Voluminous	17	39.5%
	Total	43	100%

Table 6 – ***Periampullary duodenal diverticulum type***

		Frequency	**Valid percent**
Valid	Type 1	15	34.8%
	Type 2	23	53.5%
	Type 3	5	11.7%
	Total	43	100%

Evaluation of the success of the ERCP had pursued two essential parameters: cannulation rate and duration of the procedure. In Group A, there had been 27 (62.8%) cases with easy cannulation, 11 (25.6%) cases of difficult cannulation (two solved by using needle-knife) and five (11.6%) cases of cannulation failures. In Group B, easy cannulation was more frequent, occurring in 46 (83.6%) of the patients, difficult cannulations in nine (16.4%) cases and none proved impossible (Table 7). ERCP bile duct cannulation, which proved difficult (or impossible), was significantly associated with duodenal diverticulum (χ^2=8.807, p=0.0122) (Table 8). Duration of the procedure was similar in the two groups: 27.36±6.867 minutes in Group A and 28.63±11.265 minutes in Group B, respectively (Table 9). In our study, 17 (39.5%) patients in the group with diverticula have never had bile duct stones, compared to nine (16.4%) cases of the control group.

Table 7 – ***Influence of PAD over success rate of cannulation***

2-Way summary table: observed frequencies (group_std. problem); marked cells have counts >10				
	Easy cannulation	***Difficult cannulation***	***Impossible cannulation***	***Row – Totals***
Diverticula, *N*	27	11	5	43
Percent	62.79%	25.58%	11.63%	
Control, *N*	46	9	0	55
Percent	83.64%	16.36%	0%	
Total	73	20	5	98

PAD: Periampullary diverticula; *N*: No. of cases.

Table 8 – ***Statistics: influence of PAD over success rate of cannulation***

Statistics: group (2) × cannulation (3) (group_std. problem)			
	Chi-square	***df***	***p***
Pearson's *chi*-square	8.807881	2	0.01223
Maximum-Likelihood *chi*-square	10.66133	2	0.00484
Phi	0.2997938		
Contingency coefficient	0.2871667		
Cramér's *V*	0.2997938		
Kendall's tau *b* & *c*	*b*=-0.252146	*c*=-0.224073	
Gamma	-0.525391		
Spearman's rank *rho*	-0.25717	*t*=-2.607	0.01058

PAD: Periampullary diverticula; *N*: No. of cases.

Table 9 – ***Procedure time (minutes)***

Diverticula	***N***	**Media**	**SEM**	**SD**	**Minimum**	**Maximum**
Present	43	28.63	1.718	11.265	15	95
Absent*	55	27.36	0.926	6.867	13	45
Total	98	27.92	0.913	9.033	13	95

N: No. of cases; SEM: Standard error of the mean; SD: Standard deviation.

The sizes of PAD were estimated using a sphincterotome with a scale on the tip. PAD were classified according to the position of the major papilla from the endoscopic view in three types (Figure 1, A–C): type 1, the major papilla was located inside of the diverticula (Figure 2); type 2, the major papilla was located at the edge of the diverticula (Figure 3); type 3, the major papilla was located outside of the diverticula (Figure 4).

The rate of complications was similar in terms of peri-procedural bleeding (three cases in both groups), peri-procedural perforation (no event in any of the two groups) and post-ERCP pancreatitis (six cases in the group with diverticula compared to three cases in the control group), but there was a statistically significant difference in the case of post-ERCP infections (cholangitis): five cases in the control group *vs.* no event in patients with diverticulum, probably on the account on the absence of infections in the active group.

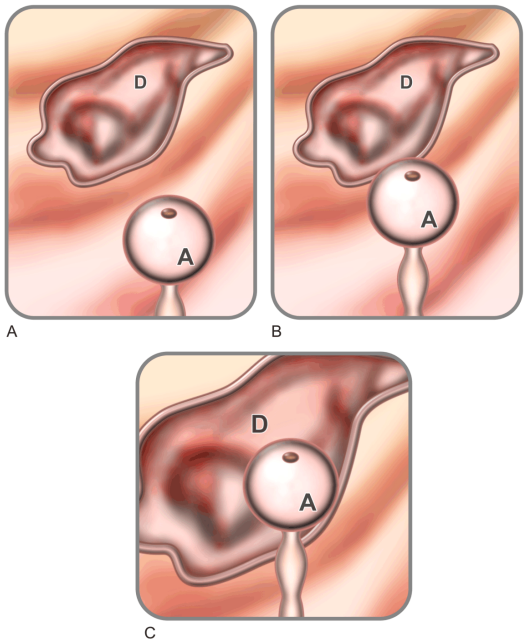

Figure 1 – ***Types of periampullary diverticulum: (A) Type 1 PAD with papilla outside the diverticula; (B) Type 2 PAD with papilla at the edge of the diverticula; (C) Type 3 PAD with papilla inside the diverticula. A: Ampulla of Vater; D: Diverticula; PAD: Periampullary diverticula.***

