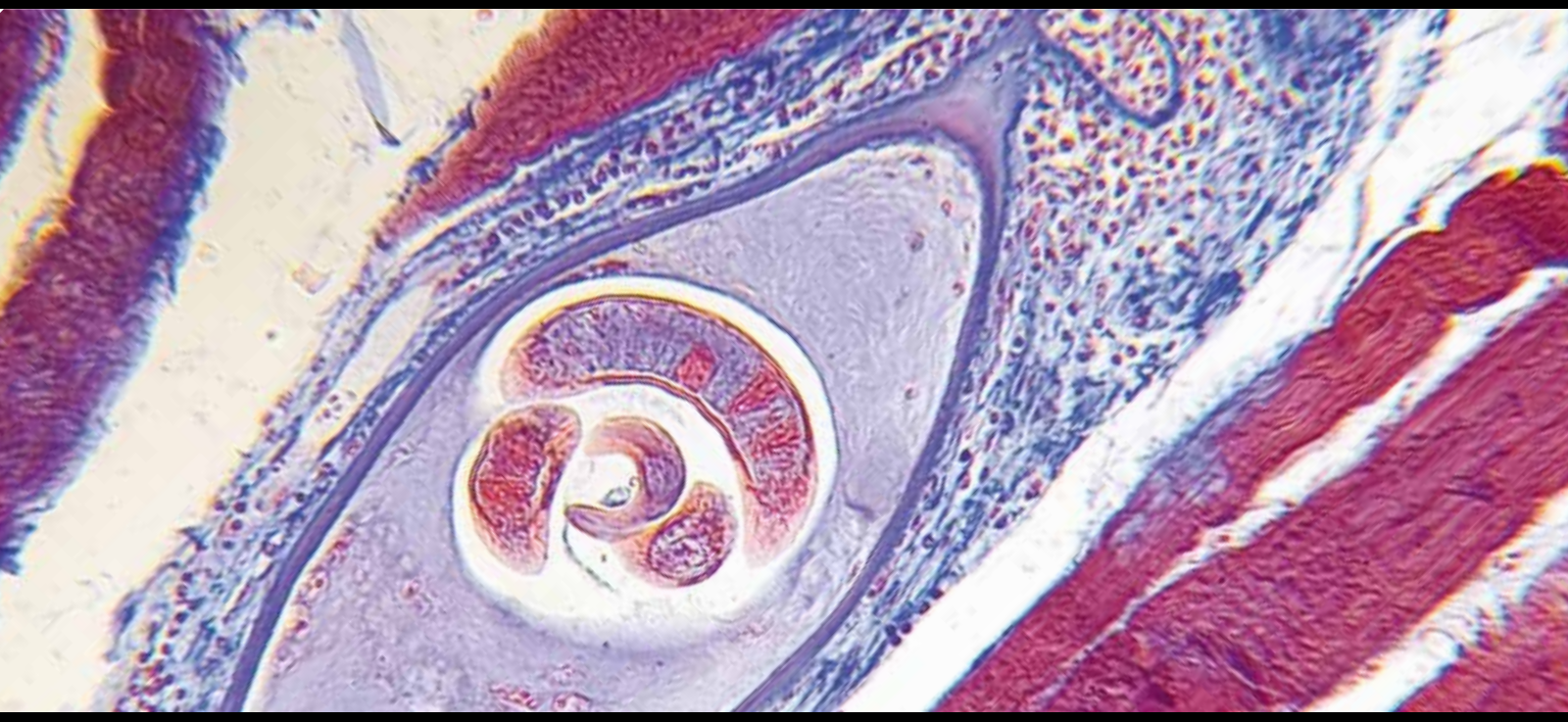
Gastroenterology Research and Practice

# Advances in Diagnosis and Treatment of Biliopancreatic Diseases

Guest Editors: Fauze Maluf-Filho, Jose G. de la Mora Levy, and Carlos G. Micames



# Advances in Diagnosis and Treatment of Biliopancreatic Diseases

Gastroenterology Research and Practice

# Advances in Diagnosis and Treatment of Biliopancreatic Diseases

Guest Editors: Fauze Maluf-Filho, Jose G. de la Mora Levy, and Carlos G. Micames

Copyright © 2012 Hindawi Publishing Corporation. All rights reserved.

This is a special issue published in "Gastroenterology Research and Practice." All articles are open access articles distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

# Editorial Board


Juan G. Abraldes, Spain
Firas H. Al-Kawas, USA
Gianfranco D. Alpini, USA
A. Andoh, Japan
Everson Artifon, Brazil
Stanley Ashley, USA
Mala Banerjee, India
Giovanni Barbara, Italy
Ramón Bataller, Spain
Edmund J. Bini, USA
E. Björnssön, Sweden
Sedat Boyacioglu, Turkey
David A. A. Brenner, USA
Peter Bytzer, Denmark
Brooks D. Cash, USA
A. Castells, Spain
Roger W. Chapman, UK
Pierre-Alain Clavien, Switzerland
Vito D. Corleto, Italy
Silvio Danese, Italy
Gianfranco F. Delle Fave, Italy
Cataldo Doria, USA
Peter V. Draganov, USA
R. Eliakim, Israel
Mohamad A. Eloubeidi, USA
P. Enck, Germany
Maria Eugenicos, UK
D. Fan, China
Fabio Farinati, Italy
R. Fass, USA
Davide Festi, Italy
Alfred Gangl, Austria
K. Geboes, Belgium
Edoardo G. Giannini, Italy
P. Gionchetti, Italy
Guillermo A. Gomez, USA
Bob Grover, UK
B. J. Hoffman, USA
Jan D. Huizinga, Canada
Haruhiro Inoue, Japan
Michel Kahaleh, USA
John Kellow, Australia
Spiros D. Ladas, Greece
Greger Lindberg, Sweden
Lawrence L. Lumeng, USA
P. Malfertheiner, Germany
Ariane Mallat, France
Nirmal S. Mann, USA
Gerassimos Mantzaris, Greece
Fabio Marra, Italy
Sergio Morini, Italy
Bjørn Moum, Norway
Zeynel Mungan, Turkey
Robert Odze, USA
Stephen O'Keefe, USA
John Nicholas Plevris, UK
Massimo Raimondo, USA
J. F. Rey, France
Lorenzo Rossaro, USA
Muhammad Wasif Saif, USA
Hirozumi Sawai, Japan
Hakan Senturk, Turkey
Orhan Sezgin, Turkey
Eldon A. Shaffer, Canada
Matthew Shale, UK
Prateek Sharma, USA
Bo Shen, USA
Stuart Sherman, USA
Davor Stimac, Croatia
M. Storr, Canada
Andrew Thillainayagam, UK
H. Tilg, Austria
Vasundhara Tolia, USA
keith Tolman, USA
Christian Trautwein, Germany
Dino Vaira, Italy
David Hoffman Van Thiel, USA
Takuya Watanabe, Japan
Peter James Whorwell, UK
Charles Melbern Wilcox, USA
Y. Yamaoka, USA

# Contents

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 421969, 2 pages
doi:10.1155/2012/421969

*Editorial*

# Advances in Diagnosis and Treatment of Biliopancreatic Diseases

**Fauze Maluf-Filho,[1] Jose G. de la Mora Levy,[2] and Carlos G. Micames[3]**

[1] *Gastrointestinal Endoscopy Unit, Department of Gastroenterology, Instituto do Cancer do Estado de São Paulo (ICESP), São Paulo University, São Paulo, SP, Brazil*
[2] *Endoscopy Unit, Instituto Nacional de Cancerología, Mexico City, Mexico*
[3] *Hospital Bella Vista, University of Puerto Rico, Mayaguez, Puerto Rico, USA*

Correspondence should be addressed to Fauze Maluf-Filho, fauze.maluf@terra.com.br

Received 5 March 2012; Accepted 5 March 2012

Copyright © 2012 Fauze Maluf-Filho et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Management of biliopancreatic diseases has seen great progress in recent years. Innovations in endoscopy have allowed gastroenterologists to assist in the care of many conditions of the biliary tree and pancreas, which were previously only managed surgically. Outcomes for many of these endoscopic interventions are comparable to their surgical counterpart. However, endoscopists taking care of these patients should be well aware of the limitations of their procedures and the advantages of surgery for certain patients.

This special issue will address some of the main challenges faced today by physicians taking care of patients with pancreatic and biliary diseases. Endosonography, or endoscopic ultrasound (EUS), which previously was only considered a diagnostic tool, has now emerged as a useful therapeutic technique. In contrast, endoscopic retrograde cholangiopancreatography, or ERCP, has now become mainly a therapeutic tool. Some ERCP techniques have been adopted by endosonographers and allowed interventions for draining bile ducts and peripancreatic fluid collections, previously considered outside the realm of endoscopy. Despite the advances in outcomes and minimal invasiveness of EUS and ERCP-guided interventions, several risks and complications still remain. Pancreatitis is a well-recognized complication of ERCP with a significant incidence that has not been reduced greatly throughout recent years. Numerous studies have looked at ways of decreasing the risk of this dreadful complication. This special issue will discuss and review the problem of post-ERCP pancreatitis, a topic that raises a high level of concern for many who do this procedure, and ways to reduce its risk, especially in patients considered at high risk for developing this complication.

Incidental pancreatic cysts continue to pose a diagnostic dilemma for gastroenterologists and surgeons alike. Despite the ability of safely obtaining a tissue sample during EUS examination, the utility of cytopathology in determining the exact nature of these lesions remains limited. More recently, DNA analysis of fluid obtained during aspiration has shown promise in improving the diagnostic accuracy of EUS-FNA. However, the effect of these newer tests in terms of deciding when to observe versus surgically resect in many of these incidental cysts remains to be proven. Pancreatologists agree that a reliable method for determining the nature and prognosis of pancreatic cystic neoplasms is required for improving the management strategy in asymptomatic patients.

Abdominal pain is a cardinal symptom of chronic pancreatitis. The effectiveness of medical therapy, in the form of pancreatic enzyme supplementation or octreotide injections, is dismal. Pain relief can certainly be obtained with the use of narcotic medications, but at the cost of significant side effects, such as constipation, sedation, and drug dependence. Endoscopic alternatives for improving pain in chronic pancreatitis include those guided by ERCP, such as intraductal stone removal, stricture dilation, or drainage procedures, and EUS-guided celiac plexus block. This special issue will review the ERCP-guided interventions and discuss the efficacy of EUS-guided celiac plexus neurolysis for the treatment of pain in patients with pancreatic cancer.

As advances in endoscopy and surgical innovations are introduced into the field of biliary and pancreatic diseases, many diseases previously requiring complicated surgeries with prolonged recovery are now being managed by minimally invasive techniques. Many of these procedures have a reduced risk when compared to their surgical alternative. However, long-term efficacy and patient risk factors need close consideration when deciding between different management alternatives. Many, if not all, biliary and pancreatic disorders require a close interaction between gastroenterologist and surgeon. The phrase "*No man is an island*" by John Donne (1572–1631) emphasizes the importance of consensus between specialists and should always be in the minds of those managing patients with biliopancreatic diseases.

*Fauze Maluf-Filho*
*Jose G. de la Mora Levy*
*Carlos G. Micames*

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 860879, 5 pages
doi:10.1155/2012/860879

*Review Article*

# The Endoscopic Management of Pain in Chronic Pancreatitis

**Adam J. Goodman and Frank G. Gress**

*Division of Gastroenterology and Hepatology, Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY 11203, USA*

Correspondence should be addressed to Adam J. Goodman, adam.goodman@downstate.edu

Received 3 October 2011; Revised 26 January 2012; Accepted 10 February 2012

Academic Editor: Carlos G. Micames

Copyright © 2012 A. J. Goodman and F. G. Gress. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Pain resulting from chronic pancreatitis is often debilitating and difficult to manage. Many approaches have been used to treat these patients, including narcotic analgesia, antidepressants, pancreatic enzymes, octreotide, denervation procedures, such as celiac plexus block, and various palliative, decompression, or drainage procedures. Many of these procedures can be performed endoscopically, while others require a more invasive, surgical approach. The effectiveness of these therapies is not only highly variable but also often controversial. This review will discuss the endoscopic options for pain management in patients with chronic pancreatitis and their utility in treating this difficult disease.

## 1. Introduction

Pain resulting from chronic pancreatitis is often difficult to manage. Many approaches have been used to treat these patients, including narcotic analgesia, antidepressants, pancreatic enzymes, octreotide, denervation procedures (most commonly CPB), and various palliative, decompression, or drainage procedures [1–13]. The effectiveness of these therapies is not only highly variable but also often controversial. Opioid analgesics are probably used most often and can treat pain effectively, but they are associated with numerous side effects, including constipation, delirium, nausea, and the potential for addiction in patients with chronic pancreatitis [14, 15]. Nonpharmacologic methods of pain control may improve quality of life and minimize drug-related side effects [14]. Endoscopic management of pain in chronic pancreatitis consists of procedures aimed at reducing neurogenic sensation, such as celiac plexus block, or drainage procedures aimed at alleviating outflow obstruction of the pancreatic duct.

## 2. Celiac Plexus Block

The celiac plexus lies anterior to the aorta at the level of the celiac artery. Most of the sensory nerves returning from the pancreas and other intraabdominal viscera pass through the celiac ganglion and splanchnic nerves. Interruption of these fibers may lessen pain in patients with chronic pancreatitis [16]. Celiac plexus block (CPB), a temporizing treatment, most commonly refers to injection of a steroid and long-acting local anesthetic into the celiac plexus to control pain associated with chronic pancreatitis. In contrast, celiac plexus neurolysis (CPN) generally refers to injection of alcohol or phenol, a more permanent agent, into the celiac axis area [16]. This technique induces a chemical splanchnicectomy that ablates the nerve fibers that transmit pain and is used in patients with pancreatic cancer; however, it is not usually employed in patients with pain mediated by chronic pancreatitis.

CPB has traditionally been performed via various percutaneous and surgical approaches [17]. Recently, the EUS-guided approach has gained acceptance since it offers the most direct access to the celiac plexus. Wiersema and coworkers [14, 16, 18] recognized the anatomic advantage that EUS provides in visualizing the celiac region and were successful in performing transgastric EUS-guided celiac plexus blocks with results similar to the more traditional approaches. The timing of the block relative to pain onset may predict response. One study which aimed to look at CPN showed that it was more effective when the block was performed early after pain onset [19]. This result was postulated to be related to contribution of visceral and somatic nerves late in the disease and pain apparently deriving mainly

from the celiac plexus early on; however, it is unclear if this translates into patients with chronic pancreatitis and the use of CBP for pain relief [16, 19]. More recently, it has been proposed that direct injection into the celiac ganglia, multiple injections in the area of the ganglia, or bilateral injections around the celiac ganglia are safe and may be more beneficial in providing sustained pain relief [20–22]. These studies are contradictory, however, and better prospective trials are needed to determine if these approaches make an improvement over the standard technique of EUS-guided CPB.

Several studies have shown that EUS-guided CPB has a beneficial role in the treatment of pain induced by chronic pancreatitis [23, 24]. An initial study of 18 patients with chronic pancreatitis showed a reduction in pain in 50% (5 of 10) of EUS-guided CPB compared with 25% (2 of 8) of CT-guided blocks [23]. This improvement in pain persisted for up to 24 weeks in 30% of responders. A cost comparison showed a $200 saving for EUS-guided CPB compared with CT-guided CPB. Another report of 90 patients by the same investigators found a significant improvement in overall pain scores in 55% at 4 weeks and 8 weeks of follow-up [24]. However, a persistent benefit beyond 24 weeks was observed in only 10% of patients. Pain relief was more likely in older patients (>45 years old) and patients who had not had previous surgery for chronic pancreatitis. A recent meta-analysis aimed to look at the efficacy of CPB for improving pain in patients with chronic pancreatitis showed that the overall percentage who obtained pain relief with this procedure was 32.7% (Table 1) and that very few good quality studies exist [25]. A major issue with all of these studies is the lack of long-term follow-up. Further, prospective studies with long-term follow-up are needed to clarify what role EUS-guided CBP will play in the management of painful chronic pancreatitis.

