

## Role of endoscopic retrograde cholangiopancreatography in pancreatic diseases

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to the limited number of patients and the expertise required to attempt these procedures.

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### Abstract

Over the last 15 years, endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a diagnostic tool to one that is primarily used to provide therapy. This development occurred first for biliary disorders and subsequently to a lesser extent for pancreatic diseases. Computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography and endoscopic ultrasonography suggest a diagnosis in the majority of patients with pancreatic diseases today and can help physicians and patients avoid unnecessary ERCP. However, a selected number of patients with pancreatic diseases may benefit from pancreatic endotherapy and avoid complex surgery and chronic use of medications. Pancreatic sphincterotomy, pancreatic stenting and pancreatic cyst drainage are some of the most effective and challenging endoscopic pancreatic interventions and should be performed with caution by expert therapeutic endoscopists. There has been a paucity of randomized studies investigating endoscopic techniques in comparison with surgery and medical therapy for the treatment of most benign and malignant pancreatic disorders due

### INTRODUCTION

Pancreatic diseases are among the most challenging disorders of the digestive system. A wide range of benign conditions present both diagnostic and therapeutic challenges to the gastroenterologist and surgeon<sup>[1]</sup>. These include acute pancreatitis (including recurrent), chronic pancreatitis, pancreatic duct stones, pancreatic leaks, pseudocysts and strictures. Symptoms exhibited by patients with these disorders can be disabling. Endoscopic treatments for these benign disorders have evolved in the last decades and remain a viable, cost-effective alternative to more invasive surgical or radiological methods<sup>[2]</sup>. In addition, endoscopic therapy can provide palliation for inoperable malignant pancreatic diseases, such as pancreatic cancer with biliary and duodenal obstruction<sup>[3]</sup>.

Endoscopic pancreatic therapy has been developed

much more slowly than the endoscopic treatment of biliary disorders. There are many reasons for this, but the main one appears to be a fear of inducing pancreatitis after even the contrast injection or just sphincteric manipulation. It has become clear however, that techniques initially restricted to biliary endotherapy can also be used in the pancreas in selected individuals<sup>[4]</sup>. Thus, sphincterotomy and attempts at stone retrieval and stricture treatment were first used in chronic pancreatitis patients in whom the procedure-related risk was much lower than in patients with normal anatomy or sphincter of Oddi dysfunction. More and more use of these techniques has resulted from studies showing that small-caliber stents placed into the pancreatic duct after a sphincterotomy or repeated manipulation of the papilla significantly reduce the incidence and severity of procedure-related pancreatitis. Despite this general observation, however, there have still been very few large series, controlled trials and critical reviews of these techniques.

The introduction of advanced radiological and imaging techniques has limited the diagnostic role of endoscopic retrograde cholangiopancreatography (ERCP), but sometimes the information provided during a therapeutic procedure is also useful for diagnostic purposes. In this editorial, we will focus on the current role of ERCP for the diagnosis and especially the treatment of pancreatic disorders.

## ENDOSCOPIC DIAGNOSIS OF CHRONIC PANCREATITIS

ERCP and endoscopic ultrasonography (EUS) are the principal endoscopic methods to assess patients with chronic pancreatitis and complement radiologic methods [computed tomography (CT) scans, magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography]. Both ERCP and EUS can establish the diagnosis of chronic pancreatitis<sup>[1,5]</sup>. ERCP allows detection of pancreatic duct changes including ductal dilation, strictures, abnormal side branches, communicating pseudocysts, pancreatic duct stones and pancreatic duct leaks. ERCP is highly effective in visualizing these ductal findings (sensitivity for the diagnosis of chronic pancreatitis of 71%-93% and a specificity of 89%-100%). The Cambridge Classification, which assesses the main pancreatic duct and side branches is a widely accepted system for scoring ductal findings seen on ERCP<sup>[6]</sup>. Unfortunately, pancreatography is imperfect and care should be taken not to overinterpret minor findings seen on ERCP. Conversely, ERCP may not detect changes of less advanced chronic pancreatitis. When the diagnosis of chronic pancreatitis is sought, ERCP should be reserved for patients in whom the diagnosis is still unclear after non-invasive pancreatic function testing or other non-invasive (CT, MRI) or less invasive (EUS) imaging studies have been performed<sup>[7,8]</sup>. Although ERCP can be used to obtain information about ductal anatomy to define the level and degree of obstruction and the presence of strictures and stones, it does not

provide information regarding the surrounding pancreatic parenchyma. EUS can provide high-resolution images of both the ductal structures and the parenchyma<sup>[9]</sup>. There is good interobserver agreement in the diagnosis of chronic pancreatitis by EUS, and EUS may detect early chronic pancreatitis in a reliable manner compared with ERCP<sup>[10]</sup>.