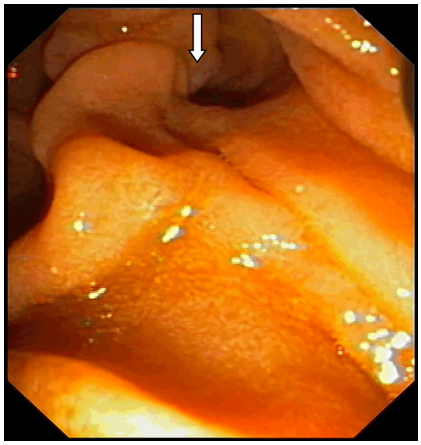

Figure 2 – ***Type 1 PAD: the major papilla was located inside of the diverticula (the arrow points the major papilla orifice). PAD: Periampullary diverticula.***

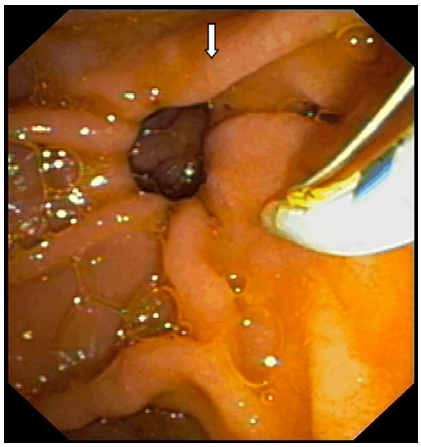

Figure 3 – ***Type 2 PAD: the major papilla was located at the edge of the diverticula (the arrow points the major papilla orifice). PAD: Periampullary diverticula.***

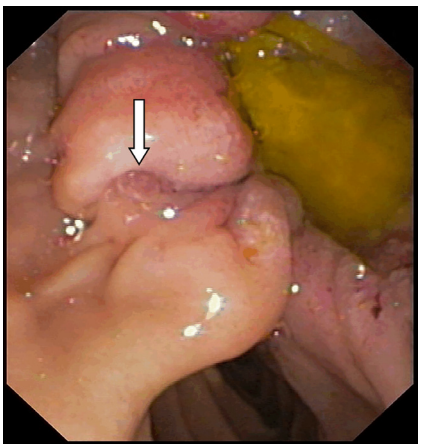

Figure 4 – ***Type 3 PAD: the major papilla was located outside of the diverticula (the arrow points the major papilla orifice). PAD: Periampullary diverticula.***

Discussions

The presence of diverticula has not been associated with a higher frequency of choledocholithiasis, as most data from the literature show [6, 8]. The study has followed in the first phase the incidence and type of PAD in candidates for ERCP. The percentage of 12.07% of PAD identified at ERCP is within the margins described in literature, as assessed between 10–20% [9]. The distribution by types of PAD in our study defines 18.6% type 1 diverticula, 25.6% type 2 diverticula, and 55.8% type 3 diverticula, meeting the proportion observed in other studies, in the majority of which, type 3 is the most common, being described in more than half of cases: 63.3% reported by Örmeci *et al.* [10], and 62.1% by Sun *et al.* [11].

Most researchers have reported a significantly higher frequency of PAD in the elderly, an aspect also proven in our study, the average age in the group with diverticula being 69.95 years, compared with 55.35 years in the control group. With regard to gender, studies present either a slight association of PAD to the female gender [12] or similar gender breakdown [10]. In our research, we noted a minimal association with the female gender, but also in the context of the predominance of females in both groups. We found an OR of 1.099 for female patients, associating a weak positive risk.

Our study confirmed that the presence of diverticula increased the difficulty of cannulation (by 25.6% in Group A *vs.* 16.3% in Group B) and the rate of failed ERCP (11.6% in Group A *vs*. 0% in Group B). Perhaps the main reason of failed cannulation in patients with PAD is the impossibility of identifying the papilla, particularly in type 1 PAD, with the papilla hidden inside the diverticulum. We also noticed that the deep positioning of the papilla inside the diverticulum or in a low position, immediately in the proximity of the margin of the diverticulum was associated with difficult cannulations, but the low number of such cases did not allow us to perform a statistical analysis. Literature data are contrasting in this aspect, as there are both studies showing that the presence of diverticula is an impediment to ERCP [8], but also data that suggests that the existence of PAD can facilitate successful ERCP [7].

In general, the presence of PAD significantly correlates with the presence of choledocian calculi [8, 13], but this has not been demonstrated in our study, where 60.5% of patients in Group A had bile stones, compared with 83.6% of the control group. A possible explanation could be the higher percentage of malignancies diagnosed pre-ERCP in the active group.

