

Endoscopic retrograde pancreatography: When should we do it?

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Author contributions: All authors contributed to this paper.

Conflict-of-interest statement: No conflict of interest is declared by any of the authors.

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Received: May 16, 2015

Peer-review started: May 16, 2015

First decision: June 18, 2015

Revised: June 24, 2015

Accepted: August 13, 2015

Article in press: August 14, 2015

Published online: August 25, 2015

Abstract

Endoscopic retrograde pancreatography (ERP) is an accurate imaging modality in the diagnosis of pancreatobiliary diseases. However, its use has been substantially reduced due to the invasiveness of procedure, the risk of complications and the

widespread availability of non-invasive cross-section imaging techniques (computed tomography, magnetic resonance imaging, and endoscopic ultrasound). Since the introduction of endoscopic sphincterotomy, ERP has transformed from diagnostic method to an almost exclusively therapeutic procedure. Pancreatic duct injection substantially increased the risk of post-ERP pancreatitis (1.6%-15.7%); therefore, according to international guidelines ERP is recommended only in cases where biliary intervention is required. However, the role of ERP in the management of pancreatic diseases is currently not clearly defined, but in some cases the filling of pancreatic duct may provide essential information complementing the results of non-invasive imaging techniques. The aim of this publication is to systematically summarize the literature dealing with the diagnostic yield of ERP. We would like to define the precise indications of ERP and overview a diagnostic protocol of pancreatic diseases depending on international guidelines and the opinion of Hungarian experts, because it may improve the diagnostic accuracy, minimize the burden of patients and reduce the risk of procedure related complications.

Key words: Endoscopic retrograde cholangiopancreatography; Endoscopic pancreatography; Autoimmune pancreatitis; Pancreas divisum; Chronic pancreatitis

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Core tip: Since the development and widespread availability of non-invasive imaging techniques the importance of diagnostic endoscopic pancreatography (ERP) has substantially reduced. However, in some complicated cases or during pancreatic interventional endoscopic procedures such as minor papilla sphincterotomy, pancreatic sphincterotomy, pancreatic stent implantation, ERP may provide essential information. This article seeks to summarize the results of previous studies and recommendations of international guidelines

to define the diagnostic yield and correct indications of ERP.

Bor R, Madácsy L, Fábíán A, Szepes A, Szepes Z. Endoscopic retrograde pancreatography: When should we do it? *World J Gastrointest Endosc* 2015; 7(11): 1023-1031 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i11/1023.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i11.1023>

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure that provides radiological visualization of the detailed structure and the pathological changes of the biliary tree and pancreatic ducts by injection of contrast agent into the common bile duct (CBD) and the main pancreatic duct (MPD). Since its development in 1968, it has become a widely used and accurate imaging modality in the diagnosis of pancreatobiliary diseases^[1]. Since the introduction of endoscopic sphincterotomy in 1974^[2], ERCP has become the most important minimal invasive treatment method for various biliary and pancreatic diseases including bile duct or pancreatic duct stones (choledocholithiasis or wirsungolithiasis), benign and malignant biliary and pancreatic duct obstructions. Recently ERCP has transformed from a diagnostic method to an almost exclusively therapeutic procedure due to the widespread availability of noninvasive cross-section imaging techniques such as abdominal ultrasound (AUS), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS)^[3]. Numerous studies emphasize the disadvantages of ERCP such as post-ERCP complications and the burden to patients. In a meta-analysis of 21 prospective trials the incidence of mild-to-moderate complications reached 5.17%, and that of severe events up to 1.67%^[4] (Table 1). Post-ERCP pancreatitis (PEP) is the most frequent complication with approximately 3.5% but its incidence ranges widely (1.6%-15.7%) depending on the patient selection and the definition of pancreatitis^[5-7]. Pancreatic duct injection substantially increased the risk of PEP, therefore the role of diagnostic endoscopic pancreatography (ERP) gradually decreased. International guidelines recommend ERCP only in cases where biliary intervention is required^[3-8], but the indication of ERP is not clearly defined. According to the current guidelines routine rectal administration of 100 mg diclofenac or indomethacin immediately before or after ERCP is strongly recommended to prevent PEP. In patients with MPD filling and increased patient or procedure related risk factors for PEP temporary application of prophylactic small caliber pancreatic stents is also recommended to reduce the risk of severe PEP^[9].