## PANCREATIC DUCT STRICTURES

The finding of a pancreatic duct stricture often poses a diagnostic dilemma regarding the specific cause. The cause of a pancreatic duct stricture is likely to include one or more of the following: chronic pancreatitis, pancreatic neoplasm (benign or malignant), pseudocyst or traumatic injury (blunt or penetrating)<sup>[2]</sup>. Filling defects such as protein plugs or stones may resemble a stricture. Cancer is the most feared cause of pancreatic duct stricture and should be considered in all patients in whom a pancreatic duct stricture is identified. Patients older than 50 years presenting with single or multiple episodes of acute pancreatitis, who have a pancreatic duct stricture, must have malignancy included in the differential diagnosis, particularly in the absence of alcohol abuse.

Changes in ductal anatomy other than the stricture should be looked for when examining the pancreatogram. This includes irregularity in contour or dilation of the pancreatic duct or of the secondary radicles. The presence of a single stricture with proximal dilation and normal distal ductal anatomy is suggestive of a neoplastic cause. Changes noted throughout the duct, particularly distally to the stricture, in addition to the anticipated proximal dilation, are usually suggestive of chronic pancreatitis. The presence of multiple strictures and dilations in a "chain-of-lakes" appearance is characteristic of chronic pancreatitis. Unfortunately, none of these features suggestive of a diagnosis of chronic pancreatitis is absolute in ruling out pancreatic cancer in individual patients because patients with chronic pancreatitis are at increased risk for pancreatic cancer. Therefore, the pancreatogram alone is not sufficient to rule out pancreatic cancer in patients with chronic pancreatitis, and if there is a clinical suspicion, aggressive attempts to obtain tissue should be made to establish a diagnosis<sup>[11]</sup>. Physicians should have a low threshold to perform EUS to more closely and thoroughly examine the pancreatic parenchyma, with fine-needle aspiration of any areas felt to be suspicious for possible malignancy. Obtaining serum CA 19-9 levels may be helpful in patients considered to harbor a malignancy, although levels can be elevated in patients with chronic pancreatitis in the absence of cancer.

Benign strictures of the main pancreatic duct are generally due to inflammation or fibrosis around the main pancreatic duct. Because ductal obstruction may lead to pain or acute pancreatitis superimposed on chronic pancreatitis, endoscopic therapy with balloon dilation or pancreatic duct stents for the treatment of dominant pancreatic duct strictures has been evaluated. Stricture dilation may be required to facilitate stent placement or stone removal.

Data regarding the role of endoscopic therapy in treating main pancreatic duct strictures are inconsistent. Some, but not all, authors have reported high success rates (75% to 94%) in treating pain by stenting of pancreatic duct strictures<sup>[2,4,12]</sup>. In addition, although some authors have correlated clinical improvement to a decrease in the diameter of the main pancreatic duct upstream, others have not. Pancreatic stents are prone to occlusion and patients undergoing endoscopic therapy for pancreatic duct strictures may require frequent stent exchanges. Symptomatic improvement may persist after pancreatic stent removal despite persistence of the stricture. Confounding factors in the literature on pancreatic stent therapy are other therapies performed at the time of stent placement (e.g. pancreatic sphincterotomy, pancreatic stone removal) and the tendency of the chronic pancreatitis pain to wax and wane and decrease with time as deterioration of pancreas function occurs<sup>[13]</sup>. The optimum duration of stent placement, stent number and diameter and degree of balloon dilation are not known. Complications related to endoscopic therapy of pancreatic duct strictures include pain, pancreatitis, stent occlusion, proximal or distal stent migration, duodenal erosions, pancreatic infection, ductal perforation, and bleeding from pancreatic sphincterotomy.

The role of placing multiple stents in the pancreatic duct has been assessed by Costamagna *et al.*<sup>[12]</sup>. Nineteen patients with severe chronic pancreatitis and with a single pancreatic stent through a refractory dominant stricture in the pancreatic head underwent removal of this stent followed by balloon dilation of the stricture and insertion of the maximum number of stents allowed by the tightness of the stricture and the caliber of the pancreatic duct diameter. Stents were removed after 6-12 mo. The median number of stents placed through the major or minor papilla was three; their diameter ranged from 8.5 to 11.5 Fr and length from 4 to 7 cm. During a mean follow-up of 38 mo after stent removal, 84% of patients were asymptomatic, and 11% had symptomatic stricture recurrence. No major complications were recorded. This study showed that endoscopic multiple stenting of a dominant pancreatic duct stricture is feasible and safe.