CPB is a generally effective, safe, and well-tolerated procedure. The three most common complications are transient hypotension (20% to 40%), transient diarrhea (4% to 38%), and transient increase in pain (9%), which are expected in CPB performed via any route [16, 26, 27]. Interruption of the plexus can result in a sympathetic blockade [28]. Clinical manifestations of sympathetic blockade can include diarrhea and hypotension resulting from a relative unopposed visceral parasympathetic activity. Mesenteric vasodilation accounts for the hypotension, which resolves in approximately 2 days. Diarrhea and increase in baseline pain are also usually limited to 2 days. Less common complications include unilateral paresis or paraplegia, pneumothorax, loss of sphincter function, retroperitoneal bleeding, renal puncture, and prolonged gastroparesis [14, 16, 27, 29]. In addition, cephalic spread of the neurolytic agent may result in involvement of the cardiac nerves and plexus affecting the heart and surrounding thoracic structures [30]. Compared to alternative approaches, EUS guidance may decrease the incidence of complications because the needle does not traverse the paraspinal region or somatic nerves or traverse the diaphragm and pleural space [1, 14, 16]. Infectious complications are uncommon but potentially serious. In a series of 90 patients, only 1 patient developed an infectious complication (peripancreatic abscess), which resolved with a 2-week course of antibiotics [24]. The authors reasoned that there might have been a predisposition to infection owing to gastroduodenal colonization with bacteria because the patient was taking a proton pump inhibitor. They suggested that prophylactic antibiotics should be considered in patients who are receiving acid suppression.

Table 1: Meta-analysis of EUS-guided celiac plexus block for chronic pancreatitis. The lower end of the confidence interval was used as the overall percentage of pain relief (adapted from Kaufman et al. [25]).

| Study | Pain relief reported out of total patient (average) | 95% CI |
|---|---|---|
| Gress et al. [23] | 5/10 (50%) | (0.2836-1) |
| Gress et al. [24] | 50/90 (56%) | (0.4689-1) |
| Levy et al. [20] | 5/13 (38%) | (0.2217-1) |
| O'Toole et al. [31] | 20/31 (65%) | (0.4912-1) |
| LeBlanc et al. [21] | 27/51 (53%) | (0.4215-1) |
| Stevens et al. [32] | 16/26 (62%) | (0.3272-1) |
| Over all Studies | 123/221 (56%) | (0.3272-1) |

## 3. ERCP-Guided Therapies

Patients with chronic pancreatitis associated with dilation of the main pancreatic duct, stone disease, or strictures may develop symptoms of severe abdominal pain. In addition to celiac plexus block, this pain can be treated endoscopically with procedures aimed at draining the main pancreatic duct, removing stones, and dilating strictures. ERCP with pancreatic sphincterotomy, dilation of strictures, placement of stents, and stone extraction has become a mainstay of therapy in patients with painful chronic pancreatitis as recent studies have shown that on average, over 65% of patients with strictures or stones treated with endoscopic therapy have shown improvement in their pain [33]. Many studies over the last 20 years have attempted to address the question as to whether endoscopic therapy for the control of pain in chronic pancreatitis is effective. The results of selected published studies on pain relief after endotherapy for chronic pancreatitis are summarized in Table 2.

Experienced practitioners with advanced ERCP skills should only perform endoscopic therapies for chronic pancreatitis. In experienced hands, endoscopic pancreatic sphincterotomy is safe and effective and allows the therapeutic endoscopist access to the main pancreatic duct. This is usually performed under direct visualization with a pull-type sphincterotome after deep cannulation and guidewire insertion. The major risks of the procedure include pancreatitis, bleeding, and perforation. In addition, there is a risk of pancreatic sphincter stenosis that is considered a late complication after pancreatic sphincterotomy [34]. Once access to the main pancreatic duct is achieved, small stones can be removed endoscopically with success [35]. However, large, impacted stones usually require extracorporeal shock wave lithotripsy (ESWL) prior to attempted endoscopic removal. ESWL is a low-risk procedure where calcific pancreatic duct stones are usually identified by X-ray prior to the procedure.

Table 2: Selected studies on pain relief with pancreatic endotherapy.

| Author | Year | Number of cases | Procedure performed | Pain relief (%) |
|---|---|---|---|---|
| McCarthy et al. [44] | 1988 | 33 | PS, stent | 80 |
| Sauerbruch et al. [45] | 1992 | 24 | PS, stent, ESWL | 50 |
| Delhaye et al. [46] | 1992 | 123 | PS, stent, ESWL | 37 |
| Binmoeller et al. [47] | 1995 | 93 | PS, stent, ESWL | 64 |
| Adamek et al. [48] | 1999 | 70 | PS, stent, ESWL | 54 |
| Rösch et al. [33] | 2002 | 1018 | PS, stent, ESWL | 85 |
| Díte et al. [49] | 2003 | 36 | PS, stent, ESWL | 65 |
| Delhaye et al. [41] | 2004 | 56 | PS, stent, ESWL | 78 |
| Gabbrielli et al. [50] | 2005 | 22 | PS, stent, ESWL | 100 |
| Costamagna et al. [43] | 2006 | 19 | PS, stent (multiple) | 84 |

PS; pancreatic sphincterotomy, ESWL: extracorporeal shock-wave lithotripsy.

Then a fluid cushion is applied to the front and back of the patient, and shock waves are passed through the identified stones. This results in fragmentation of stones in chronic calcific pancreatitis allowing the endoscopist to then attempt to obtain complete clearance of the main pancreatic duct [35]. Multiple sessions of ESWL may be required in attempt to clear the pancreatic duct, and the success rate for complete clearance of the main pancreatic duct and resolution of pain has been at best approximately 75% [36]. There are some studies to suggest that ESWL alone, without combined endoscopic therapy, may be enough in the treatment of chronic calcific pancreatitis. A randomized controlled trial by Dumonceau and colleagues in 2007 aimed to answer this question [37]. There were 55 patients in the study, and the follow-up was 2 years. They were able to show that ESWL is a safe and effective treatment alone, without combined endoscopic therapy. Most studies looking at the role of ESWL performed to date have shown mixed efficacy due to the small sample sizes in the studies. A recent meta-analysis performed by Guda et al. aimed to overcome this problem and included 17 studies from 1989 to 2002 with a total of 588 subjects. Their data showed that ESWL is both effective in clearance of stones from the pancreatic duct and in relief of pain from chronic pancreatitis [38]. In addition, there is newer literature to suggest that the timing of ERCP after ESWL may increase the success rate of this procedure [39]. This study suggests waiting at least 2 days after ESWL before attempting ERCP and ductal clearance possibly due to ESWL-induced edema of the pancreatic duct. Long-term success of these procedures is variable, and many patients will have recurrent pain attacks after short-term successful clearance of the main pancreatic duct. This is thought, at least partially, to be due to stone migration or recurrence and responds to repeated attempts at endoscopic clearance of the main pancreatic duct [40]. Other studies have suggested that endotherapy with ESWL and pancreatic duct drainage will provide long-term pain relief for up to two-thirds of patients [41]. The authors' practice is to perform ESWL on patients with chronic, calcific pancreatitis, associated with large pancreatic duct stones that are not amenable to endoscopic removal at the time of initial ERCP. After ESWL is completed, ERCP and repeat attempt at ductal decompression are then performed.

Pancreatic duct strictures are usually caused by fibrosis around the main pancreatic duct as a result of the chronic inflammation seen in the disease process. Strictures that are focal and located towards the head and neck region of the pancreas are more amenable to endoscopic therapy. A recent prospective study was able to show a decrease in pain after ERCP with dilation and stent placement in 89% of patients; however after 2 years of follow-up 30% of patients had relapsed and required further therapy [42]. In attempt to perform more definitive therapy for pancreatic duct strictures, some investigators have attempted placing multiple stents into the main pancreatic duct in order to dilate refractory strictures and improve PD drainage. Costamagna and colleagues were able to show that during a mean follow-up of 38 months, 84% of patients remained asymptomatic. Only 5.5% of patients had a persistent stricture after multiple stenting, and only 10.5% of patients had symptomatic stricture recurrence [43].

## 4. Surgical Treatment Options

It is the prevailing belief by most endoscopists, including the authors, that endoscopic therapy should be attempted prior to surgical intervention. Endoscopic therapy is less invasive and shows similar results in the short term compared with surgical alternatives. Díte and colleagues presented data on the first randomized controlled trial comparing endoscopic versus surgical therapy, the latter consisting of resection and drainage procedures [49]. A total of 72 patients were randomized, and the initial success rate was similar in both groups. However, long-term follow-up favored complete absence of pain in the surgical group. This study was limited by the fact that ESWL was not performed, and repeat endoscopic therapy was not allowed for pain recurrence. A more recent randomized controlled trial comparing surgical drainage (pancreaticojejunostomy) versus endoscopic therapy showed that the surgical alternative was superior in improving pain in patients with chronic pancreatitis and a dilated pancreatic duct [51]. Although this study has been criticized for its small numbers, possible selection bias, and lack of rigorous endoscopic therapy, Cahen and colleagues were able to show complete or partial pain relief in 75% of surgically treated patients versus a 32% success rate in endoscopically treated patients. In addition, these investigators have recently published their 5-year follow-up results showing that 68% of the endoscopically treated patients required additional drainage

procedures, compared with 5% in the surgery group ($P = 0.001$) [52]. They also report that 47% of the patients in the endoscopy group eventually received surgery. In the long term, despite comparable levels of quality of life and pancreatic function between the surgical and endoscopic management group, surgery was still superior, in terms of pain relief (80% versus 38%, $P = 0.042$). Although endoscopic therapy is still considered first-line treatment, these randomized trials comparing surgical and endoscopic therapy should give the endoscopist pause to think about the procedures being offered to a patient for the treatment of pain in chronic pancreatitis.

In conclusion, endoscopic therapy aimed at treating pain in patients with chronic pancreatitis consists of EUS-guided celiac plexus block and therapeutic ERCP procedures combined with ESWL that are all aimed at draining an obstructed pancreatic duct. As a result they have the potential to work well in patients with large duct disease, but they do not work well in patients with small duct chronic pancreatitis. Endoscopic management is safe and effective for many patients, but pain relief is often short lived requiring multiple repeat procedures. Endoscopic technologies as well as therapeutic techniques continue to evolve, and as such, improvements will likely be seen in the endoscopic management of chronic pancreatitis in the future.

## References


[1] F. Fugere and G. Lewis, "Coeliac plexus block for chronic pain syndromes," *Canadian Journal of Anaesthesia*, vol. 40, no. 10, pp. 954–963, 1993.

[2] R. H. Hastings and W. R. McKay, "Treatment of benign chronic abdominal pain with neurolytic celiac plexus block," *Anesthesiology*, vol. 75, no. 1, pp. 156–158, 1991.

[3] J. W. C. Leung, M. Bowen Wright, and W. Aveling, "Coeliac plexus block for pain in pancreatic cancer and chronic pancreatitis," *British Journal of Surgery*, vol. 70, no. 12, pp. 730–732, 1983.

[4] S. Arner and B. A. Meyerson, "Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain," *Pain*, vol. 33, no. 1, pp. 11–23, 1988.

[5] H. J. McQuay, M. Tramèr, B. A. Nye, D. Carroll, P. J. Wiffen, and R. A. Moore, "A systematic review of antidepressants in neuropathic pain," *Pain*, vol. 68, no. 2-3, pp. 217–227, 1996.

[6] P. Malfertheiner, D. Mayer, M. Büchler, J. E. Domínguez-Muñoz, B. Schiefer, and H. Ditschuneit, "Treatment of pain in chronic pancreatitis by inhibition of pancreatic secretion with octreotide," *Gut*, vol. 36, no. 3, pp. 450–454, 1995.

[7] H. Halgreen, N. Thorsgaard Pedersen, and H. Worning, "Symptomatic effect of pancreatic enzyme therapy in patients with chronic pancreatitis," *Scandinavian Journal of Gastroenterology*, vol. 21, no. 1, pp. 104–108, 1986.

[8] A. Malesci, E. Gaia, A. Fioretta et al., "No effect of long-term treatment with pancreatic extract on recurrent abdominal pain in patients with chronic pancreatitis," *Scandinavian Journal of Gastroenterology*, vol. 30, no. 4, pp. 392–398, 1995.

[9] J. Mossner, J. Secknus, J. Meyer, C. Niederau, and G. Adler, "Treatment of pain with pancreatic extracts in chronic pancreatitis: results of a prospective placebo-controlled multicenter trial," *Digestion*, vol. 53, no. 1-2, pp. 54–66, 1992.

[10] T. Ferrer-Brechner, "Anesthetic management of cancer pain," *Seminars in Oncology*, vol. 12, no. 4, pp. 431–437, 1985.

[11] H. H. Stone and E. J. Chauvin, "Pancreatic denervation for pain relief in chronic alcohol associated pancreatitis," *British Journal of Surgery*, vol. 77, no. 3, pp. 303–305, 1990.

[12] E. L. Bradley III, "Long-term results of pancreatojejunostomy in patients with chronic pancreatitis," *American Journal of Surgery*, vol. 153, no. 2, pp. 207–213, 1987.

[13] J. S. Markowitz, D. W. Rattner, A. L. Warshaw, R. L. Roosi, C. P. Shoemaker, and W. B. Goldfarb, "Failure of symptomatic relief after pancreaticojejunal decompression for chronic pancreatitis: strategies for salvage," *Archives of Surgery*, vol. 129, no. 4, pp. 374–380, 1994.

[14] M. J. Levy and M. J. Wiersema, "EUS-guided celiac plexus neurolysis and celiac plexus block," *Gastrointestinal Endoscopy*, vol. 57, no. 7, pp. 923–930, 2003.

[15] M. Zenz, M. Strumpf, and M. Tryba, "Long-term oral opioid therapy in patients with chronic nonmalignant pain," *Journal of Pain and Symptom Management*, vol. 7, no. 2, pp. 69–77, 1992.

[16] B. J. Hoffman, "EUS-guided celiac plexus block/neurolysis," *Gastrointestinal Endoscopy*, vol. 56, no. 4, pp. S26–S28, 2002.

[17] S. Mercadante and F. Nicosia, "Celiac plexus block: a reappraisal," *Regional Anesthesia*, vol. 23, no. 1, pp. 37–48, 1998.

[18] M. J. Wiersema and L. M. Wiersema, "Endosonography-guided celiac plexus neurolysis," *Gastrointestinal Endoscopy*, vol. 44, no. 6, pp. 656–662, 1996.

[19] S. Ischia, A. Ischia, E. Polati, and G. Finco, "Three posterior percutaneous celiac plexus block techniques: a prospective, randomized study in 61 patients with pancreatic cancer pain," *Anesthesiology*, vol. 76, no. 4, pp. 534–540, 1992.

[20] M. J. Levy, M. D. Topazian, M. J. Wiersema et al., "Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block," *American Journal of Gastroenterology*, vol. 103, no. 1, pp. 98–103, 2008.

[21] J. K. LeBlanc, J. DeWitt, C. Johnson et al., "A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain," *Gastrointestinal Endoscopy*, vol. 69, no. 4, pp. 835–842, 2009.

[22] A. V. Sahai, V. Lemelin, E. Lam, and S. C. Paquin, "Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness," *American Journal of Gastroenterology*, vol. 104, no. 2, pp. 326–329, 2009.

[23] F. Gress, C. Schmitt, S. Sherman, S. Ikenberry, and G. Lehman, "A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain," *American Journal of Gastroenterology*, vol. 94, no. 4, pp. 900–905, 1999.

[24] F. Gress, C. Schmitt, S. Sherman, D. Ciaccia, S. Ikenberry, and G. Lehman, "Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience," *American Journal of Gastroenterology*, vol. 96, no. 2, pp. 409–416, 2001.

[25] M. Kaufman, G. Singh, S. Das et al., "Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer," *Journal of Clinical Gastroenterology*, vol. 44, no. 2, pp. 127–134, 2010.

[26] D. D. Davies, "Incidence of major complications of neurolytic coeliac plexus block," *Journal of the Royal Society of Medicine*, vol. 86, no. 5, pp. 264–266, 1993.

[27] E. Eisenberg, D. B. Carr, and T. C. Chalmers, "Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis," *Anesthesia and Analgesia*, vol. 80, no. 2, pp. 290–295, 1995.

[28] R. B. Patt and S. Reddy, "Spinal neurolysis for cancer pain: indications and recent results," *Annals of the Academy of Medicine Singapore*, vol. 23, no. 2, pp. 216–220, 1994.

[29] K. D. Lillemoe, J. L. Cameron, H. S. Kaufman et al., "Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial," *Annals of Surgery*, vol. 217, no. 5, pp. 447–457, 1993.

[30] P. A. J. Hardy and J. C. D. Wells, "Coeliac plexus block and cephalic spread of injectate," *Annals of the Royal College of Surgeons of England*, vol. 71, no. 1, pp. 48–49, 1989.

[31] T. M. O'Toole, N. J. Shire, S. S. Chauhan et al., "Predictors of response to EUS-guided celiac plexus blockade for abdominal pain in patients with chronic pancreatitis," *Gastrointestinal Endoscopy*, vol. 65, article AB209, 2007.

[32] T. Stevens, G. Zucarro, J. A. Dumot et al., "Longitudinal study of endoscopic ultrasound guided celiac plexus blockade (EUS-CPB) for treatment of painful chronic pancreatitis (CP)," *The American Journal of Gastroenterology*, vol. 102, no. S178, Abstract 169, 2007.