The aim of this article is to systematically review

Table 1 Frequency of procedure related complications of endoscopic retrograde pancreatography (6.85%) depending on the results of endoscopic retrograde pancreatography^[4]

	Mild to moderate	Severe	Death
Pancreatitis	3.07%	0.40%	0.11%
Bleeding	0.95%	0.39%	0.05%
Perforation		0.60%	0.06%
Infection	1.15%	0.28%	0.11%
Total	5.17%	1.67%	0.33%

the literature dealing with the diagnostic yield of ERP in various pancreatic diseases, and to define the principles and indications of ERP depending on the recommendations of international guidelines and the opinion of Hungarian experts (Tables 2 and 3).

PANCREAS DIVISUM

Pancreas divisum (PD) is the most common congenital anomaly of the pancreas in which the dorsal and ventral pancreatic duct drain separately into the duodenum. Recently ERP has been the gold standard imaging modality for the diagnosis of PD due to its high diagnostic accuracy^[10,11], but the rate of complete pancreatography and the success of minor papilla cannulation significantly influence the sensitivity of ERP^[12] (Figure 1). The high rate of complications is the greatest disadvantage of ERP, therefore noninvasive procedures, such as MRCP and EUS are increasingly spreading worldwide in this indication as well. Sensitivity and specificity of MRCP in the detection of PD is 52%-73.3% and 96.8%-97%, and the diagnostic accuracy can further be improved with the use of secretin stimulation (73.3%-86% and 97%)^[13,14] (Figure 2). A comparison study carried out by Lai *et al.*^[15] has shown that adequate evaluation of the pancreatic duct by EUS is possible in 78% of cases, and the sensitivity, specificity, and positive and negative predictive values for EUS are 95%, 97%, 86%, and 99%.

ERP has an important therapeutic role in the endoscopic treatment (including minor papillotomy with or without pancreatic duct stenting) of patients with symptomatic PD. There is no prospective randomized controlled trial comparing endoscopic and surgical therapy, but previous retrospective studies could not detect any differences between the pooled overall response rates of the two treatment groups (endoscopic vs surgical treatment 54.3-79.2 vs 51.4-83.3 depending on the indication)^[16].

ACUTE PANCREATITIS

The importance of ERCP in the identification of the etiology of acute pancreatitis (AP) has rapidly decreased in the recent decades due to the widespread availability of noninvasive imaging modalities^[17]. The diagnosis of uncomplicated AP is mainly based on the clinical symptoms, elevated serum levels of pancreatic enzymes

Table 2 Indication of endoscopic retrograde pancreatography based on the opinion of Hungarian experts

	Indicated	Slightly indicated	Not indicated	Description
Pancreas divisum	83.6%	16.7%	0%	During therapeutic intervention
Acute pancreatitis	16.7%	50%	33.3%	Recurrent "idiopathic" acute pancreatitis
Chronic pancreatitis	83.3%	16.7%	0%	Complicated chronic pancreatitis (MPD stricture, pancreatic duct stones, chronic abdominal pain, obstructive jaundice)
Autoimmune pancreatitis	66.7%	33.3%	0%	Suspicion of autoimmune pancreatitis which has not identified by noninvasive imaging techniques
Pancreatic neoplasia	0%	50%	50%	Suspicion of pancreatic neoplasia with obstructive jaundice
Pancreatic cystic neoplasia	0%	16.7%	83.3%	In case of IPMN ERP associated with high risk of complications Pancreatic cysts and pseudocysts generally do not communicate with the pancreatic duct therefore the ERP cannot identify them
Pancreatic injury	100%	0%	0%	Suspicion of pancreatic ductal injury in stable patients
Postoperative pancreatic fistula	100%	0%	0%	Suspicion of pancreatic fistula Suspicion of fistula formation

ERP: Endoscopic pancreatography; MDP: Main pancreatic duct; IPMN: Intraductal papillary mucinous neoplasms.