## PANCREATIC DUCT STONES

Obstructing pancreatic duct stones may contribute to abdominal pain or acute pancreatitis in patients with chronic pancreatitis. ERCP provides direct access to the pancreatic duct for evaluation and treatment of symptomatic pancreatic duct stones. In one randomized trial comparing endoscopic and surgical therapy, surgery was superior for long term pain reduction in patients with painful obstructive chronic pancreatitis<sup>[14]</sup>. However, because of its lower degree of invasiveness, endotherapy may be preferred, reserving surgery as second-line therapy for patients in whom endoscopic therapy fails or is ineffective. Pancreatic stone removal can be challenging. Frequently the stone configuration and size, coupled with pancreatic duct strictures, occlude the lumen. Adjuvant endoscopic ap-

proaches such as stricture dilation, intraductal lithotripsy and pancreatic sphincterotomy may be needed. Even when accessible, pancreatic duct stones (which are often dense and hardened) may be impacted, requiring extracorporeal shock wave lithotripsy (ESWL) to fragment the stones, before endoscopic removal can be achieved. Multiple ESWL sessions may be required and success rate in complete duct clearance and duct decompression exceeds 50%<sup>[3,15,16]</sup>. Intraductal lithotripsy guided by pancreatoscopy has also been used to fragment pancreatic stones.

Most series have shown improvement in pain with pancreatic endotherapy. Some encouraging short-term results and long-term 5 years follow-up results showing improvements in pain (77%-100% and 54%-86%, respectively) have been reported<sup>[17-19]</sup>. Although modest, these success rates are acceptable in the context of traditionally difficult-to-manage groups of patients.

## ENDOSCOPIC PAIN MANAGEMENT IN CHRONIC PANCREATITIS

The ideal treatment for patients with pancreatic duct stones, dilated pancreatic ducts and pain is not known. The stones can be easily removed coincidentally with the performance of a surgical drainage procedure, such as pancreaticojejunostomy. Alternatively, however, they can be fragmented by ESWL and removed endoscopically after sphincterotomy of the pancreatic duct. Stones can be cleared by this approach in roughly 80% of patients, and approximately 50% of these have long-term relief of their symptoms<sup>[20]</sup>. Dumonceau *et al.*<sup>[21]</sup> conducted a randomized trial comparing pain relief after ESWL alone *vs* in combination with endoscopic drainage of the main pancreatic duct in patients with painful calcified chronic pancreatitis. Two years after trial intervention, 10 (38%) and 13 (45%) patients of the ESWL alone group and of the ESWL combined with endoscopy group, respectively, had presented pain relapse. In both groups, a similar and significant decrease was seen after treatment in the number of pain episodes/year (mean decrease, 3.7 episodes). Thus, there was no difference between the treatment groups, and the treatment costs per patient were three times higher in the ESWL combined with endoscopy group compared with the ESWL alone group.

An alternative involves the use of stents placed in the pancreatic duct endoscopically. Reports indicate that 30%-76% of patients receiving such stents have symptomatic improvement over a period of 14 to 36 mo of observation. Although these results seem encouraging, a criticism is that most of the data reported to date have been from relatively short-term, non-randomized studies. The issue is further complicated by the fact that pancreatic duct stents may not be entirely harmless; for example, they may cause further pancreatic duct changes and potentiation of chronic pancreatitis. Endoprosthesis occlusion and migration also seem to be relatively common.

There have been two randomized controlled trials comparing endoscopic therapy with surgery for the pallia-

tion of pain in chronic pancreatitis<sup>[14,22]</sup>. After 5 years of follow-up, pain was absent in 14%-16% of patients treated with endoscopy and in 36%-40% of patients treated with surgery. Based on these trials, it appears that surgery provides better pain relief compared to endoscopy, but even surgery fails to provide substantial pain relief in more than half of the patients. Due to its low degree of invasiveness, however, endotherapy can be offered as a first-line treatment, with surgery being performed in cases of failure and/or recurrence.