[33] T. Rösch, S. Daniel, M. Scholz et al., "Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up," *Endoscopy*, vol. 34, no. 10, pp. 765–771, 2002.

[34] G. I. Papachristou and T. H. Baron, "Complication of therapeutic endoscopic retrograde cholangiopancreatography," *Gut*, vol. 56, no. 6, pp. 854–868, 2007.

[35] S. Sherman, G. A. Lehman, R. H. Hawes et al., "Pancreatic ductal stones: frequency of successful endoscopic removal and improvement in symptoms," *Gastrointestinal Endoscopy*, vol. 37, no. 5, pp. 511–517, 1991.

[36] G. Costamagna, A. Gabbrielli, M. Mutignani et al., "Extracorporeal shock wave lithotripsy of pancreatic stones in chronic pancreatitis: immediate and medium-term results," *Gastrointestinal Endoscopy*, vol. 46, no. 3, pp. 231–236, 1997.

[37] J. M. Dumonceau, G. Costamagna, A. Tringali et al., "Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial," *Gut*, vol. 56, no. 4, pp. 545–552, 2007.

[38] N. M. Guda, S. Partington, and M. L. Freeman, "Extracorporeal shock wave lithotripsy in the management of chronic calcific pancreatitis: a meta-analysis," *Journal of the Pancreas*, vol. 6, no. 1, pp. 6–12, 2005.

[39] J. T. Merrill, D. K. Mullady, D. S. Early, R. R. Azar, S. A. Edmundowicz, and S. S. Jonnalagadda, "Timing of endoscopy after extracorporeal shock wave lithotripsy for chronic pancreatitis," *Pancreas*, vol. 40, no. 7, pp. 1087–1090, 2011.

[40] M. J. Farnbacher, C. Schoen, T. Rabenstein, J. Benninger, E. G. Hahn, and H. T. Schneider, "Pancreatic duct stones in chronic pancreatitis: criteria for treatment intensity and success," *Gastrointestinal Endoscopy*, vol. 56, no. 4, pp. 501–506, 2002.

[41] M. Delhaye, M. Arvanitakis, G. Verset, M. Cremer, and J. Devière, "Long-term clinical outcome after endoscopic pancreatic ductal drainage for patients with painful chronic pancreatitis," *Clinical Gastroenterology and Hepatology*, vol. 2, no. 12, pp. 1096–1106, 2004.

[42] A. Weber, J. Schneider, B. Neu et al., "Endoscopic stent therapy for patients with chronic pancreatitis: results from a prospective follow-up study," *Pancreas*, vol. 34, no. 3, pp. 287–294, 2007.

[43] G. Costamagna, M. Bulajic, A. Tringali et al., "Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results," *Endoscopy*, vol. 38, no. 3, pp. 254–259, 2006.

[44] J. McCarthy, J. E. Geenen, and W. J. Hogan, "Preliminary experience with endoscopic stent placement in benign pancreatic diseases," *Gastrointestinal Endoscopy*, vol. 34, no. 1, pp. 16–18, 1988.

[45] T. Sauerbruch, J. Holl, M. Sackmann, and G. Paumgartner, "Extracorporeal lithotripsy of pancreatic stones in patients with chronic pancreatitis and pain: a prospective follow up study," *Gut*, vol. 33, no. 7, pp. 969–972, 1992.

[46] M. Delhaye, A. Vandermeeren, M. Baize, and M. Cremer, "Extracorporeal shock-wave lithotripsy of pancreatic calculi," *Gastroenterology*, vol. 102, no. 2, pp. 610–620, 1992.

[47] K. F. Binmoeller, P. Jue, H. Seifert, W. C. Nam, J. Izbicki, and N. Soehendra, "Endoscopic pancreatic stent drainage in chronic pancreatitis and a dominant stricture: long-term results," *Endoscopy*, vol. 27, no. 9, pp. 638–644, 1995.

[48] H. E. Adamek, R. Jakobs, A. Buttmann, M. U. Adamek, A. R. J. Schneider, and J. F. Riemann, "Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy," *Gut*, vol. 45, no. 3, pp. 402–405, 1999.

[49] P. Díte, M. Ružicka, V. Zboril, and I. Novotný, "A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis," *Endoscopy*, vol. 35, no. 7, pp. 553–558, 2003.

[50] A. Gabbrielli, M. Pandolfi, M. Mutignani et al., "Efficacy of main pancreatic-duct endoscopic drainage in patients with chronic pancreatitis, continuous pain, and dilated duct," *Gastrointestinal Endoscopy*, vol. 61, no. 4, pp. 576–581, 2005.

[51] D. L. Cahen, D. J. Gouma, Y. Nio et al., "Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis," *New England Journal of Medicine*, vol. 356, no. 7, pp. 676–684, 2007.

[52] D. L. Cahen, D. J. Gouma, P. Laramée et al., "Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis," *Gastroenterology*, vol. 141, no. 5, pp. 1690–1695, 2011.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 627095, 7 pages
doi:10.1155/2012/627095

*Research Article*

# Reconstruction by Pancreaticogastrostomy versus Pancreaticojejunostomy following Pancreaticoduodenectomy: A Meta-Analysis of Randomized Controlled Trials

**YinFeng Shen and WenYin Jin**

*Surgery, Chinese Medicine Hospital of Hubei Province, Hubei University of Chinese Medicine, Wuhan 430061, China*

Correspondence should be addressed to WenYin Jin, 1549572729@qq.com

Received 30 August 2011; Revised 13 October 2011; Accepted 9 November 2011

Academic Editor: Jose G. de la Mora-Levy

Copyright © 2012 Y. Shen and W. Jin. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Objectives*. The aim of our study was to evaluate and compare the results of pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ) after pancreaticoduodenectomy (PD). *Methods*. Published data of randomized clinical trials (RCTs) comparing the clinically relevant outcomes of PG versus PJ after PD were analyzed. Two reviewers assessed the quality of each trial and collected data independently. The Cochrane Collaboration's RevMan 5.0 software was used for statistical analysis. Proportions were combined, and the odds ratio (OR) with its 95% CI was used as the effect size estimate. *Results*. Four RCTs published in 1995 or later were included in this meta-analysis, in which 276 patients underwent PG and 277 patients underwent PJ followed PD. In the combined results of PG versus PJ, a significant difference in the morbidity of intra-abdominal complications (OR, 0.34; 95% CI, 0.23–0.49; $P < 0.00001$) was found, but no significant difference could be found for pancreatic fistula (OR, 0.69; 95% CI, 0.42–1.12 , $P = 0.13$) mortality (OR, 1.09; 95% CI, 0.42–2.83; $P = 0.87$), recovery with no complications (OR, 1.26; 95% CI, 0.90–1.78; $P = 0.18$), biliary fistula (OR, 0.55; 95% CI, 0.22–1.35; $P = 0.19$), or in delayed gastric emptying (OR, 0.55; 95% CI, 0.33–1.01; $P = 0.06$). *Conclusions*. Current RCTs suggest that PG is better than PJ for pancreatic reconstruction after PD.

## 1. Introduction

With dramatic improvement in operative mortality, pancreaticoduodenectomy (PD) has become increasingly accepted as a safe and appropriate operation for selected patients with periampullary tumors, pancreatic head cancer, benign neoplasms, and other non-neoplastic conditions such as chronic pancreatitis [1]. With advances in treatment techniques, the mortality rate of PD has decreased to below 5% in many institutions around the world in recent years [1–5]. However, even with these advancements in operative technique and postoperative management, postoperative morbidity of intra-abdominal complications remains high even in large series [4]. The most common complications after PD are pancreatic fistula, delayed gastric emptying, biliary fistula, and wound infection [6–8]. They often contribute significantly to prolonged hospitalization and mortality [6]. Leakage from the pancreatic anastomosis remains the single most important cause of morbidity and sometimes mortality [1].

Recently, considerable attention has been focused on refinements in operative technique for PD, especially on the management of the pancreatic remnant, with the intent to decrease the incidence of pancreatic fistula. These efforts include technical modifications such as the pancreatojejunal anastomosis technique, the pancreatogastric anastomosis, and external drainage of the pancreatic duct [5]. Pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ) have been the most commonly used method of restoring pancreatioenteric continuity after PD. Some retrospective studies [9–11] and one RCT [12] have reported lower pancreatic fistula rate with PG instead of PJ, and a recent meta-analysis [13] suggested that the safer means of pancreatic reconstruction after PD was PG. However, 3 RCTs [14–16] showed PG and PJ to be similar in regards to pancreatic fistula rates, and a recent meta-analysis concluded [17] that PG and PJ were not different in terms of pancreatic fistula rate or overall morbidity rate.

Thus, in order to establish which is the best technique for pancreatoenteric anastomosis, it is important to identify

the definition of pancreatic fistula used, before any series of patients can be compared [1]. To evaluate and compare the results of PG and PJ after PD, we performed an up-to-date meta-analysis to PG versus PJ including all RCTs, and when appropriate and possible, to establish the sources of heterogeneity in the results.

## 2. Materials and Methods

*2.1. Data Sources.* We performed a systematic review of the literature published between 1990 and July 2011. To identify studies published from 1990 to July 2011, we performed a comprehensive search of abstracts in the MEDLINE database, OVID database, Springer database, the Science Citation Index, and the Cochrane Library database with use of the following search terms: "pancreaticoduodenectomy," "pancreaticogastrostomy," "pancreaticojejunostomy," with limitations to Randomized Controlled Trial, Humans. Reports in any language were eligible for inclusion. To avoid double counting, two data extractors compared the articles for participating institutions and inclusion criteria. Unpublished research was not included.

*2.2. Inclusion and Exclusion Criteria.* Only RCTs were included. Any etiology for PD was eligible, and there was no limitation because of race, gender, or age. Comparator intervention was considered PG, while control intervention was considered PJ.

*2.3. Statistical Analysis.* Two independent reviewers extracted data by using a specially developed form and entered it into the freeware program Review Manager (Version 5.0 for Windows, Cochrane Collaboration, Oxford, UK, 2008), respectively. The odds ratio (OR) for each trial was calculated from the number of evaluable patients, and ORs with their two-sided 95% CIs were used for dichotomous outcomes as the confirmatory effect size estimate and test criterion. For continuous variables, weighted mean difference (WMD) was calculated with 95% confidence intervals. In the course of data combination, heterogeneity was evaluated with the Cochran Q test. The fixed-effects model and random-effects model were applied. The hypothesis tests were based on the 95% CIs, and $P$ values were used for illustration. All $P$ values were two-sided, and $P < 0.05$ was considered statistically significant. To determine the potential risk bias in the overall results from the inclusion of studies that violated some of the eligibility criteria, sensitivity analysis and publication bias analysis were performed.

## 3. Results

*3.1. Trial and Patient Characteristics.* A total of 398 studies were retrieved, and the process of identifying relevant trials is shown in Figure 1. Among these 398 studies, 369 were excluded because of trial design, 29 studies were potentially appropriate clinical trials to be included in the meta-analysis, 15 were excluded because of absence of randomization, and 9 were excluded RCTs for other reasons. Finally, five RCTs were included [12, 14–16], which were all published as full articles; clinically relevant outcomes for our study could not be extracted from one of these five, thus leaving four RCTs for meta-analysis. Among these 4 studies, there were a total of 276 patients that underwent PJ and 277 patients that underwent PJ. The main characteristics of the four included studies are reported in Table 1.

Table 1: Characteristics of RCTs Included in the study.

| Author | Year | Total No. | Setting | AC | Operation |
|---|---|---|---|---|---|
| Bassi et al. [15] | 2005 | 151 | Single center | Adequate | PPPD or PD |
| Duffas et al. [16] | 2005 | 149 | Multicenter | Adequate | PPPD or PD or ER |
| Fernàndez-Cruz et al. [12] | 2008 | 108 | Single center | Adequate | PPPD |
| Yeo et al. [14] | 1995 | 145 | Single center | Adequate | PPPD or PD |

Abbreviation: AC = allocation concealment; PPPD = pylorus-preserving pancreaticoduodenectomy; PD =pancreaticoduodenectomy; ER = extended resection. *PPPD or PD plus resections extended to other organs (colon, small intestines, mesenteric portal confluence, liver, biliary tree).

*3.2. Results of Meta-Analysis*

*3.2.1. Morbidity of IACs.* The intra-abdominal complications (IACs) included pancreatic, biliary, or digestive tract fistula, intra-abdominal collections (either infected [abscess] or not), acute pancreatitis, cholangitis; intra-abdominal or digestive tract hemorrhage, delayed gastric emptying, and wound disruption (either infected or not). The four included RCTs involved 553 patients reported IACs. The morbidity of IACs in PG group and PJ group was 43.1% (119/276) and 66.1% (183/277), respectively. Meta-analysis showed a significant difference in morbidity of IACs between PG group and PJ group (OR, 0.34; 95% CI, 0.23–0.49; $P < 0.00001$) (Figure 2).

*3.2.2. Pancreatic Fistula.* The included RCTs reported on pancreatic fistula. The rate of pancreatic fistula in the PG group and PJ group was 12.0% (33/276) and 16.3% (45/277), respectively. Meta-analysis showed no significant difference in pancreatic fistula between PG and PJ group (OR, 0.69; 95% CI, 0.42–1.12; $P = 0.13$) (Figure 3).

*3.2.3. Mortality.* Three included RCTs involving 408 patients reported the mortality. The mortality of PG group and PJ group was 4.9% (10/203) and 3.9% (8/205), respectively. Meta-analysis showed no significant difference in mortality between PG and PJ group (OR, 1.09; 95% CI, 0.42–2.83; $P = 0.87$) (Figure 4).

*3.2.4. Recovery with No Complications.* Four included RCTs including 553 patients reported recovery with no complications. The rate of recovery with no complications in PG group and PJ group was 62.0% (171/276) and 57.0% (158/277) respectively. Meta-analysis showed no significant

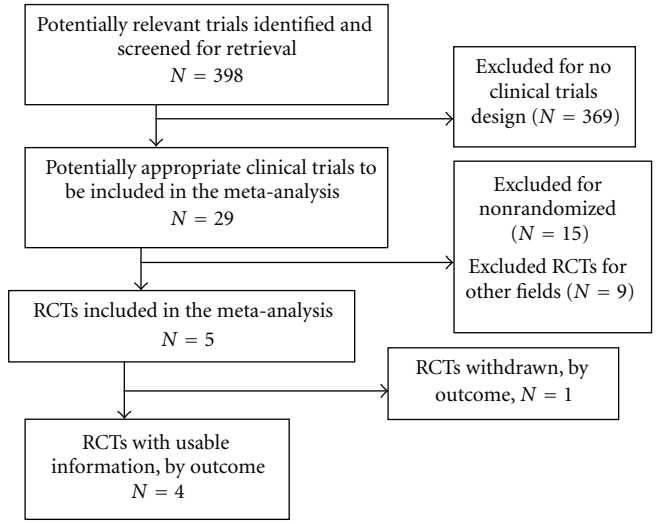



Figure 1: QUOROM flow diagram of included and excluded studies.

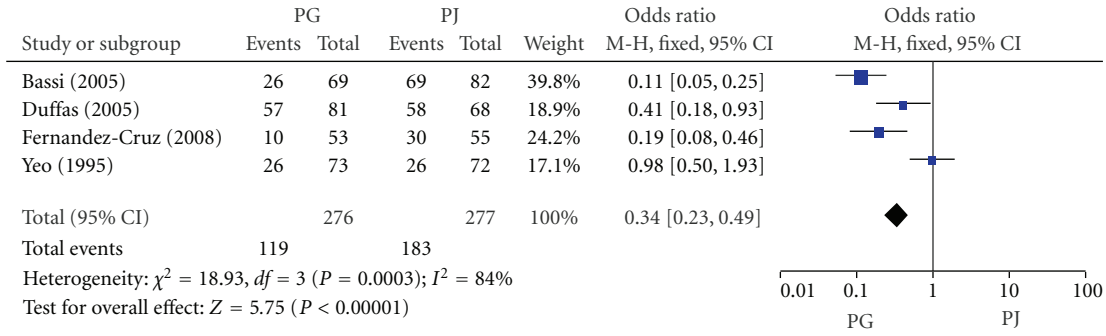



Figure 2: Forest plot of morbidity of IACs between PG and PJ.