Table 3 Indication of endoscopic retrograde pancreatography in the case of suprapapillary bile duct stenosis based on the opinion of Hungarian experts

Indicated	Not indicated	Description
50%	50%	ERP may help differentiate between cholangiocarcinoma and pancreatic illnesses

ERP: Endoscopic pancreatography.

(amylase, lipase) and the morphological changes in the pancreas on the AUS, CT or MRI images^[18]. Therapeutic ERCP with biliary sphincterotomy and removal of CBD stones can effectively improve the outcome, and according to the recent international guidelines it is indicated in acute biliary pancreatitis within 72 h, if noninvasive examinations prove the presence of acute cholangitis or raise the suspicion of CBD obstruction in association with acute pancreatitis^[19,20]. On the contrary, failed biliary cannulation and repeated MPD filling in patients with acute biliary pancreatitis may worsen the overall outcome and therefore some data suggest that small caliber prophylactic pancreatic stents may be applied as a bridging procedure to prevent complications in this group of patients^[21].

In 10%-15% of patients with recurrent acute pancreatitis if the complete noninvasive diagnostic evaluation could not reveal the exact cause and etiology, and as a consequence the diagnosis of "idiopathic" acute pancreatitis may arise. Therefore in patients with idiopathic acute pancreatitis, after the cessation of an acute inflammatory attack an ERCP with biliary and/or pancreatic sphincter of Oddi manometry, an endoscopic ultrasound, and secretin enhanced MRCP may leads to a diagnosis of biliary microlithiasis, sphincter of Oddi dysfunction, PD, cystic fibrosis, a choledochocoele, annular pancreas, an anomalous pancreatobiliary junction, small pancreatobiliary tumors, or early stage of chronic pancreatitis^[22,23].

CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is a progressive fibroinflammatory disorder with irreversible destruction of the pancreatic parenchyma and ducts. Frequently the complications, such as bile duct stenosis, obstructive jaundice, diabetes mellitus or malabsorption call the attention for the presence of the disease^[24]. In advanced stages the recognition of parenchymal fibrosis and moreover calcification is relatively easy with AUS, CT, MRI and EUS, and typical ductal alterations with ERCP or MRCP^[25]. The early recognition of CP and its differentiation from pancreatic cancer (PC) sometimes represents a real diagnostic challenge^[26]. Currently ERCP has been replaced by EUS (especially with elastography), MRI, CT, and MRCP in the early diagnosis of CP. However, ERCP plays an essential role in the more precise identification of complications such as obstructive jaundice, pancreatic stones, MPD strictures, chronic abdominal pain, and also gives the opportunity for the minimally invasive treatment (pancreatic sphincterotomy or balloon dilatation, pancreatic duct stenting, *etc.*)^[27] (Figure 3). The European Society of Gastroenterology recommends the endoscopic treatment as the first-line therapy for painful uncomplicated CP, and highlights its effectivity in the management of obstructive jaundice and pancreatic stones associated with CP^[3] (Figures 4 and 5). In cases of complicated CP the long-term efficacy of surgical intervention is superior to endoscopy in most patients^[28,29]. Despite the fact, that repeated pancreatography is usually necessary during the endoscopic intervention of the pancreatic duct, the risk of PEP is significantly reduced in CP as compared to the general population. However, the role of ERP as first examination in the diagnosis of suspected complicated CP is questionable^[6]. Therefore, in our clinical practice, we perform ERCP in CP patients only in case of chronic pancreatic pain and suspected MPD obstruction (stricture with prestenotic dilatation) based on MRCP or EUS. In these patients, pancreatic sphincterotomy, pancreatic