The rate of peri-procedural complications was similar in patients with diverticula compared with the control group in case of bleeding, perforation and pancreatitis, but there was a greater incidence of infections in the group without diverticula, possibly due to the higher incidence of benign stenosis and in the context of post-operative ERCP. In the case of patients in the post-operative period, we have retrospectively found a higher rate of bile cultures or wound secretions collected intra-operatively. Most studies show a similar rate of post-ERCP complications (hemorrhage, infection, perforation) in patients with diverticula compared to those without PAD [8, 9, 11]. In relation to post-ERCP pancreatitis, studies are not consistent. Thus, some authors have reported a greater frequency of pancreatitis in patients with PAD [14], while others claimed that the PAD would have a protective role against post-procedural pancreatitis [13, 15]. There are also studies, such as ours, which describe similar rates for post-ERCP pancreatitis in patients with or without PAD [8, 10].

Conclusions

Our study confirms that PAD are commonly found in patients who undergo ERCP, occurring more frequently with increasing age and more often, in female patients. The data obtained demonstrated that PAD can be an obstacle during the procedure and increase the rate of difficult or failed cannulation, requiring sometimes more complex interventions and additional skills for the endoscopist. Even in this context, there is no increase in the peri-procedural complications (hemorrhage, perforation, infection, pancreatitis) even with endoscopists on training performing the procedure.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Tyagi P, Sharma P, Sharma BC, Puri AS. Periampullary diverticula and technical success of endoscopic retrograde cholangiopancreatography. Surg Endosc, 2009, 23(6):1342–1345.

[2] Getsov P, Dineva S, Vladimirov B. Endoscopic retrograde cholangiopancreatography in patients with periampullary diverticula: analysis of 3259 cases. J Med Sci Public Health, 2014, 3(2):35–42.

[3] Yildirgan MI, Başoğlu M, Yilmaz I, Atamanalp SS, Balik AA, Aydinli B, Oztürk G. Periampullary diverticula causing pancreaticobiliary disease. Dig Dis Sci, 2004, 49(11–12): 1943–1945.

[4] Hagège H, Berson A, Pelletier G, Fritsch J, Choury A, Liguory C, Etienne JP. Association of juxtapapillary diverticula with choledocholithiasis but not with cholecystolithiasis. Endoscopy, 1992, 24(4):248–251.

[5] Miyazaki S, Sakamoto T, Miyata M, Yamasaki Y, Yamasaki H, Kuwata K. Function of the sphincter of Oddi in patients with juxtapapillary duodenal diverticula: evaluation by intraoperative biliary manometry under a duodenal pressure load. World J Surg, 1995, 19(2):307–312.

[6] Altonbary AY, Bahgat MH. Endoscopic retrograde cholangio-pancreatography in periampullary diverticulum: the challenge of cannulation. World J Gastrointest Endosc, 2016, 8(6):282–287.

[7] Panteris V, Vezakis A, Filippou G, Filippou D, Karamanolis D, Rizos S. Influence of juxtapapillary diverticula on the success or difficulty of cannulation and complication rate. Gastrointest Endosc, 2008, 68(5):903–910.

[8] Mohammad Alizadeh AH, Afzali ES, Shahnazi A, Mousavi M, Doagoo SZ, Mirsattari D, Zali MR. ERCP features and outcome in patients with periampullary duodenal diverticulum. ISRN Gastroenterol, 2013, 2013:217261.

[9] Egawa N, Anjiki H, Takuma K, Kamisawa T. Juxtapapillary duodenal diverticula and pancreatobiliary disease. Dig Surg, 2010, 27(2):105–109.

[10] Örmeci N, Deda X, Kalkan Ç, Tüzün AE, Karakaya F, Dökmeci A, Bahar DK, Özkan H, İdilman R, Çınar K. Impact of periampullary diverticula on bile duct stones and ampullary carcinoma. Euroasian J Hepatogastroenterol, 2016, 6(1):31–34.

[11] Sun Z, Bo W, Jiang P, Sun Q. Different types of periampullary duodenal diverticula are associated with occurrence and recurrence of bile duct stones: a case-control study from a Chinese center. Gastroenterol Res Pract, 2016, 2016:9381759.

[12] Leivonen MK, Halttunen JA, Kivilaakso EO. Duodenal diverticulum at endoscopic retrograde cholangiopancreatography, analysis of 123 patients. Hepatogastroenterology, 1996, 43(10):961–966.

[13] Tham TKC, Kelly M. Association of periampullary duodenal diverticula with bile duct stones and with technical success of endoscopic retrograde cholangiopancreatography. Endoscopy, 2004, 36(12):1050–1053.

[14] Uomo G, Manes G, Ragozzino A, Cavallera A, Rabitti PG. Periampullary extraluminal duodenal diverticula and acute pancreatitis: an underestimated etiological association. Am J Gastroenterol, 1996, 91(6):1186–1188.

[15] Zoepf T, Zoepf DS, Arnold JC, Benz C, Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients. Gastrointest Endosc, 2001, 54(1):56–61.

Corresponding author

Carol Stanciu, MD, FRCP, Professor of Gastroenterology, Institute of Gastroenterology and Hepatology, 1 Independenţei Street, 700111 Iaşi, Romania; Phone +40722–306 020, Fax +40232–246 611, e-mail: stanciucarol@yahoo.com

Received: August 31, 2018

Accepted: November 12, 2018