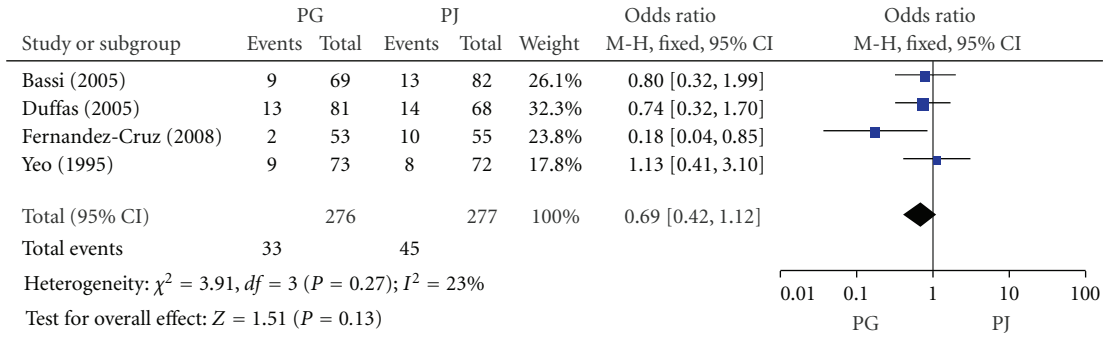



Figure 3: Forest plot of pancreatic fistula between PG and PJ.

difference in pancreatic fistula between PG and PJ group (OR, 1.26; 95% CI, 0.90–1.78; $P = 0.18$) (Figure 5).

*3.2.5. Biliary Fistula.* Biliary fistula was defined as bile in the drain fluid from the subhepatic drain (or an operatively placed drain or a subsequently placed percutaneous drain) with the level of total bilirubin exceeding the upper limit of normal. 4 included RCTs including 553 patients reported biliary fistula. The rate of biliary fistula in PG group and PJ group was 2.5% (7/276) and 4.7% (13/277), respectively. Meta-analysis showed no significant difference in biliary fistula between PG and PJ group (OR, 0.55; 95% CI, 0.22–1.35; $P = 0.19$) (Figure 6).

*3.2.6. Delayed Gastric Emptying.* Delayed gastric emptying (DGE) was defined when the nasogastric tube was maintained for ten or more days, combined with one or more of the following: vomiting after removal of nasogastric tube,

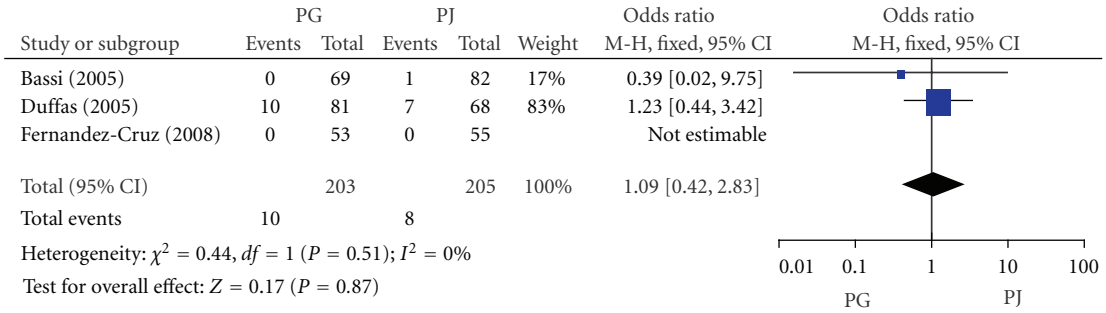



Figure 4: Forest plot of mortality between PG and PJ.

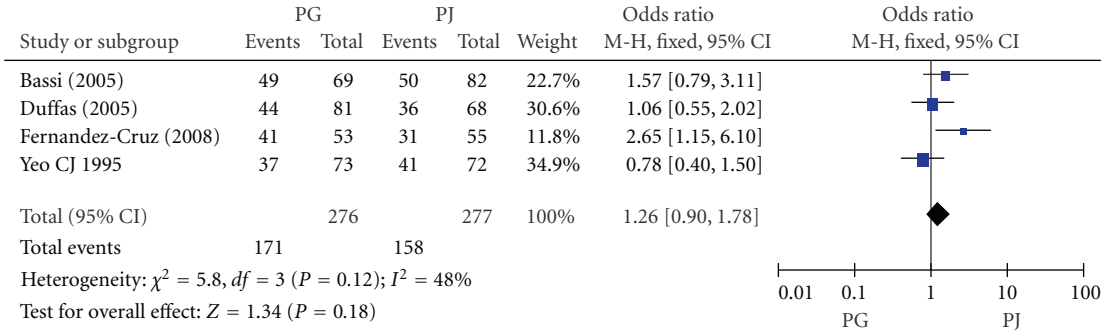



Figure 5: Forest plot of recovery with no complications between PG and PJ.

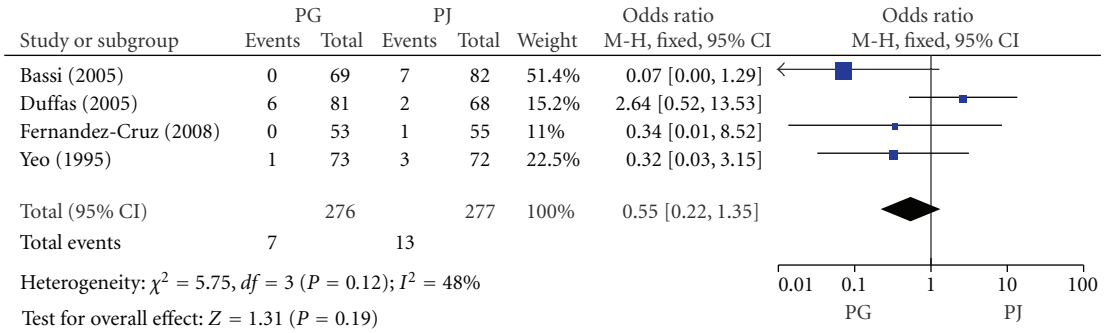



Figure 6: Forest plot of biliary fistula between PG and PJ.

reinsertion of nasogastric tube, or failure to progress with oral feeding. Three included RCTs involving 404 patients reported delayed gastric emptying. The rate of delayed gastric emptying in PG group and PJ group was 10.3% (20/195) and 16.3% (34/209), respectively. Meta-analysis showed no significant difference in delayed gastric emptying between PG and PJ group (OR, 0.55; 95% CI, 0.33–1.01; $P = 0.06$) (Figure 7).

*3.3. Sensitivity Analysis and Publication Bias.* Sensitivity analysis and publication bias estimates were performed to determine statistically significant results. For intra-abdominal complications (IACs) between PG group and PJ group, combined ORs were calculated with a fixed-effects model and a random-effects model, and the results were compared. The OR with a fixed-effects model was 0.34 (95% CI, 0.23–0.49; $P < 0.00001$); moreover, because statistically significant data are more likely to be published and the findings of the present review were mostly positive, our meta-analysis was likely influenced very little by publication bias. However, because of the small numbers of randomized controlled trials available, more detailed stratification comparisons could not make, which could have influenced the validity of our study to some extent.

## 4. Discussion

To reduce the incidence of postoperative complications, a variety of techniques [18] as well as pharmacologic prophylactic approaches [19, 20] have been used and evaluated over the years in the management of the pancreatic remnant following PD. Pancreatic anastomosis leakage remains a major

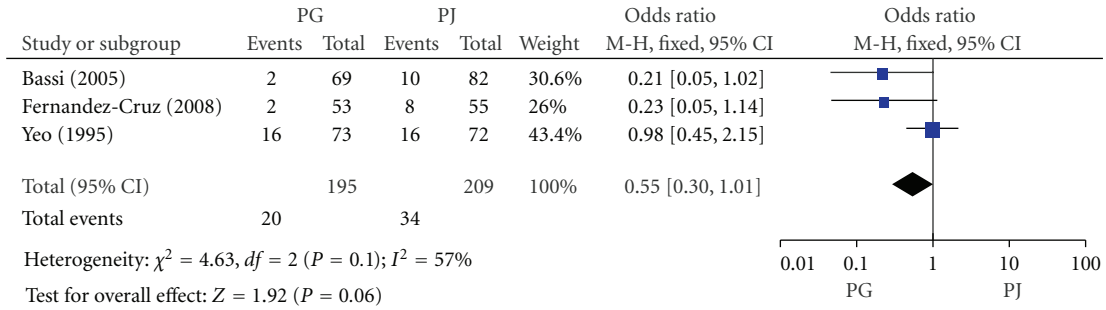



Figure 7: Forest plot of delayed gastric emptying between PG and PJ.

cause of postoperative morbidity after PD, and it contributes significantly to operative mortality. Pancreatoenteric anastomotic failure is one of the major causes of morbidity because of delayed gastric emptying, pancreatic fistula, and wound infection; pancreatic fistula can also lead to hemorrhage (intra-abdominal and/or into the digestive tract), leakage (biliary and/or digestive tract), intra-abdominal infection, wound disruption (infected or no), and even death. The most common techniques for reconstruction of pancreatic gastrointestinal continuity after PD involve a pancreaticoenteric anastomosis, usually either PJ or PG. The best technique for pancreatic anastomosis is still a challenge for the pancreatic surgeon. The pancreatojejunal anastomosis is carried out either as an end-to-end anastomosis with invagination of the pancreatic stump into the jejunum or as an end-to-side anastomosis with or without duct-to-mucosa suturing [21]. The pancreatogastric anastomosis is performed to the gastric lumen through either the gastric stump or through an anterior wall gastrostomy (in the case of pylorus-preserving PD).

The present meta-analysis showed that PG is better than PJ for pancreatic reconstruction after PD, because PG has lower morbidity of intra-abdominal complications than PJ ($P < 0.00001$), while the two techniques of anastomosis were not different in terms of pancreatic fistula rate ($P = 0.13$), mortality ($P = 0.87$), recovery with no complications rate ($P = 0.18$), biliary fistula rate ($P = 0.19$), and delayed gastric emptying rate ($P = 0.06$).

The technique of PG has several potential advantages over PJ. First, the PG anastomosis can be performed easily, because the posterior wall of the stomach lies immediately anterior to the mobilized pancreatic remnant and is usually wider than the transected pancreas. Second, with PG, the pancreatic exocrine secretions enter the potentially acidic gastric environment, precluding digestive damage of the pancreatoenteric anastomosis by activated proteolytic enzymes. In contrast with PJ, the activation of pancreatic exocrine secretions can occur more easily in the presence of intestinal enterokinase and bile. Third, PG avoids the long jejunal loop where pancreatobiliary secretions accumulate during the early postoperative period. Fourth, postoperative gastric decompression can provide constant removal of pancreatic and gastric secretions avoiding accumulation and thus tension on the anastomosis. Fifth, PG anastomosis reduces the number of anastomoses in a single loop of retained jejunum, which potentially decreases the likelihood of loop kinking. The decreased morbidity of intra-abdominal complications for PG may be the result of the aforementioned theoretical advantages. Published studies have favored PG over PJ [12, 22] although these studies are limited by their small patient populations.

It is generally accepted that compared to a fibrotic pancreatic remnant, a soft and fragile pancreatic remnant frequently results in a high pancreatic anastomosis leakage rate [23]. There are many factors which can lead to pancreatic anastomosis leakage (pancreatic fistula), including pancreatic factors (pancreatic texture, original pathology, blood supply to the pancreas remnant, pancreatic juice output, pancreatic duct size), patient factors (age, gender, level of preoperative jaundice, comorbid illness), and operative factors (operation time, blood loss, type of anastomosis, stenting of pancreatic duct) [1, 24–27]. Among these factors, the main factors include pancreatic texture [1, 27–29], pancreatic stump blood supply, pancreatic duct size [1, 29], and pancreatic juice output [27, 30]. All RCTs which were included in our study reported diverse factors (pancreatic factors, patient factors, and operation factors) which were different between the PG group and the PJ group. For pancreatic fistula, the present study showed no significant difference in two groups ($P = 0.13$). Although there is heterogeneity between the analyzed RCTs, all RCTs were conducted in specialized centers by highly experienced surgeons, and the surgical care is likely to be similar among studies. Regarding methodological quality, we consider our analyses to be relevant [31].

The results of this meta-analysis are in line with research from McKay et al. [13] and are partly similar with Wente et al. [17]. However, our meta-analysis has some limitations. First, due to the lack of specific information in the original papers, we cannot perform a subgroup analysis according to patient age and the etiology of PD; thus, it is unclear whether the advantage of PG is potentially applicable to all subgroups of patients. Second, the reported technique for PD in each RCT was variable with conventional PD, PPPD, or PD plus extended resection (Figure 1). Different operative procedures could lead to different complications. Third, other factors, such as presenting symptoms, preoperative blood parameters, the presence of comorbid illness, and preoperative biliary drainage, could influence the frequency or type of morbidity. Fourth, the definition for pancreatic

fistula also varied between RCT, with only one [14], utilizing the ISGPF criteria [24], which could influence our study. Fifth, this meta-analysis included only 553 patients and 4 RCTs, and a type II error may be possible.

In conclusion, the evidence from this formal meta-analysis suggests that PG is better than PJ for pancreatic reconstruction after PD. PG can provide an adequate reconstruction for pancreaticoenteric continuity following PD. Future large-scale, high-quality, multicenter trials are still required to clarify the issues of PG reconstruction following PD. For future experiment on PD, the question for the management of the pancreatic remnant must be addressed in the future.

## References


[1] S. V. Shrikhande, S. S. Qureshi, N. Rajneesh, and P. J. Shukla, "Pancreatic anastomoses after pancreaticoduodenectomy: do we need further studies?" *World Journal of Surgery*, vol. 29, no. 12, pp. 1642–1649, 2005.

[2] M. A. Talamini, R. C. Moesinger, H. A. Pitt et al., "Adenocarcinoma of the ampulla of Vater: a 28-year experience," *Annals of Surgery*, vol. 225, no. 5, pp. 590–600, 1997.

[3] S. Y. Peng, J. W. Wang, W. Y. Lau et al., "Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial," *Annals of Surgery*, vol. 245, no. 5, pp. 692–698, 2007.

[4] J. M. Winter, J. L. Cameron, K. A. Campbell et al., "1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience," *Journal of Gastrointestinal Surgery*, vol. 10, no. 9, pp. 1199–1211, 2006.

[5] R. T. P. Poon, S. T. Fan, C. M. Lo et al., "EXternal drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial," *Annals of Surgery*, vol. 246, no. 3, pp. 425–433, 2007.

[6] M. W. Buchler, H. Friess, M. Wagner, C. Kulli, V. Wagener, and K. Z'Graggen, "Pancreatic fistula after pancreatic head resection," *British Journal of Surgery*, vol. 87, no. 7, pp. 883–889, 2000.

[7] K. Okamoto, I. Koyama, Y. Toshimitsu et al., "Duct-to-mucosa pancreatojejunostomy for small main pancreatic duct by the parachute technique after pancreatoduodenectomy," *Hepato-Gastroenterology*, vol. 58, no. 107-108, pp. 1025–1028, 2011.

[8] W. B. Pratt, S. K. Maithel, T. Vanounou, Z. S. Huang, M. P. Callery, and C. M. Vollmer, "Clinical and economic validation of the international study group of pancreatic fistula (ISGPF) classification scheme," *Annals of Surgery*, vol. 245, no. 3, pp. 443–451, 2007.

[9] P. J. Shukla, "The challenges of improving survival following pancreatoduodenectomy for pancreatic ductal adenocarcinoma," *Annals of Surgery*, vol. 254, no. 2, pp. 385–386, 2011.

[10] H. J. Schlitt, U. Schmidt, D. Simunec et al., "Morbidity and mortality associated with pancreatogastrostomy and pancreatojejunostomy following partial pancreatoduodenectomy," *British Journal of Surgery*, vol. 89, no. 10, pp. 1245–1251, 2002.

[11] E. Oussoultzoglou, P. Bachellier, J. M. Bigourdan, J. C. Weber, H. Nakano, and D. Jaeck, "Pancreaticogastrostomy decreased relaparotomy caused by pancreatic fistula after pancreaticoduodenectomy compared with pancreaticojejunostomy," *Archives of Surgery*, vol. 139, no. 3, pp. 327–335, 2004.

[12] L. Fernàndez-Cruz, R. Cosa, L. Blanco, M. A. López-Boado, and E. Astudillo, "Pancreatogastrostomy with gastric partition after pylorus-preserving pancreatoduodenectomy versus conventional pancreatojejunostomy a prospective randomized study," *Annals of Surgery*, vol. 248, no. 6, pp. 930–937, 2008.

[13] A. McKay, S. Mackenzie, F. R. Sutherland et al., "Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy," *British Journal of Surgery*, vol. 93, no. 8, pp. 929–936, 2006.

[14] C. J. Yeo, J. L. Cameron, M. M. Maher et al., "A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy," *Annals of Surgery*, vol. 222, no. 4, pp. 580–592, 1995.

[15] C. Bassi, M. Falconi, E. Molinari et al., "Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study," *Annals of Surgery*, vol. 242, no. 6, pp. 767–773, 2005.

[16] J. P. Duffas, B. Suc, S. Msika et al., "A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy," *American Journal of Surgery*, vol. 189, no. 6, pp. 720–729, 2005.