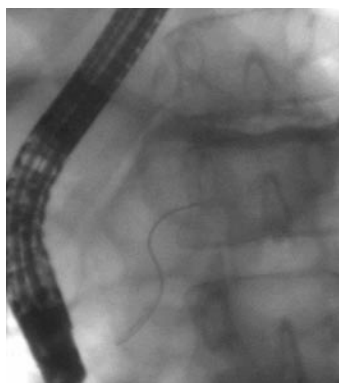


Figure 1 Endoscopic retrograde pancreatography image: Pancreas divisum with minor papilla cannulation.



Figure 3 Endoscopic pancreatography image: Chronic pancreatitis with Wirsungolithiasis.

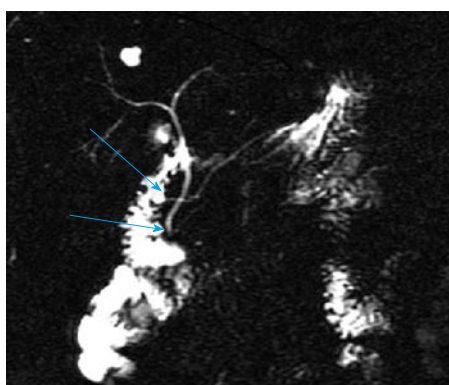


Figure 2 Secretin enhanced magnetic resonance cholangiopancreatography image: Pancreatic divisum and juxtapancreatic diverticulum.

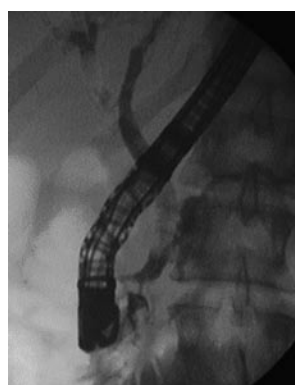


Figure 4 Endoscopic pancreatography image: Pancreatic duct stenosis with prestenotic dilatation after preventive pancreatic stent implantation.

stricture dilatation and multiple plastic or self-expanding metal stenting during ERP proved to be useful to achieve long term symptomatic improvement.

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) is an uncommon inflammatory disorder of the pancreas with a presumed autoimmune etiology^[30]. It may present with a wide variety of clinical and morphological features including painless obstructive jaundice, asymptomatic focal mass or diffuse enlargement of the pancreas which mimic PC^[31]. The diagnosis of AIP requires a multidisciplinary approach including imaging studies, histology, serology, assessment of other organ involvement and the therapeutic response to steroid treatment^[32,33]. There were differences in the diagnostic approach and the techniques used between different countries. For instance, ERP is usually ignored in Western countries to avoid PEP in contrast to Japan where this examination is usually performed^[34]. The correct diagnosis requires detailed information equally about the pancreatic parenchyma and ducts. In typical cases of AIP a diffusely enlarged or "sausage shaped" pancreas with featureless borders and/or loss of lobular architecture can be detected with AUS, CT and MRI^[35]. In 30%-40% of the cases

focal mass is found, which can lead to false diagnosis of pancreatic malignancy^[36,37]. Ductal imaging, ERP and MRCP may show a long, narrow ductal stricture (greater than one-third the length of the MPD) or multiple, non-continuous strictures without marked upstream dilatation, and side branches arising from the stricture^[38-40]. However, given that ERCP is an invasive method which debilitates the patient and can cause adverse effects (pancreatitis, bleeding), the noninvasive MRCP is becoming the first choice examination for pancreatobiliary diseases. Previous comparison studies have shown that MRCP is less sensitive in the differentiation of focal form of AIP and PC, therefore cannot completely replace ERCP for the diagnostic evaluation of AIP^[41,42]. The multicenter study carried out by Suguma *et al.*^[43] has highlighted the ability of ERP to diagnose AIP based on ERP feature alone is limited, but taken together with clinical symptoms, serology and/or histology it can be useful.