In cases of chronic pancreatitis with intractable pain where surgery is clearly indicated, ERCP can give valuable information regarding pancreatic duct configuration and exact ductal changes, according to the Cambridge classification<sup>[23,24]</sup>. In many cases, efforts such as decreasing smoking and alcohol use, taking oral pancreatic enzyme supplements, and receiving endoscopic therapies such as sphincterotomy and stent placement are usually effective in managing pain and inhibiting disease progression. Surgical options for chronic pancreatitis treatment include drainage procedures such as the Puestow procedure and resections such as pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy. ERCP can serve as a preoperative bridge therapy to partial or total pancreatectomy with autologous islet cell transplantation. The latter procedure was developed for both pain management and maintenance of pancreatic endocrine function, especially glycemic control. A few institutes in the world have performed total pancreatectomy with autologous islet transplantation, since it requires special techniques for islet processing. The effectiveness of this procedure has been reported<sup>[25,26]</sup>.

## PANCREATIC DUCT LEAKS

Pancreatic duct disruptions or leaks can occur as a result of severe acute pancreatitis or chronic pancreatitis. The causes of the disruption are usually severe inflammation or obstruction of the duct, or severe pancreatic necrosis. Pancreatic leaks can result in pancreatic ascites, pleural effusions, pseudocyst formation and internal and external pancreatic fistulas. Pancreatic duct leaks can often be treated with endoscopic placement of transpapillary stents in a manner similar to the use of biliary stents for closing bile duct leaks<sup>[27]</sup>. Endoscopic therapy is successful in closing the leaks in approximately 60% of patients. Factors associated with a better outcome in duct disruption include a partial disruption, successfully bridging the disruption with a stent and longer duration of stent placement (approximately 6 wk). There are no comparative studies of surgical, medical and endoscopic therapy for treatment of pancreatic duct leaks.

A novel treatment approach using endoscopic injection of N-butyl-2-cyanoacrylate to achieve closure of the fistula has also been reported<sup>[28]</sup>. In total, 12 patients underwent ERCP with injection of tissue glue directly into the pancreatic fistulous tract, in addition to endoscopic drainage with stent placement when this was considered

to be indicated by the endoscopist. A single session of glue injection was successful in seven patients, and a second session was required in one patient. Inadvertent injection of the cyanoacrylate into the pancreatic duct at the time of glue injection into a pancreatic fistula can be associated with chemical or obstructive pancreatitis. In contrast, the injection of glue to completely fill a disconnected ductal system usually results in glandular atrophy and has been used to avoid surgical resection in high-risk patients by some institutions<sup>[29]</sup>.

## PANCREATIC PSEUDOCYSTS

Pancreatic pseudocysts arise as a complication of chronic pancreatitis in 20%-40% of cases<sup>[5,18,30]</sup>. Endoscopic drainage and management of the pseudocyst is a less invasive alternative to surgical treatment and is safer when the site of the puncture is defined by EUS. Pseudocyst drainage should be considered (1) for symptomatic lesions due to pain, gastric outlet obstruction, early satiety, weight loss or obstructive jaundice; (2) when there are signs of infection of the pseudocyst; and (3) when progressive enlargement of the cyst takes place, even if it is asymptomatic. Special care must be taken to avoid drainage of cystic neoplasms, duplication cysts and other noninflammatory collections<sup>[5,31,32]</sup>.

A retrospective study was conducted to determine the impact of procedure experience on patient outcomes after endoscopic drainage of endoscopic pancreatic fluid collections<sup>[33]</sup>. In that large review of 175 cases, endoscopic drainage was carried out to treat pancreatic necrosis (33%), acute pseudocysts (23%), or chronic pseudocysts (44%). There was a dramatic improvement in the resolution rates of chronic pseudocysts after the first 20 procedures in comparison with former procedures (45% *vs* 93%) and a reduction in days to resolution of the pseudocyst (50 d *vs* 33 d). In patients with pancreatic necrosis there was a statistically significant decrease in the median hospital stay with greater experience (23 d *vs* 15 d). While these findings require confirmation by other groups, this study for the first time documented the importance of operator experience for patient outcomes after these often technically challenging endoscopic procedures.

Several excellent literature synopses and technical reviews on pancreatic pseudocysts have been published in recent years. These include a technical review by Ballie regarding pseudocysts in general and a subsequent article by the same author on the endoscopic management of pseudocysts<sup>[34,35]</sup>; a technical review by Hawes<sup>[36]</sup> that distinguishes between pseudocysts and other types of pancreatic fluid collection; and an excellent article by Giovannini *et al*<sup>[37]</sup> describing the use of EUS for cystogastrostomy. Finally, Rosso *et al*<sup>[38]</sup> reviewed 466 cases of endoscopically treated pseudocysts which were reported in 17 publications, comparing the results with previously published surgical series. The authors correctly concluded that pseudocysts are best handled by an integrated multidisciplinary team including pancreatic surgical specialists, gastroenterologists and



interventional radiologists. The conclusions from all these review articles are that treatment of pseudocysts can be complicated but it requires patience, expertise, adequate clinical and endoscopic skills and appropriate endoscopic accessories.