[17] M. N. Wente, S. V. Shrikhande, M. W. Müller, M. K. Diener, C. M. Seiler, and H. Friess, "Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis," *American Journal of Surgery*, vol. 193, no. 2, pp. 171–183, 2007.

[18] G. H. Sakorafas, H. Friess, B. M. Balsiger, M. W. Büchler, and M. G. Sarr, "Problems of reconstruction during pancreatoduodenectomy," *Digestive Surgery*, vol. 18, no. 5, pp. 363–369, 2001.

[19] M. G. L. Sarr and E. A. Woltering, "The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial," *Journal of the American College of Surgeons*, vol. 196, no. 4, pp. 556–565, 2003.

[20] B. Suc, S. Msika, M. Piccinini et al., "Octreotide in the prevention of intra-abdominal complications following elective pancreatic resection: a prospective, multicenter randomized controlled trial," *Archives of Surgery*, vol. 139, no. 3, pp. 288–294, 2004.

[21] J. P. Sung, R. D. Stewart, V. S. O'Hara, K. F. Westhpal, J. E. Wilkinson, and J. Hill, "A study of forty-nine consecutive whipple resections for periampullary adenocarcinoma," *American Journal of Surgery*, vol. 174, no. 1, pp. 6–10, 1997.

[22] D. M. Morris and R. S. Ford, "Pancreaticogastrostomy: preferred reconstruction for Whipple resection," *Journal of Surgical Research*, vol. 54, no. 2, pp. 122–125, 1993.

[23] U. Eiji, T. Takashi, N. Yoshiharu, T. Aimoto, and Z. Naito, "Relationship between grade of fibrosis in pancreatic stump and postoperative pancreatic exocrine activity after pancreaticoduodenectomy: with special reference to insufficiency of pancreaticointestinal anastomosis," *Journal of Nippon Medical School*, vol. 69, no. 6, pp. 549–556, 2002.

[24] C. Bassi, C. Dervenis, G. Butturini et al., "Postoperative pancreatic fistula: an international study group (ISGPF) definition," *Surgery*, vol. 138, no. 1, pp. 8–13, 2005.

[25] Y. M. Shyr, C. H. Su, C. W. Wu, and W. Y. Lui, "Does drainage fluid amylase reflect pancreatic leakage after pancreaticoduodenectomy?" *World Journal of Surgery*, vol. 27, no. 5, pp. 606–610, 2003.

[26] M. I. Van Berge Henegouwen, L. T. De Wit, T. M. Van Gulik, H. Obertop, and D. J. Gouma, "Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy:

drainage versus resection of the pancreatic remnant," *Journal of the American College of Surgeons*, vol. 185, no. 1, pp. 18–24, 1997.

[27] Y. Hamanaka, K. Nishihara, T. Hamasaki et al., "Pancreatic juice output after pancreatoduodenectomy in relation to pancreatic consistency, duct size, and leakage," *Surgery*, vol. 119, no. 3, pp. 281–287, 1996.

[28] K. Al Sharaf, I. Ihse, S. Dawiskiba et al., "Characteristics of the gland remnant predict complications after subtotal pancreatectomy," *Digestive Surgery*, vol. 14, no. 2, pp. 101–106, 1997.

[29] N. Sato, K. Yamaguchi, K. Chijiiwa, and M. Tanaka, "Risk analysis of pancreatic fistula after pancreatic head resection," *Archives of Surgery*, vol. 133, no. 10, pp. 1094–1098, 1998.

[30] R. T. P. Poon and S. T. Fan, "Decreasing the pancreatic leak rate after pancreaticoduodenectomy," *Advances in Surgery*, vol. 42, no. C, pp. 33–48, 2008.

[31] D. Moher, D. J. Cook, S. Eastwood, I. Olkin, D. Rennie, and D. F. Stroup, "Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement," *Lancet*, vol. 354, no. 9193, pp. 1896–1900, 1999.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 906381, 7 pages
doi:10.1155/2012/906381

*Review Article*

# Endoscopic Management of Peri-Pancreatic Collections

**David Keith Swartz and Jorge Obando**

*Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham, NC, USA*

Correspondence should be addressed to Jorge Obando, jorge.obando@duke.edu

Received 1 September 2011; Revised 30 October 2011; Accepted 7 November 2011

Academic Editor: Carlos G. Micames

Copyright © 2012 D. K. Swartz and J. Obando. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Endotherapy of peripancreatic fluid collections is an increasing utilized procedure in interventional endoscopy. The aim of this paper is to provide a general overview of the topic, highlighting the indications, technique, and important management issues relating to endoscopic management of the various forms of peri-pancreatic fluid collections.

## 1. Introduction

Acute pancreatitis is a common clinical problem, with an incidence of 210,000 per year in the USA [1], and is most commonly a consequence of biliary tract stones and alcohol. There is a wide spectrum of disease severity ranging from mild self-limiting disease to severe acute pancreatitis (SAP), an entity characterized by the presence of systemic and local complications. Local complications include peri-pancreatic collections, which can result in significant morbidity and mortality. Chronic pancreatitis is also a common problem causing peri-pancreatic collections, in particular pseudocysts. For many years, surgery was the major modality used to treat these entities. Endoscopic trans-gastric treatment of pseudocysts evolved in the late 1970's [2]. Percutaneous radiologically assisted procedures were also employed [3, 4] and, with the advent and development of cross-sectional imaging, were used more frequently. Endoscopic trans-gastric or trans-duodenal drainage established a role for endotherapy in the management of these problems following the publication of success in a large series [5]. The use of endosonography in the management of peri-pancreatic collections is a more recent development, but one that has rapidly evolved since its first reported use in drainage of pancreatic pseudocysts in 1992 [6]. With EUS assistance, indications for the use of endoscopic therapy were extended to include pancreatic necrosectomy in 1996 [7].

## 2. Classification of Peri-Pancreatic Collections

A consensus conference in 1992 established the currently accepted definitions of the local complications of pancreatitis in what is known as the Atlanta Classification [8]. Five major morphological entities were defined—pancreatic necrosis, acute fluid collections, pancreatic abscess, acute pseudocyst, and chronic pseudocyst. Pancreatic necrosis features diffuse or focal areas of non-viable pancreatic parenchyma, usually with associated peri-pancreatic fat necrosis. Acute fluid collections are peri-pancreatic collections of fluid, located in or near the pancreas, lacking a wall of surrounding granulation or fibrous tissue, arising more than 4 weeks after an episode of acute pancreatitis. Pancreatic abscess is a circumscribed intra-abdominal area of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis. Acute pseudocyst is a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue. An additional entity of organised pancreatic necrosis (OPN), or walled-off pancreatic necrosis (WOPN), is frequently referred to in the literature, although it is not a specific entity in the Atlanta Classification. This refers to a collection with good separation of devitalised (necrotic) tissue within a fluid-filled cavity, and an associated fibrous wall lined by granulation tissue [9], as distinct from pancreatic necrosis that is not well defined and lacks a wall (Table 1).

These morphological manifestations result from the underlying inflammation associated with acute pancreatitis. In

Table 1: Atlanta Classification of SAP—pathomorphological entities.

| Entity | Features |
|---|---|
| Pancreatic necrosis | Diffuse or focal areas of non-viable pancreatic parenchyma |
| Pancreatic abscess | Circumscribed intra-abdominal collection of pus containing little or no pancreatic necrosis |
| Acute fluid collection | Fluid collections located in or near the pancreas, lacking a surrounding wall of granulation/fibrous tissue |
| Acute pseudocyst | Collection of pancreatic juice surrounded by wall of granulation/fibrous tissue |

the case of acute fluid collections, serous or exudative reactions develop in response to inflammation early in the course of disease and are not in communication with the pancreatic ductal system [10]. Acute pseudocysts are a consequence of inflammation-induced pancreatic ductal disruption, with extravasation of pancreatic juice inducing the formation of a fibrous wall in an attempt to contain the fluid [8].

## 3. Clinical Manifestations/Indications for Intervention

*3.1. Mass Effect.* All peri-pancreatic collections can cause symptoms by virtue of their mass effect and potential to enlarge. Pain and abdominal fullness are common symptoms. Compression of adjacent organs like the stomach, duodenum, and bile duct can result in early satiety, vomiting, weight loss, and jaundice [11]. Symptoms resulting from the mass effect of fluid collections, in particular pseudocysts, are frequently the precipitant for endoscopic treatment.

*3.2. Infection.* All peri-pancreatic collections have the potential to become infected, spontaneously through translocation of normal gut flora, and via iatrogenic means in the setting of instrumentation of a previously sterile collection of tissue or fluid. As expected, enteric gram-negative organisms, in particular *Enterococcus*, *Pseudomonas*, and *Klebsiella*, tend to be the most commonly implicated [12], although *Candida* species are not uncommonly associated [13].

Infected pseudocysts, pancreatic abscesses, and infected necrosis are all potentially amenable to endoscopic management with the aim of removing the infected focus.

*3.3. Hemorrhage/Perforation.* Hemorrhage is an uncommon but serious complication of pancreatic fluid collections. Compression of an adjacent vessel and subsequent erosion can result in pseudoaneurysm formation, with potential for rupture and hemorrhage. The most common site for pseudoaneurysm formation is the splenic artery. Rupture of an aneurysm into a pseudocyst or WOPN can result in hemosuccus pancreaticus [14]. Perforations of pseudocysts into the peritoneum and bowel are well described although uncommon potential complications [15, 16].

*3.4. Size.* Non-randomized data from published series have identified pseudocyst size as a significant predictor of need for intervention, with pseudocysts of greater than 6 cm in size requiring intervention in more than 2/3 of cases [17]. On the basis of this, some advocate treatment of cysts greater than 6 cm in size, even in the absence of other clinical symptoms. However, series with long-term follow-up suggest that asymptomatic cysts can usually be managed conservatively, regardless of size.

## 4. Therapeutic Modalities

*4.1. Surgery.* Surgical management has long been considered the gold-standard for management of peri-pancreatic collections, and was the main treatment modality for many years, prior to the availability of less invasive options. In general, surgical management provides direct access to the peri-pancreatic collection with multiple means of drainage, at the cost of being more invasive and universally requiring general anesthesia. For surgical management of pseudocysts, open external drainage is now generally not deemed appropriate, and internal drainage via formation of a cystgastrostomy or cystenterostomy is the preferred option [18]. Success rates with resolution of cysts using surgical methods is high, but with relatively high complication rates in the range of 24–40% [19–22] and mortality of 5.8% [19]. Laparoscopic approaches have been used more recently, although there is little data comparing outcomes with the open approach. These procedures are associated with around a 10% conversion rate, but a much lower complication and mortality rate of around 12% and 1% respectively [23–27].

*4.2. Percutaneous Radiological Drainage.* Percutaneous drainage of pseudocysts and abscesses is most commonly performed under CT guidance, with either external (direct puncture of the cyst through the anterior abdominal wall) or internal drainage (direct puncture with placement of double-pigtail stents to form a cystgastrostomy under fluoroscopic or endoscopic guidance).

External drainage has a significant failure rate, particularly in the setting of abnormal pancreatic ductal anatomy, and rates of cutaneous fistula formation have been reported to be as high as 50% in certain settings [28].

With the internal technique, success in catheter placement is usually achievable more than 90% of the time, with an immediate complication rate of around 6% and a mortality rate of 1%. Secondary infection with abscess formation is not uncommon, occurring in around 11% [29]. Complete resolution of the pseudocyst with this method has been reported as 88% or more in several small series [30, 31].

*4.3. Endoscopic Therapy*

*4.3.1. Pseudocysts.* Reported success rates for endoscopic treatment of pseudocysts are very high, ranging from 91 to 100% in the published literature [32–34]. Better technical success rates are achieved with EUS-guided procedures.

*4.3.2. Abscess.* By the Atlanta Classification, a pancreatic abscess contains no solid necrotic material. Whilst this situation results in high clinical success rates with endoscopic management, such a situation is actually quite uncommon, as the majority of infected peri-pancreatic fluid collections tend to be associated with some degree of necrosis [10]. Because of this, data on outcomes for abscess drainage is limited. What does appear apparent is that, compared with pseudocyst drainage, endoscopic management has a lower success rate and a higher rate of complications. Older retrospective data suggested no difference in outcome with pseudocyst and abscess drainage [35]. In a recent prospective study, the success rate for abscess drainage was 80%, with a complication rate of 30%, mainly in the form of perforation [36]. This data supports a more cautious approach to abscesses compared with pseudocysts.

*4.3.3. Pancreatic Necrosis.* The technique of endoscopic necrosectomy for pancreatic necrosis has evolved over the last 10 year. With increased experience, outcomes have significantly improved, to the point that this technique has superseded other forms of intervention as the first-line management where technically feasible. Reported rates of successful resolution of walled-off pancreatic necrosis exceed 75%, with a relatively low mortality rate. In up to 20% or more of cases, walled-off necrosis persists despite endoscopic management, and surgical or radiological intervention may still be required [12, 13]. The most recent data comes from a large multicenter retrospective series of 104 patients examining endoscopic necrosectomy for symptomatic necrosis [37]. This study reported successful resolution of pancreatic necrosis in 91%, with a complication rate of 14%.

Certain disease and patient-related factors have been shown to impart a higher failure rate in endoscopic necrosectomy and should influence decisions regarding the management modality used. Extension of the collection into the paracolic gutters, a collection size greater than 15 cm, and patients with comorbid diabetes mellitus have all been associated with lower success rates with endoscopic therapy [12].

*4.4. Comparison of Therapeutic Modalities.* Few studies have set out to directly compare the therapeutic modalities available for management of peri-pancreatic fluid collections. Most of those that have were small in size, and there are no randomized studies comparing the various techniques.

A large population-based analysis comparing surgical with percutaneous management of pancreatic pseudocysts [20] demonstrated significant differences in favor of surgical management in relation to complications, length of stay (15 days versus 21 days), and inpatient mortality (2.8% versus 5.9%).

Generally, the choice of therapeutic modality employed depends on the characteristics of the collection, patient factors, local expertise, and physician preference.

## 5. Assessment Prior to Endoscopic Therapy

An adequate assessment of the nature and anatomical relations of peri-pancreatic fluid collections is necessary prior to endoscopic therapy, in order to maximize success and minimize complication rates.

*5.1. Cross-Sectional Imaging.* Imaging with CT or MRI provides important information about the nature of peri-pancreatic fluid collections in a non-invasive fashion. Contrast-enhanced CT scanning is the most commonly employed technique and is able to provide information on size of the collection, presence and thickness of a wall, presence of internal debris, and contrast-enhancement characteristics that suggest tissue necrosis. Contrast-enhanced, multidetector row CT scan is the best imaging modality to exclude alternative diagnoses, assess severity, and identify complications [38]. Pancreatic MRI is an alternative imaging modality, with evidence to suggest a greater ability to detect solid components within a fluid collection and therefore better distinguish pseudocysts from walled-off necrosis [39]. This advantage means that MRI assessment should be strongly considered as part of the workup of pancreatic fluid collections prior to endotherapy. The presence of a mature wall is a prerequisite for endoscopic intervention, and so pre-intervention imaging guides decision-making on the timing and appropriateness of potential management strategies. MRCP can provide important details on the relationship of peri-pancreatic fluid collections to the pancreatic duct and identify pathology associated with a disconnected pancreatic tail. If a collection can be demonstrated to communicate with the PD, endoscopic management may need to address the pancreatic fistula, in addition to the cyst itself (see Section 6.3).

*5.2. Use of Endosonography.* Although utilization of EUS to assess peri-pancreatic fluid collections is not essential, it has been demonstrated to provide multiple advantages.

The use of EUS is indicated to visualize and avoid vessels or varices that may exist along the path of the needle or fistula to be created. It is also indicated when a cyst does not have a bulge into the GI lumen. It has traditionally been considered that 1 cm is the maximum recommended distance between the GI lumen and the cyst cavity when considering endoscopic therapy.

The addition of an EUS assessment of peri-pancreatic fluid collections prior to endoscopic intervention can result in a change in management in up to 1/3 of patients. Changes can result from alternative diagnoses other than peri-pancreatic fluids collections, and identification of anatomical and vascular factors preventing endoscopic management [40]. This is particularly important in patients with portal hypertension, where vessels are more likely to be interposed between the GI tract and the peri-pancreatic collection [41]. The presence of significant solid debris within a collection can often be seen on EUS, even in settings where radiological imaging had failed to identify such elements. Such a finding suggesting pancreatic necrosis may well change a decision to intervene in what was previously thought to be a pseudocyst, due the risk of converting sterile necrosis into infected necrosis.

For these reasons and others, studies have consistently demonstrated an increased success rate with utilization of

EUS. In a randomized trial, EUS use resulted in as much as a 66% increase in success [42]. The largest randomized trial comparing the techniques demonstrated a 91% success rate with employment of EUS, compared with 72% when not used. Most failures without EUS use were due to the non-bulging nature of the collection. When EUS was used in these cases, drainage was successful [43].