PANCREATIC NEOPLASIA

Previously ERCP was the gold standard in the diagnosis of PC. Localized MPD stenosis with focal ductal branch dilation and with distal dilation of MPD ("double duct" sign) were the most frequently detectable morphological



Figure 5 Endoscopic pancreatography image: Bile duct and pancreatic duct stent implantation in chronic pancreatitis.



Figure 6 Endoscopic retrograde pancreatography image: Postoperative pancreaticopleural fistula.

changes^[44,45]. The current role of ERCP is therapeutic rather than diagnostic. In cases of inoperable locally advanced and metastatic pancreatic malignancy the development of obstructive jaundice constitutes an absolute indication of ERCP^[46]. Malignant biliary stenosis may be treated with plastic, but preferably with self-expandable metallic stent implantation^[3]. Pancreatography, ERCP-guided brush cytological sampling and/or biopsy of the pancreatic duct may be useful to prove malignancy, but EUS-guided fine needle aspiration (EUS-FNA) is the first-choice sampling procedure in suspected unresectable pancreatic solid and cystic lesions due to minimal invasiveness, lower complication rate and higher sensitivity compared to ERCP sampling^[47]. A meta-analysis performed by Li *et al.*^[48] showed that ERCP combined with EUS was associated with a high diagnostic yield compared to ERCP or EUS alone, but the complete length of procedures substantially increased, however, it can be reduced if the two examination are performed under the same sedation, but the rate of complication not changed^[49].

CYSTIC PANCREATIC LESIONS

Cystic pancreatic lesions represent a great diagnostic problem because of the morphological similarities between benign and malignant cysts and because of the possibility of malignant transformation^[50] and the increasing number of the detected lesions due to the improvement of the abdominal imaging modalities and their availabilities. The differentiation between the four types of pancreatic cystic neoplasms (PCN) substantially may influence the therapeutic approach. Serous cystadenomas (SCA) and solid pseudopapillary neoplasms (SPN) are associated with lower malignant potential compared to intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Previously ERP was the gold standard diagnostic procedure in the identification and classification of IPMN. Diffuse or segmental dilation of the MPD or its side branches connected to the cyst can be recognized on the ERP images, with no other cause of the dilatation.

The pathognomonic characteristic of IPMN is the gaping orifice of Vater papilla with thick mucus oozing (fish mouth papilla)^[51]. The international consensus guidelines do not recommend the routine ERP for the morphological and cytological diagnosis of IPMN (fluid sampling or brushing of MPD) due to the invasiveness of the procedure and the high risk of complications. Currently MRCP, EUS and EUS-guided sampling are most preferred^[52,53]. The other malignant cyst type and the pancreatic pseudocysts generally do not communicate with the pancreatic duct, therefore the ERP cannot identify them.

PANCREATIC INJURY

Blunt pancreatic trauma can frequently lead to acute pancreatitis with or without MPD disruption. Pancreatic injuries caused by blunt abdominal trauma are relatively rare with an overall incidence of 0.2%-12%^[54]. Pancreatic injury occurs as a result of the traumatic compression of the pancreas between the vertebral column and the anterior abdominal wall. Pancreatic injury is more common in children and young adults because of decreased protective intra-abdominal fat. CT is the primary imaging modality of choice in patients with blunt abdominal trauma, with the sensitivity for pancreatic parenchymal injury between 67%-85%^[55]. Although pancreatic ductal injury can frequently be detected with non-invasive MRCP, ERCP is the most accurate diagnostic tool for the assessment of ductal injury^[56]. Besides, it can also provide endoscopic treatment. Delays in ERCP have led to significantly higher complication rates^[57]. Although ERCP is the most useful procedure for the diagnosis of pancreatic ductal injury in stable patients, surgery should be considered without hesitation if the patient's condition is unstable. Recently, some case series proved that pancreatic duct plastic stent placement with and without pancreatic sphincterotomy can be an effective endoscopic therapy in resolving pancreatic duct disruption and preventing chronic fistula formation^[58]. Although stent implantation can improve the clinical condition and resolve fistula and pseudocyst, stent induced ductal stricture is a major

long-term complication.