## BILIARY OBSTRUCTION IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

Distal common bile duct strictures have been reported to occur in 2.7% to 45.6% of patients with chronic pancreatitis. These strictures can occur from inflammation, fibrosis, or compression from a pseudocyst or a pancreatic stone<sup>[17,39]</sup>. Because long-standing biliary obstruction can lead to secondary biliary cirrhosis or recurrent cholangitis, biliary decompression is recommended in patients with clinically significant obstruction (e.g. cholestasis or jaundice). Surgical biliary bypass is the standard approach for managing chronic common bile duct strictures. Endoscopic therapy has been used as an alternative to surgery<sup>[40]</sup>. Plastic biliary stents are a useful short-term treatment for chronic pancreatitis-induced common bile duct strictures in the setting of cholestasis, jaundice or cholangitis and may be used as a long-term treatment approach in poor surgical candidates. Unfortunately, long-term success rates are as low as 7.7%-10% in some studies when single large-bore stents are used<sup>[41,42]</sup>. The use of multiple stents with frequent stent exchanges and balloon dilations over a long period of time (up to 1-2 years) may be more efficacious than single stents for the treatment of these strictures. Patient selection is critical in this setting because patients need to return frequently for stent changes. Poor compliance to follow-up can lead to biliary sepsis from stent occlusion<sup>[43-45]</sup>.

Self-expanding metal stents (SEMS) have been used for the treatment of benign biliary strictures. Uncovered metal stents have given good 3-year results for poor operative candidates, while reports for covered metal stents have given mixed results. The routine use of metal stents for benign biliary strictures is not recommended at this time<sup>[46-49]</sup>.

Several randomized controlled trials have demonstrated the superiority of SEMS to polyethylene stents for the treatment of malignant distal biliary obstruction, because they have a longer duration of patency (plastic stents occlude at a median of 3 to 6 mo after placement) and consequently have been shown to be more cost-effective<sup>[50,51]</sup>. The choice of plastic (e.g. polyethylene) stents *vs* SEMS has been debated in the literature and data suggest that SEMS should be preferentially used when life expectancy exceeds 6 mo, whereas polyethylene stents are more cost-effective in patients who are expected to live less than 4 mo<sup>[52,53]</sup>. However, it is not always easy to predict patient survival at presentation.

There can be significant delays between diagnosis and surgery in patients with resectable pancreatic cancer and

obstructive jaundice when neoadjuvant therapy is used or when there is limited access to surgery. In these instances, placement of SEMS at the time of initial ERCP has been advocated for relief of obstructive jaundice. Recently, it was reported that the costs of stenting alone were identical when using either plastic or metal stents for biliary obstruction drained for more than 30 wk before surgery in patients with resectable pancreatic cancer<sup>[54]</sup>. In the polyethylene group, 16 of 42 patients (38%) required 3 or more ERCPs before surgery and 7 more underwent palliative surgery in the setting of unresectable disease. If actual costs associated with stent-related complications had been included in the calculation, then the balance would have turned in favor of SEMS, because stent-related complications were 15% *vs* 93% after insertion of metal *vs* plastic stents, respectively.

With newly designed stents arriving on the market from different manufacturers, it remains to be established whether covered SEMS are more effective than uncovered in palliating obstructive jaundice and whether complications associated with SEMS (i.e. migration, cholecystitis and occlusion) can be reduced<sup>[55,56]</sup>. Only comparative multicenter studies can answer these questions.

## CONCLUSION

ERCP is useful for the diagnosis of chronic pancreatitis but it should be reserved for patients in whom the diagnosis has not been established by non-invasive or less invasive procedures. ERCP and pancreatic endotherapy can be effective in patients with pancreatic strictures, pancreatic duct leaks, pancreatic duct stones and pancreatic pseudocysts. However, the most important advance with regard to ERCP is the palliative or preoperative treatment of biliary obstruction caused by chronic pancreatitis or malignant pancreatic disease. Metal stents offer better long-term relief compared to plastic stents and should be preferred in patients with a life expectancy of more than 4 to 6 mo. Expertise in ERCP is a prerequisite for effective pancreatic endotherapy.

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