## 6. Technique

*6.1. Pseudocyst Drainage.* Pseudocyst drainage is usually fairly straightforward technically when done on a cyst with no solid component. The aim is to create a permanent fistula between the cyst and the adjacent GI tract, typically the stomach or the duodenum. The location of the fistula should not matter since the fluid will empty into the GI tract by pressure effect. We try to avoid the very high stomach as stents may interfere with the GE junction, although many times this is an area that is very well visualized with the endosonoscope and appealing, given that the endoscope is straight and short.

The technique involves advancing a wire into the cyst. The cyst cavity can be pierced either with a 19-gauge EUS needle under EUS guidance or with a needle-knife if not using EUS. A wire can then be advanced under fluoroscopy into the cyst, and typically it is seen coiling inside the cyst. We feel that injection of contrast into the cyst is not always necessary. We prefer the Boston Scientific 450 cm, 0.035′ Superstiff Jagwire, which may counteract the early coiling of the double-pigtail stent as it is being deployed later in the procedure. If using the EUS needle, it is important not to pull the wire back into the needle since there is concern for shearing a piece of the wire by the sharp needle tip.

The next step after the wire is in place is to dilate the tract. We prefer to see whether a dilation balloon will be able to pierce the gastric wall into the cyst and favor the Hurricane 8–10 mm biliary dilation balloon, given its flexible tip, and stiff shaft due to the presence of a stylet. If we are unsuccessful, we then use either the needle-knife with 1-2 mm of the needle out, with ERBE sphincterotomy settings, or a cystotome (Cystotome, Wilson Cook). The tract is pierced with the thin sheath and immediately dilated with the thicker sheath, using 80–100 watts of pure-cut current.

The tract is then balloon-dilated under fluoroscopy to 10 mm for 1 minute. Typically after deflating the balloon, a large amount of turbid, yellowish fluid emanates from the tract.

In our practice, a minimum of three double-pigtail stents are then placed if possible. It is typically difficult to advance a 10 Fr stent through the endosonoscope lumen, especially if there are 2 wires in the cyst. In these cases, we either place 7 Fr stents or switch the endoscope for a therapeutic, larger-channel endoscope.

Selection of stent size depends on the size of the pseudocyst. For smaller cysts (10 cm in diameter), we prefer 10 Fr, 4 cm stents. For larger cysts, we prefer placing 10 Fr, 7 cm stents, although there is no data to guide this practice. Placing a 10 Fr double-pigtail stent can be challenging given the tendency of the stent to recover its shape as soon as it comes out of the endoscope channel, hence the use of the Superstiff Jagwire from initial cyst puncture. Care should be taken to ensure the stent is deployed correctly and does not migrate into the pseudocyst lumen.

Follow-up at our institution is typically with a CT scan at 4 weeks and a clinic visit for review, with an endoscopic stent removal procedure shortly thereafter, assuming the cyst has resolved. There has been a recent study that supports keeping stents in-situ for a longer period of time, with superior results obtained with stent durations of up to 2 years [44]. The pancreatic ductal anatomy also influences stent duration. If a disconnected tail is seen, it is likely that the disconnected pancreas will continue draining into the cyst cavity. To promote a more mature fistula and prevent early closure, we tend to leave the stents for a longer time, about three months, in these cases.

*6.2. Necrosectomy.* In the first session of necrosectomy, our technique is similar to the one described for pseudocyst management. The goal at this point is to drain the liquid component of the cyst. Stents are placed as previously described. The second session typically takes place a few days later. These procedures can be time-consuming, so they are performed under general anesthesia.

At subsequent sessions, the stents are removed and a wire is placed in the cyst cavity under fluoroscopy. The tract is dilated to 16–18 mm, and a therapeutic endoscope is advanced into the cavity guided by the wire. Care is needed not to over-insufflate the cyst cavity with air. The instruments selected to remove non-viable material will depend on whether the necrotic debris is semi-solid or solid. For liquefied or semi-solid debris, irrigation via the jet port is usually helpful, although suctioning may only clog the channel if there are large particles. In order to gain the greatest efficiency of solid tissue removal, instruments we use (in order of preference) are nets, (Nakao-Spider, ConMed; Roth, US Endoscopy), baskets (Twister, Boston Scientific), snares, or biopsy forceps to break large blocks of necrosis. This choice of instruments is subjective and depends entirely on physician preference and the nature of the material to be removed. The scope is advanced into the cavity as many times as needed to remove as much debris as possible. The stents are replaced at the end of the procedure.

The procedure is typically repeated 3-4 times, at weekly intervals, in order to obtain complete clearance of necrotic tissue. The patient is typically covered with antibiotics. Although the number of sessions required is highly variable and dependent on the nature of the cavity and extent of necrosis, studies examining the issue have found the median number of session required to be 3, with up to 12 sessions being required in some cases [12].

*6.3. Adjunctive Therapy*

*6.3.1. Management of the Pancreatic Duct.* The etiologies of pancreatic fluid collections, particularly those that occur in the setting of acute pancreatitis, are related to disruption to the pancreatic ductal system. As a sequelae of this, pancreatic fistulas are commonly seen. Any direct communication of

the pancreatic ductal system with the fluid collection means that pancreatic glandular secretions have a passage through which to enter and propagate the collection. If endoscopic drainage of a collection is performed, pancreatic fistulae are a cause of potential recurrence. As such, integrity of the pancreatic duct is a prerequisite for successful endoscopic therapy in the long term. For this reason, the importance of appropriate assessment of the anatomical relationship of the pancreatic duct to the peri-pancreatic collection prior to endoscopic treatment with MRCP or ERCP cannot be understated. Should a pancreatic fistula be identified, consideration should be given to performing trans-papillary drainage. This procedure involves passage of a hydrophilic guidewire through the pancreatic duct and either into the collection through the fistula or upstream of the fistulous tract in the pancreatic duct. A pancreatic sphincterotomy and placement of a pancreatic stent are then performed. Such intervention has been shown to improve treatment outcomes in patients undergoing endoscopic transmural drainage of a pancreatic fluid collection [45]. The duration of pancreatic stent placement depends upon the time taken for resolution of the collection and the presence of duct strictures or stones, which may require a prolonged course of stent placement. Sealing of persistent pancreatic fistula with cyanoacrylate glue has been described and is a part of the treatment protocol for managing pancreatic fistulae in certain centers [46].

*6.3.2. Nasocystic Drainage.* Placement of a nasocystic drain following initial access into a peri-pancreatic fluid collection allows for interval access to the collection for interventions such as lavage and administration of antibiotics. This is of particular benefit in walled-off pancreatic necrosis, where multiple sessions are required to adequately clear necrotic tissue. Use of the nasocystic catheter to perform lavage with normal saline in between endoscopic sessions has been shown to reduce rates of super-infection in this setting [47].

## 7. Complications of Endotherapy

General complications include severe bleeding and perforation. Prevention of this requires adequate pre-intervention assessment of the presence of a mature wall, ensuring close proximity of the GI wall to the collection, and addressing any coagulation abnormalities.

Secondary infection prevention requires use of prophylactic antibiotics. We tend to use ciprofloxacin for a period of up to 7 days.

*7.1. Pseudocysts.* Endoscopic pseudocyst drainage is generally a safely performed procedure. With current techniques, experienced operators have perforation rates as low as 1.2%, with bleeding rates of less than 1%. Perforation appears to be more common with pseudocysts in the uncinate region of the pancreas. Migration of stents occurs in less than 1% of cases. Infection rates are in the region of 5% [48].

*7.2. Pancreatic Necrosis.* Endoscopic necrosectomy of walled-off pancreatic necrosis is a more involved undertaking and occurs in a patient population that is usually sicker than those with pseudocysts. As such, complication rates are higher, being as high as 26% in the largest studies. The most common complications are bleeding and perforation, occurring in 54% and 21%, respectively, in the GEPARD study, with a mortality rate of 7.5% [13]. Given that endoscopic necrosectomy by definition involves operation outside the confines of the GI tract, air embolism is a potential complication not seen with other peri-pancreatic fluid collections, with a rate of 8% [13]. This complication can potentially be overcome by use of $CO_2$ instead of air for insufflation.

## 8. Recent Advances and Future Developments

*8.1. Forward-Viewing EUS Biopsy Capability.* The standard EUS imaging platform currently available on the market for therapeutic interventions is the curvilinear echoendoscope, which provides an oblique view of the imaged tissue region. This results in practical disadvantages in the management of peri-pancreatic fluid collections as the accessories are advanced out of the scope tip at an acute angle. The mechanical force of the accessory onto the structure to be targeted tends to push the scope away from the area of interest, creating problems with adequate visualization and maintenance of direction. In addition, the angle of the scope tip that needs to be maintained for appropriate positioning is often problematic from an anatomical perspective. A forward-viewing echoendoscope with a working channel in line with the scope shaft has been developed to overcome these problems (Olympus). Although not yet commercially available, the limited data available on its usefulness in a variety of interventional procedures is encouraging [49]. It has proven effective in allowing drainage of pancreatic pseudocysts when use of the oblique-viewing echoendoscope has failed for technical reasons [50].

*8.2. Use of SEMS.* One drawback of using plastic stents to maintain the tract between a fluid collection and the enteric lumen is the tendency of these stents to migrate or become blocked. Self-expanding metal stents have been used in an attempt to overcome these problems [51], although migration may still be an issue. New stent designs with a larger diameter (20–25 mm) have been developed for use in pancreatic necrosectomy, with the advantage of maintaining a tract through which an endoscope can pass over multiple sessions, without having to change the stent on each occasion [52].

## 9. Conclusion

Management of the complications of severe acute pancreatitis, and peri-pancreatic fluid collections in general, has come a long way over the last 20 years. The employment of endoscopic management for these conditions is becoming more widespread as technologies and techniques continue to evolve. The available evidence highlights the first-line role for endoscopic management is certain situations, such as pseudocyst drainage, with increasing support for its utility in treatment of conditions such as infected pancreatic necrosis,

in the appropriate clinical setting. The role of endoscopic management will continue to be refined as more long-term data becomes available, and management algorithms are more solidly established. The need to better define evidence-based optimal practice, and to develop appropriate device technology, provides fertile ground for clinical researchers and equipment manufacturers alike in advancing this cutting-edge area of endoscopy.

## References


[1] M. W. Russo, J. T. Wei, M. T. Thiny et al., "Digestive and liver diseases statistics, 2004," *Gastroenterology*, vol. 126, no. 5, pp. 1448–1453, 2004.

[2] B. H. G. Rogers, N. J. Cicurel, and R. W. Seed, "Transgastric needle aspiration of pancreatic pseudocyst through an endoscope," *Gastrointestinal Endoscopy*, vol. 21, no. 3, pp. 133–134, 1975.

[3] D. P. MacErlean, P. J. Bryan, and J. J. Murphy, "Pancreatic pseudocyst: management by ultrasonically guided aspiration," *Gastrointestinal Radiology*, vol. 5, no. 3, pp. 255–257, 1980.

[4] S. Hancke and J. F. Pedesen, "Percutaneous puncture of pancreatic cysts guided by ultrasound," *Surgery Gynecology and Obstetrics*, vol. 142, no. 4, pp. 551–552, 1976.

[5] M. Cremer, J. Deviere, and L. Engelholm, "Endoscopic management of cysts and pseudocysts in chronic pancreatitis: long-term follow-up after 7 years of experience," *Gastrointestinal Endoscopy*, vol. 35, no. 1, pp. 1–9, 1989.

[6] H. Grimm, K. F. Binmoeller, and N. Soehendra, "Endosonography-guided drainage of a pancreatic pseudocyst," *Gastrointestinal Endoscopy*, vol. 38, no. 2, pp. 170–171, 1992.

[7] T. H. Baron, W. G. Thaggard, D. E. Morgan, and R. J. Stanley, "Endoscopic therapy for organized pancreatic necrosis," *Gastroenterology*, vol. 111, no. 3, pp. 755–764, 1996.

[8] E. L. Bradley and C. F. Frey, "A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992," *Archives of Surgery*, vol. 128, no. 5, pp. 586–590, 1993.

[9] R. Carter, "Percutaneous management of necrotizing pancreatitis," *HPB*, vol. 9, no. 3, pp. 235–239, 2007.

[10] G. G. Tsiotos and M. G. Sarr, "Management of fluid collections and necrosis in acute pancreatitis," *Current Gastroenterology Reports*, vol. 1, no. 2, pp. 139–144, 1999.

[11] C. L. Yeh, K. H. Lai, G. H. Lo et al., "Endoscopic treatment in a patient with obstructive jaundice caused by pancreatic pseudocyst," *Journal of the Chinese Medical Association*, vol. 66, no. 9, pp. 555–559, 2003.

[12] G. I. Papachristou, N. Takahashi, P. Chahal, M. G. Sarr, and T. H. Baron, "Peroral endoscopic drainage/debridement of walled-off pancreatic necrosis," *Annals of Surgery*, vol. 245, no. 6, pp. 943–951, 2007.

[13] H. Seifert, M. Biermer, W. Schmitt et al., "Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study)," *Gut*, vol. 58, no. 9, pp. 1260–1266, 2009.

[14] Y. Toyoki, K. Hakamada, S. Narumi, M. Nara, K. Ishido, and M. Sasaki, "Hemosuccus pancreaticus: problems and pitfalls in diagnosis and treatment," *World Journal of Gastroenterology*, vol. 14, no. 17, pp. 2776–2779, 2008.

[15] E. L. Bradley and J. L. Clements, "Transenteric rupture of pancreatic pseudocysts: management of pseudocystenteric fistulas," *American Surgeon*, vol. 42, no. 11, pp. 827–837, 1976.

[16] K. Ocran and W. Wermke, "Perforation of a pancreatic pseudocyst induced by abdominal sonography," *Zeitschrift fur Gastroenterologie*, vol. 42, no. 3, pp. 243–246, 2004.

[17] C. J. Yeo, J. A. Bastidas, A. Lynch-Nyhan, E. K. Fishman, M. J. Zinner, and J. L. Cameron, "The natural history of pancreatic pseudocysts documented by computed tomography," *Surgery Gynecology and Obstetrics*, vol. 170, no. 5, pp. 411–417, 1990.

[18] S. Bergman and W. S. Melvin, "Operative and nonoperative management of pancreatic pseudocysts," *Surgical Clinics of North America*, vol. 87, no. 6, pp. 1447–1460, 2007.

[19] V. V. Gumaste and C. S. Pitchumoni, "Pancreatic pseudocyst," *Gastroenterologist*, vol. 4, no. 1, pp. 33–43, 1996.

[20] J. M. Morton, A. Brown, J. A. Galanko, J. A. Norton, I. S. Grimm, and K. E. Behrns, "A national comparison of surgical versus percutaneous drainage of pancreatic pseudocysts: 1997–2001," *Journal of Gastrointestinal Surgery*, vol. 9, no. 1, pp. 15–21, 2005.

[21] R. Heider, A. A. Meyer, J. A. Galanko, and K. E. Behrns, "Percutaneous drainage of pancreatic pseudocysts is associated with a higher failure rate than surgical treatment in unselected patients," *Annals of Surgery*, vol. 229, no. 6, pp. 781–789, 1999.

[22] H. Spivak, J. R. Galloway, J. R. Amerson et al., "Management of pancreatic pseudocysts," *Journal of the American College of Surgeons*, vol. 186, no. 5, pp. 507–511, 1998.

[23] A. E. Park and B. T. Heniford, "Therapeutic laparoscopy of the pancreas," *Annals of Surgery*, vol. 236, no. 2, pp. 149–158, 2002.

[24] T. Mori, N. Abe, M. Sugiyama, and Y. Atomi, "Laparoscopic pancreatic cystgastrostomy," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 9, no. 5, pp. 548–554, 2002.

[25] P. Hauters, J. Weerts, B. Navez et al., "Laparoscopic treatment of pancreatic pseudocysts," *Surgical Endoscopy and Other Interventional Techniques*, vol. 18, no. 11, pp. 1645–1648, 2004.

[26] A. Hindmarsh, M. P. N. Lewis, and M. Rhodes, "Stapled laparoscopic cystgastrostomy: a series with 15 cases," *Surgical Endoscopy and Other Interventional Techniques*, vol. 19, no. 1, pp. 143–147, 2005.

[27] A. Dávila-Cervantes, F. Gómez, C. Chan et al., "Laparoscopic drainage of pancreatic pseudocysts," *Surgical Endoscopy and Other Interventional Techniques*, vol. 18, no. 10, pp. 1420–1426, 2004.

[28] W. H. Nealon, M. Bhutani, T. S. Riall, G. Raju, O. Ozkan, and R. Neilan, "A unifyoing concept: pancreatic ductal anatomy both predicts and determines the major complications resulting from pancreatitis," *Journal of the American College of Surgeons*, vol. 208, no. 5, pp. 790–799, 2009.