POSTOPERATIVE PANCREATIC FISTULA

Postoperative pancreatic fistula (POPF) formation is a frequent and severe complication of pancreatic surgery^[59,60]. Its incidence ranges from 2% to 51% depending on the definition used. POPF was defined by International Study Group on Pancreatic Fistula as a measurable drain output on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity^[61]. In the early postoperative phase the upper abdominal discomfort associated with fever, tachycardia, slower recovery and persistently high drain output raises the suspicion of postoperative complication, such as pancreatic fistula (Figure 6). The amylase level of drain fluid is extremely elevated in a typical case^[62]. ERCP and MRCP are the two most widely used imaging modality in the confirmation of POPF with high diagnostic accuracy. In case of pancreaticopleural fistula their sensitivity may reach to 78% and 80%^[63]. Recently ERCP was the most preferred investigation for confirming the diagnosis of POPF, but its use is reduced due to invasive nature and elevated risk of infective complications arising from fistula filling. However, it has the advantage of direct visualization of MPD and precise location of fistula, and the ability to simultaneously perform endoscopic therapeutic maneuvers^[64].

PANCREATOBILIARY MALJUNCTION

Pancreatobiliary maljunction (PBM) is a rare congenital malformation in which the CBD and the pancreatic duct are united outside the duodenal wall with or without dilation of CBD^[65]. The sphincter of oddi is located in the distal part of the common channel, therefore it cannot properly regulate the outflow of biliopancreatic juice, resulting regurgitation of bile into the MPD and pancreatic juice into the CBD. The elevated intraductal pressure often causes dilatation of CBD, and the chronic biliopancreatic reflux increases the risk of development of malignancy. The diagnosis of PBM is based on the identification of the anomalous union between the pancreatic and bile ducts by ERCP, MRCP, EUS or intraductal ultrasound. ERCP is the most accurate imaging method, and it provides an opportunity for the biliary intervention (biliary stone extraction, stent implantation) and bile sampling as well. High biliary levels of pancreatic enzymes are suggestive of regurgitation of pancreatic juice into the common bile duct^[66]. In atypical PBM cases with relatively short common channel, the diagnostic accuracy of MRCP and EUS is lower, but they are very effective in the detection of PBM associated pancreatobiliary cancers at an early stage^[67].

CONCLUSION

ERP is still one of the most accurate diagnostic procedures in patients with suspected pancreatic ductal

disorders, including idiopathic acute recurrent pancreatitis, chronic pancreatitis, pancreatic ductal injuries and fistula formation, pancreatic cystic neoplasms and early pancreatic cancer. However, before performing ERP, endoscopists should carefully evaluate the extent of the clinically necessary pancreatogram, if there any, to establish the diagnosis. Increasingly widespread application of noninvasive methods for the diagnosis of pancreatobiliary diseases (such as MRCP and EUS), and less frequent use of diagnostic ERP could dramatically decrease post-ERCP complications. In contrast, pancreatic interventional endoscopic procedures, such as pancreatic sphincterotomy, dilatations and pancreatic stent implantation are necessitates for complete pancreatic ductal contrast filling and analysis of digitally enhanced pancreatogram with fluoroscopy to completely understand the anatomy and intraductal pathology before the initiation of endoscopic therapy.

In case of distal biliary obstruction, when the non-invasive imaging modalities are available we do not recommend the filling of pancreatic duct, selective biliary drainage is proposed. ERP should be considered in case of suspected pancreatic ductal abnormalities, such as pancreatic injury, fistula or congenital malformation, and when pancreatic ductal intervention is necessary.

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P- Reviewer: Kubota K, Zhu YL **S- Editor:** Ji FF **L- Editor:** A
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