[29] F. W. Henriksen and S. Hancke, "Percutaneous cystogastrostomy for chronic pancreatic pseudocyst," *British Journal of Surgery*, vol. 81, no. 10, pp. 1525–1528, 1994.

[30] R. P. Davies, M. R. Cox, T. G. Wilson, R. C. Bowyer, R. T. A. Padbury, and J. Toouli, "Percutaneous cystogastrostomy with a new catheter for drainage of pancreatic pseudocysts and fluid collections," *CardioVascular and Interventional Radiology*, vol. 19, no. 2, pp. 128–131, 1996.

[31] B. A. Sacks, J. J. Greenberg, D. H. Porter et al., "An internalized double-J catheter for percutaneous transgastric cystogastrostomy," *American Journal of Roentgenology*, vol. 152, no. 3, pp. 523–526, 1989.

[32] L. C. Hookey, S. Debroux, M. Delhaye, M. Arvanitakis, O. Le Moine, and J. Devière, "Endoscopic drainage of pancreatic-fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes," *Gastrointestinal Endoscopy*, vol. 63, no. 4, pp. 635–643, 2006.

[33] L. Weckman, M. L. Kylänpää, P. Puolakkainen, and J. Halttunen, "Endoscopic treatment of pancreatic pseudocysts," *Surgical Endoscopy and Other Interventional Techniques*, vol. 20, no. 4, pp. 603–607, 2006.

[34] M. Giovannini, C. Pesenti, A. L. Rolland, V. Moutardier, and J. R. Delpero, "Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope," *Endoscopy*, vol. 33, no. 6, pp. 473–477, 2001.

[35] C. V. Lopes, C. Pesenti, E. Bories, F. Caillol, and M. Giovannini, "Endoscopic-ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts and abscesses," *Scandinavian Journal of Gastroenterology*, vol. 42, no. 4, pp. 524–529, 2007.

[36] R. Sadik, E. Kalaitzakis, A. Thune, J. Hansen, and C. Jönson, "Eus-guided drainage is more successful in pancreatic pseudocysts compared with abscesses," *World Journal of Gastroenterology*, vol. 17, no. 4, pp. 499–505, 2011.

[37] T. B. Gardner, N. Coelho-Prabhu, S. R. Gordon et al., "Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series," *Gastrointestinal Endoscopy*, vol. 73, no. 4, pp. 718–726, 2011.

[38] E. J. Balthazar, "Acute pancreatitis: assessment of severity with clinical and CT evaluation," *Radiology*, vol. 223, no. 3, pp. 603–613, 2002.

[39] D. E. Morgan, T. H. Baron, J. K. Smith, M. L. Robbin, and P. J. Kenney, "Pancreatic fluid collections prior to intervention: evaluation with MR imaging compared with CT and US," *Radiology*, vol. 203, no. 3, pp. 773–778, 1997.

[40] P. Fockens, T. G. Johnson, H. M. Van Dullemen, K. Huibregtse, and G. N. J. Tytgat, "Endosonographic imaging of pancreatic pseudocysts before endoscopic transmural drainage," *Gastrointestinal Endoscopy*, vol. 46, no. 5, pp. 412–416, 1997.

[41] P. V. J. Sriram, A. J. Kaffes, G. V. Rao, and D. N. Reddy, "Endoscopic ultrasound-guided drainage of pancreatic pseudocysts complicated by portal hypertension or by intervening vessels," *Endoscopy*, vol. 37, no. 3, pp. 231–235, 2005.

[42] S. Varadarajulu, J. D. Christein, A. Tamhane, E. R. Drelichman, and C. M. Wilcox, "Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos)," *Gastrointestinal Endoscopy*, vol. 68, no. 6, pp. 1102–1111, 2008.

[43] D. H. Park, S. S. Lee, S. H. Moon et al., "Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial," *Endoscopy*, vol. 41, no. 10, pp. 842–848, 2009.

[44] M. Arvanitakis, M. Delhave, M. A. Bali et al., "Pancreatic fluid collections: a randomised control trial regarding stent removal after endoscopic transmural drainage," *Gastrointestinal Endoscopy*, vol. 65, no. 4, pp. 609–619, 2007.

[45] J. M. Trevino, A. Tamhane, and S. Varadarajulu, "Successful stenting in ductal disruption favorably impacts treatment outcomes in patients undergoing transmural drainage of peripancreatic fluid collections," *Journal of Gastroenterology and Hepatology*, vol. 25, no. 3, pp. 526–531, 2010.

[46] S. Seewald, B. Brand, S. Groth et al., "Endoscopic sealing of pancreatic fistula by using N-butyl-2-cyanoacrylate," *Gastrointestinal Endoscopy*, vol. 59, no. 4, pp. 463–470, 2004.

[47] G. A. Cote, M. Ansstas, S. A. Edmundowicz, S. Jonnalagadda, D. Mullady, and R. R. Azar, "Endoscopic treatment of pancreatic fluid collections: role for debridment with a nasocystic drain at the time of initial endoscopy," *Gastrointestinal Endoscopy*, vol. 69, no. 5, pp. AB332–AB333, 2009.

[48] S. Varadarajulu, J. D. Christein, and C. M. Wilcox, "Frequency of complications during EUS-guided drainage of pancreatic fluid collections in 148 consecutive patients," *Journal of Gastroenterology and Hepatology*, vol. 26, no. 10, pp. 1504–1508, 2011.

[49] J. M. Trevino and S. Varadarajulu, "Initial experience with the prototype forward-viewing echoendoscope for therapeutic interventions other than pancreatic pseudocyst drainage," *Gastrointestinal Endoscopy*, vol. 69, no. 2, pp. 361–365, 2009.

[50] R. P. Voermans, P. Eisendrath, M. J. Bruno, O. Le Moine, J. Devière, and P. Fockens, "Initial evaluation of a novel prototype forward-viewing US endoscope in transmural drainage of pancreatic pseudocysts," *Gastrointestinal Endoscopy*, vol. 66, no. 5, pp. 1013–1017, 2007.

[51] J. P. Talreja, V. M. Shami, J. Ku, T. D. Morris, K. Ellen, and M. Kahaleh, "Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stentsv," *Gastrointestinal Endoscopy*, vol. 68, no. 6, pp. 1199–1203, 2008.

[52] S. Belle, P. Collet, S. Post, and G. Kaehler, "Temporary cyst-gastrostomy with self-expanding metallic stents for pancreatic necrosis," *Endoscopy*, vol. 42, no. 6, pp. 493–495, 2010.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 503098, 5 pages
doi:10.1155/2012/503098

*Clinical Study*

# The Efficacy and Safety of Endoscopic Ultrasound-Guided Celiac Plexus Neurolysis for Treatment of Pain in Patients with Pancreatic Cancer

**Anna Wiechowska-Kozłowska,[1] Klaudiusz Boer,[1] Maciej Wójcicki,[2,3] and Piotr Milkiewicz[1,3]**

[1] *Department of Endoscopy, Ministry of Internal Affairs Hospital, Ul. Jagielonska 44, 70-362 Szczecin, Poland*
[2] *Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, M. Curie Hospital, 71-455 Szczecin, Poland*
[3] *The Liver Unit, Pomeranian Medical University, 70-111 Szczecin, Poland*

Correspondence should be addressed to Anna Wiechowska-Kozłowska, annamwk@wp.pl

Received 23 August 2011; Accepted 23 October 2011

Academic Editor: Fauze Maluf-Filho

Copyright © 2012 Anna Wiechowska-Kozłowska et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Introduction.* Celiac plexus neurolysis is used in pain management of patients with advanced and unresectable pancreatic cancer. We retrospectively analyzed efficacy and safety of endoscopic ultrasound- (EUS-) guided celiac plexus neurolysis in patients treated in our unit. *Methods.* Twenty nine subjects with unresectable pancreatic cancer and severe pain despite pharmacological treatment underwent EUS-guided celiac plexus neurolysis with 98% ethanol. Patients scored their pain according to a 0–10 point scale and were interviewed 1-2 weeks and 2-3 months after the procedure. *Results.* Twenty five (86%) patients reported improvement in their pain at 1-2 weeks following the procedure. Of these, 7 (24%) reported substantial improvement (decrease in pain by more than 50%) and 4 (14%) complete disappearance of pain. Pain relief was still present in 76% of patients after 2-3 months. Treatment-related side effects included hypotonia in 1 patient, severe pain immediately postprocedure in 2 patients, and short episodes of diarrhea in 3 patients. *Conclusion.* Endoscopic ultrasound- (EUS-) guided celiac plexus neurolysis is a safe and effective treatment of severe pain from advanced pancreatic cancer.

## 1. Introduction

Treatment of pain in patients with advanced pancreatic cancer is one of the most important goals of palliative care. It is estimated that pain occurs in 80–85% of patients with unresectable pancreatic tumors [1, 2]. Despite the improved effectiveness of pharmacotherapy, treatment of severe pain from inoperable pancreatic cancer remains an important clinical issue. Conventional drugs do not provide adequate analgesia and many adverse effects are also seen with opioids. Therefore, interventional or surgical methods of pain treatment are attractive alternatives in such patients [3, 4]. For example, celiac plexus neurolysis destroys the plexus that plays a crucial role in transmitting pain of pancreatic origin. The procedure involves direct injection of a chemical agent, a solution of alcohol or glycol, into the celiac plexus ganglia [1–5].

Percutaneous celiac plexus neurolysis was first performed by Kapisa in 1914. Since then, it has been performed by many techniques for access, and with a variety of chemicals [6]. Percutaneous neurolysis under radiologic guidance is the most commonly applied. The needle is first introduced into the region of the celiac plexus under fluoroscopic guidance. A mixture of alcohol or phenol with the addition of contrast medium is administered. A limitation of this method is the lack of direct visualization of the celiac trunk, resulting in only an approximation of location of the puncture site. As a result, the risk of vascular or neurologic complications is higher when accessed from the lumbar region. CT-guided neurolysis is a modification with similar limitations as fluoroscopy [4].

Intraoperative celiac plexus neurolysis during surgery is seldomly used because in most cases, the diagnosis of unresectable pancreatic cancer is established without the need for

laparotomy. Such patients usually require endoscopic stenting of the biliary tree and adequate pain control [3].

Endoscopic ultrasound- (EUS-) guided celiac plexus neurolysis was first described by Wiersema in 1996 [7]. The authors visualized the celiac plexus with EUS and then performed neurolysis via the transgastric route, achieving results comparable to percutaneous neurolysis. In the following 10 years, the endoscopic technique has been accepted as an alternative method of celiac plexus neurolysis, and is now applied in many centers [8–21].

We aimed to assess the safety and efficacy of EUS-guided celiac plexus neurolysis for pain management in patients with advanced and unresectable pancreatic cancer. This is the first reported experience with this technique in Poland.

## 2. Methods

Thirty two patients diagnosed with advanced and unresectable pancreatic adenocarcinoma were selected as candidates for EUS-guided celiac plexus neurolysis. The indication in all cases was severe abdominal pain requiring the use of opioids. Neurolysis was not performed in 3 patients because of the inability to visualize the celiac plexus with EUS due to atypical anatomy. Thus, between May 2008 and May 2009, 29 patients ultimately underwent EUS-guided celiac plexus neurolysis. All procedures were performed by 2 gastroenterologists (A. Wiechowska-Kozłowska and P. Milkiewicz) with extensive experience in EUS (both performed more than 1000 examinations). The linear type EUS endoscope (Olympus GF-UCT 160-OL5) with "spray" needles (ECHO 20 CPN, Cook Ireland) was used in all cases.

Fourteen (48%) men and 15 (52%) women, mean age 62 (range 33–81) years, underwent the procedure. The diagnosis of advanced and unresectable cancer of the pancreatic head ($n = 13$; 45%), the head and body ($n = 3$, 10%), the body ($n = 9$; 31%), and the tail of the pancreas ($n = 4$; 14%) was made based on abdominal computed tomography and EUS. Tumors were considered unresectable when distant metastases and/or locally advanced tumors were present (i.e., tumor infiltration of the celiac trunk, superior mesenteric artery or vein, and the retroperitoneum and periaortic area). Eighteen (56%) patients had advanced local disease and 14 (44%) were diagnosed with metastasis disease. Adenocarcinoma of the pancreas was confirmed in all patients with fine-needle aspiration biopsy under percutaneous ($n = 11$) or endoscopic ($n = 18$) ultrasound guidance. 11 (38%) patients underwent palliative chemotherapy with gemcitabine.

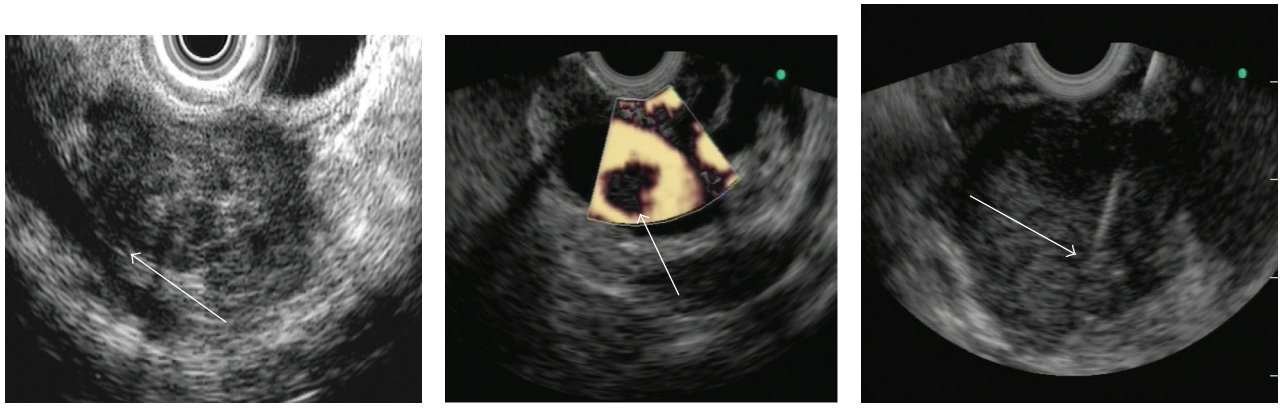
Contraindications to the procedure included coagulation disorders (INR > 1.5), platelet count <50,000, or previous disease and treatment of the upper gastrointestinal tract that would make endoscopic access impossible. These contraindications were not present in included patients. After discussing the principles of the procedure, its consequences, the possibility of partial or no reduction of pain, and complications, informed consent was obtained in all patients.

The procedure was performed in the left lateral position after intravenous administration of 2.5 mg of midazolam. Clinical parameters such as heart rate, blood pressure, oxygen saturation, and ECG were routinely monitored during the procedure. The antibiotics prophylactic was not used. The first stage was assessment of tumor location, confirming its advanced and unresectable stage (Figure 1). Anatomic landmarks (celiac trunk and aorta visible from the lesser curvature of the stomach) were visualized first. The needle was introduced directly into the celiac plexus and surrounding area under direct visualization of the vessels with the Doppler mode. The aspiration test was routinely performed (2 mL of saline followed by aspiration), in order to exclude intravascular puncture. A small amount of analgesic (2 mL of 2% lidocaine) was administered, followed by injection of 98% alcohol solution (Figure 2). This was performed three times: twice on either side of the aorta and 1 directy to the celiac plexus. Altogether, 3 punctures of the celiac plexus were performed with the total application of 6 mL of lidocaine and 20 mL of 98% alcohol. During alcohol injection, a typical hyperechogenic shadow was observed and patients experienced exacerbation of pain in this region despite administration of analgesia.

After the procedure, patients were observed for 24 hours, with clinical evaluation and measurement of vital signs. 27 patients were discharged on the next day while 2 patients remained in the hospital for 2 days due to exacerbating pain. All the patients were instructed to attempt to gradually discontinue the use of pain medication. The assessment of efficacy and related morbidity was based upon a survey carried out prior to the procedure; on day 1, 1-2 weeks, and 2-3 months following the procedure. The effectiveness of treatment was assessed based on the 11-point pain scale (0 points, no pain; 10 points, maximal pain). The reduction or discontinuation of pain medication was also considered. The incidence and types of complications were evaluated by clinical evaluation during and after the procedure, and by surveying all patients on the degree of pain, changes in bowel movements, neurological disturbances, and other clinical symptoms. Analysis was retrospective and was based on the hospital and endoscopy suit charts.

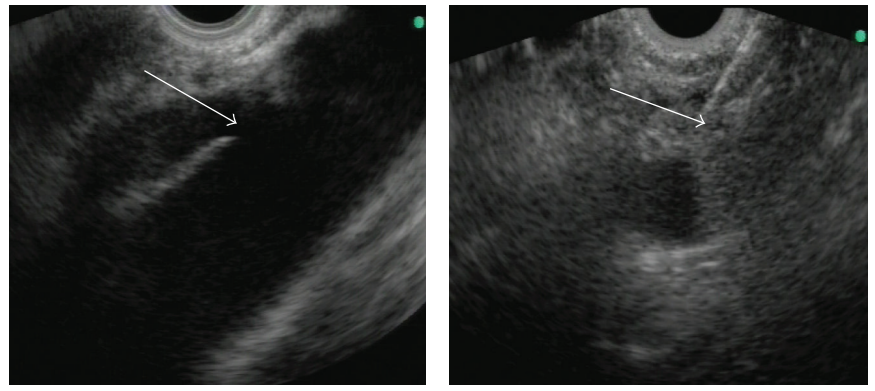
## 3. Results

An average pain score of 7.9 (range 6–10) was observed in all patients prior to the procedure, requiring the use of nonsteroid anti-inflammatory drugs and narcotic analgesics. One-two weeks following treatment, full pain resolution (0-1 points) was observed in 4 (14%) patients, who completely stopped taking pain medications. Seven (24%) patients had a reduction in pain by more than 50% while 9 (31%) patients had a reduction in pain by 30–50%. In 5 (17%) patients, a small improvement (reduction of pain by <30%) was found. In 4 (14%) patients, pain remained unchanged. Two-three months following the procedure, 4 patients died due to disease progression. These included 1 patient in whom neurolysis was fully effective, 1 patient with pain reduction by 30–50%, 1 patient with pain reduction of <30%, and 1 in whom the procedure was ineffective. Subsequent assessment (2-3 months postprocedure) was performed in 25 patients. Two (8%) patients were pain free and 5 (20%) patients maintained pain relief of more than 50%. Seven (28%)



(a) (b) (c)

Figure 1: Images of endoscopic ultrasound in advanced pancreatic cancer: (a) tumor invading the vasculature, (b) portal vein thrombosis in advanced pancreatic cancer, (c) fine-needle aspiration biopsy of the pancreatic tumor.



(a) (b)

Figure 2: Endoscopic ultrasound-guided celiac plexus neurolysis: (a) typical location of the plexus with the celiac trunk (arrow) at the aorta, (b) puncture of the celiac plexus with administration of alcohol under endoscopic ultrasound guidance.

patients reported a 30–50% pain reduction while 5 (20%) and 6 (24%) patients had slight (<30%) or no improvement, respectively (Figure 3).

A short but significant episode of hypotension requiring intervention occurred in 1 patient immediately after procedure. This normalized after treatment with an i.v. saline. Two patients reported a temporary but significant increase in pain immediately after procedure, requiring analgesics in increasing doses during the hospital stay. Both patients were discharged home after two days. One patient was pain free at discharge and 1 had a significant (>50%) reduction in pain. Three patients reported an increased frequency of bowel movements (4-5 stools daily) although no chronic diarrhea was observed in any patient.

## 4. Discussion

Celiac plexus neurolysis for pain management has been used for almost 100 years in patients with advanced abdominal malignancy [6]. The procedure is performed either or intraoperatively, with varying efficacy. According to the metaanalysis of 24 studies, including 1145 patients who underwent the percutaneous technique (mostly from the posterior approach), pain reduction was observed in 90% and 70–90% of patients at 2 weeks and 3 months following the procedure, respectively [4]. Patients who underwent percutaneous neurolysis experienced significant pain relief, enabling reduction of analgesic doses and improved quality of life [2, 14–16, 20]. However, serious neurological complications were observed in 2% of patients (paralysis, paresis, paresthesia of the lower extremities, pneumothorax, pleural empyema) [2, 4, 14, 16, 21]. Intraoperative abdominal or thoracoscopic celiac plexus destruction by direct alcohol injection or surgical transection of ganglia have been applied with an efficacy comparable to the percutaneous technique [3].

The ideal procedure should preferably be highly efficacious, with low complication rates, and the least invasive. Proper visualization of the celiac plexus followed by precise administration of proper pharmacological agents all appear

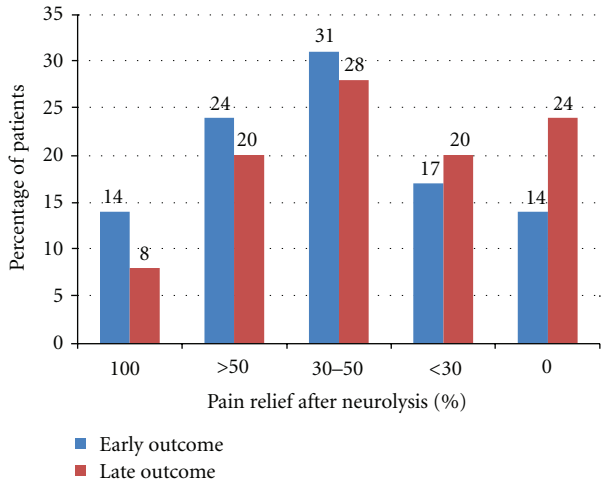



Figure 3: Efficacy of endoscopic ultrasound-guided celiac plexus neurolysis: (i) early outcome (1-2 weeks after treatment), (ii) late outcome (2-3 months after treatment).

to be fundamental prerequisites for successful and safe neurolysis. Alcohol ablation is approximately twice as effective, compared with ablation using phenol [19]. Moreover, alcohol ablation is not associated with mutagenesis [19]. The introduction of EUS in the 1980s for imaging abdominal organs, including the pancreas, made it possible to precisely visualize the celiac plexus. The application of interventional endoscopy in the 1990s permitted the performance of controlled biopsies, drainage, or injection of drugs into tissues surrounding the stomach or duodenum under ultrasonographic guidance. Such procedures were previously performed surgically or percutaneously only.

Wiersema was pioneered celiac plexus neurolysis under EUS guidance in 1996, demonstrating high efficacy in patients with advanced abdominal malignancy (significant pain reduction in 79–88%) with low morbidity [7]. Subsequent studies confirmed these findings, showing a short-term success rate of 78%, which decreased to 30% after 12 weeks of follow-up, in particular, when no chemotherapy was applied [11].

In our study, the effectiveness observed early following treatment appeared lower, since significant pain reduction was reported in 69% of patients, while 31% had slight or no improvement. Late response to treatment, assessed 2-3 months following the procedure, was significant in a relatively large (56%) number of patients.

The inability to completely control the pain in all patients as well as reduction of pain relief over time was observed in several studies [5, 8–10, 13, 20]. The reason why alcohol injection into the plexus did not completely eliminate pain may be explained by pathologic studies of the plexus following treatment [19]. Alcohol injection resulted in only partial destruction, and degeneration and fibrosis of nerve fibers and ganglia [19]. As a result, continued transmission of pain stimuli is still possible, although reduced in most patients [19]. The site of injection is also important and should preferably be performed at the most complex, ganglia-rich location within the celiac plexus. Bilateral injection (on both sides of the plexus) is more effective compared with single injection in the center of the plexus [17]. In order to destroy as many nerves and ganglia as possible, we routinely applied the triple injection method to the center of the plexus and bilaterally. This is different, compared with other reports that describe a single injection of a standard dose (20 mL) of the drug [11, 12, 16]. The prospective studies comparing different injection methods and applying different types of needles have a potential to explain differences in effectiveness of this procedure. In view of its limited efficacy, any efforts towards its improvement appear justified, including increasing the dosage and changing the mode of injection. Repeated procedures may also be of value in some cases, as is injection of steroids into the plexus in patients with chronic pancreatitis.

Optimal timing for EUS-guided celiac plexus neurolysis is controversial. As in our study, it may be applied in a very advanced stage in patients requiring narcotic analgesia. Some authors, however, recommend the performance of neurolysis early in the course of disease, before pharmacotherapy with opioids has even been started [1, 16, 17]. In such cases, efficacy and safety may be increased.

Our study shows that EUS-guided celiac plexus neurolysis is associated with a very low risk of complications. There was no significant treatment-related morbidity observed in any patients.

## 5. Conclusion

EUS-guided celiac plexus neurolysis is a safe and effective treatment of severe pain in patients with advanced pancreatic cancer. It provides significant short-term pain relief in the majority of patients. However, its efficacy is limited, indicating the need for further studies aimed at improving the method.

## References

[1] J. C. Moore and D. G. Adler, "Celiac plexus neurolysis for pain relief in pancreatic cancer," *Journal of Supportive Oncology*, vol. 7, no. 3, pp. 83–90, 2009.

[2] B. M. Yan and R. P. Myers, "Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer," *American Journal of Gastroenterology*, vol. 102, no. 2, pp. 430–438, 2007.

[3] T. Cieniawa, J. Wordliczek, and J. Dobrogowski, "Skuteczność śródoperacyjnej neurodestrukcji splotu trzewnego z zastosowaniem neurolizy chemicznej u chorych z nowotworami zlokalizowanymi w nadbrzuszu," *Polska Medycyna Paliatywna*, vol. 3, pp. 342–352, 2004.

[4] E. Eisenberg, D. B. Carr, and T. C. Chalmers, "Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis," *Anesthesia and Analgesia*, vol. 80, no. 2, pp. 290–295, 1995.

[5] E. Polati, G. Finco, L. Gottin, C. Bassi, P. Pederzoli, and S. Ischia, "Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer," *British Journal of Surgery*, vol. 85, no. 2, pp. 199–201, 1998.

[6] M. Kappis, "Erfahrungen mit local anasthesie bie bauchoperationen," *Vehr Dtsch Gesellsch Chir*, vol. 43, pp. 87–89, 1914.

[7] M. J. Wiersema and L. M. Wiersema, "Endosonography-guided celiac plexus neurolysis," *Gastrointestinal Endoscopy*, vol. 44, no. 6, pp. 656–662, 1996.

[8] M. Abedi and A. M. Zfass, "Endoscopic ultrasound-guided (neurolytic) celiac plexus block," *Journal of Clinical Gastroenterology*, vol. 32, no. 5, pp. 390–393, 2001.
[9] A. Chak, "What is the evidence for EUS-guided celiac plexus block/neurolysis?" *Gastrointestinal Endoscopy*, vol. 69, no. 2, pp. S172–S173, 2009.
[10] D. Collins, I. Penman, G. Mishra, and P. Draganov, "EUS-guided celiac block and neurolysis," *Endoscopy*, vol. 38, no. 9, pp. 935–939, 2006.
[11] N. T. Gunaratnam, A. V. Sarma, I. D. Norton, and M. J. Wiersema, "A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain," *Gastrointestinal Endoscopy*, vol. 54, no. 3, pp. 316–324, 2001.
[12] M. J. Levy and M. J. Wiersema, "EUS-guided celiac plexus neurolysis and celiac plexus block," *Gastrointestinal Endoscopy*, vol. 57, no. 7, pp. 923–930, 2003.
[13] M. J. Levy, M. D. Topazian, M. J. Wiersema et al., "Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block," *American Journal of Gastroenterology*, vol. 103, no. 1, pp. 98–103, 2008.
[14] A. J. Michaels and P. V. Draganov, "Endoscopic ultrasonography guided celiac plexus neurolysis and celiac plexus block in the manangement of pain due to pancreatic cancer and chronic pancreatitis," *World Journal of Gastroenterology*, vol. 13, no. 26, pp. 3575–3580, 2007.
[15] I. D. Penman and T. Rösch, "EUS 2008 Working Group document: evaluation of EUS-guided celiac plexus neurolysis/block," *Gastrointestinal Endoscopy*, vol. 69, pp. 28–31, 2009.
[16] S. R. Puli, J. B. K. Reddy, M. L. Bechtold, M. R. Antillon, and W. R. Brugge, "EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review," *Digestive Diseases and Sciences*, vol. 54, no. 11, pp. 2330–2337, 2009.
[17] A. V. Sahai, V. Lemelin, E. Lam, and S. C. Paquin, "Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness," *American Journal of Gastroenterology*, vol. 104, no. 2, pp. 326–329, 2009.
[18] N. Schmulewitz and R. Hawes, "EUS-guided celiac plexus neurolysis-technique and indication," *Endoscopy*, vol. 35, no. 8, pp. S49–S53, 2003.
[19] Q. N. H. Tran, S. Urayama, and F. J. Meyers, "Endoscopic ultrasound-guided celiac plexus neurolysis for pancreatic cancer pain: a single-institution experience and review of the literature," *Journal of Supportive Oncology*, vol. 4, no. 9, pp. 460–462, 2006.
[20] S. Varadarajulu and M. B. Wallace, "Applications of endoscopic ultrasonography in pancreatic cancer," *Cancer Control*, vol. 11, no. 1, pp. 15–22, 2004.
[21] J. H. Vranken, W. W. A. Zuurmond, F. J. Van Kemenade, and M. Dzoljic, "Neurohistopathologic findings after a neurolytic celiac plexus block with alcohol in patients with pancreatic cancer pain," *Acta Anaesthesiologica Scandinavica*, vol. 46, no. 7, pp. 827–830, 2002.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 395345, 5 pages
doi:10.1155/2012/395345

*Clinical Study*

# Correlation between Endosonographic and Doppler Ultrasound Features of Portal Hypertension in Patients with Cirrhosis

**A. Wiechowska-Kozłowska,[1] K. Zasada,[2] M. Milkiewicz,[3] and P. Milkiewicz[4,5]**

[1] *Department of Endoscopy, Ministry of Internal Affairs Hospital, 70-382 Szczecin, Poland*
[2] *Department of Radiology, M. Curie Hospital, Szczecin, Poland*
[3] *Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Szczecin, Poland*
[4] *Department of Hepatology and Liver Transplantation, M. Curie Hospital, Szczecin, Poland*
[5] *Liver Unit, Pomeranian Medical University, SPSK2, Szczecin, Poland*

Correspondence should be addressed to A. Wiechowska-Kozłowska, annamwk@wp.pl

Received 22 August 2011; Accepted 9 October 2011

Academic Editor: Fauze Maluf-Filho

Copyright © 2012 A. Wiechowska-Kozłowska et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Purpose*. Endoscopic ultrasound (EUS) permits the detailed visualization of clinically significant features of portal hypertension; however, it is an invasive procedure that is not widely available. The aim of this cross-sectional study was to determine whether a correlation exists between the features of portal hypertension detected using both Doppler ultrasound and EUS in subjects with liver cirrhosis. *Materials and Methods*. Analyzed cohort included 42 patients who underwent a detailed Doppler ultrasound focusing on the parameters of blood flow in the portal/splenic vein as well as an endoscopic/EUS procedure that included the assessment of the size and localization of "deep" varices. *Results*. The size of "deep" oesophageal varices detected with EUS exhibited no correlation with the parameters assessed by Doppler ultrasound. However, the size of the "deep" gastric varices detected using EUS correlated with the time averaged maximum velocity ($T_{max}$ as well as $V_{min}$, $V_{max}$) for the portal vein using Doppler ultrasound and exhibited a correlation with the $V_{max}$ and $T_{max}$ for the splenic vein. No significant correlation was determined between the diameter of the azygous vein and the thickness of the gastric wall when seen on EUS versus the parameters measured with Doppler ultrasound. *Conclusion*. EUS provides important information regarding the features of portal hypertension, and in the case of "deep" oesophageal varices exhibits a limited correlation with the parameters detected by Doppler ultrasound. Thus, despite its invasiveness, EUS is a method that provides a reliable and unique assessment of the features of portal hypertension in patients with liver cirrhosis.

## 1. Background

Endosonography (EUS), a combination of both endoscopy and ultrasound, is a helpful tool for the assessment of portal hypertension in patients with cirrhosis [1–3]. However, gastroduodenoscopy remains the method of choice in the diagnosis of varices even though it only allows for the detection of varices of extrinsic (superficial) circulation of the oesophagus and stomach. EUS has a significantly higher sensitivity regarding the diagnosis of portal hypertension in comparison to gastroduodenoscopy and permits visualization of collaterals belonging to intrinsic (deep) venous circulation, which, if large, can significantly increase the risk of variceal bleeding [4–6]. Unfortunately EUS is an invasive procedure and remains not widely available [7–11]. On the other hand, Doppler ultrasound is a noninvasive method that provides precise information regarding blood flow in major vessels of the abdomen [12]. Doppler ultrasound is frequently used for the assessment of this aspect of portal hypertension. However, the potential relationship between the EUS and Doppler ultrasound results concerning portal hypertension have yet to be studied. The aim of this cross-sectional study was to establish whether the features of increased portal pressure detected with EUS show any correlation with the findings detected using Doppler ultrasound.

Table 1: Demographic and clinical data of examined patients with liver cirrhosis ($n = 42$).

| | |
|---|---|
| Age years (mean ± SD) | 54 ± 12 |
| Gender (M/F) | 23/19 |
| Etiology: | |
| (i) Viral and alcohol ($n$, %) | 29 (69) |
| (ii) Autoimmune ($n$, %) | 9 (21) |
| (iii) Cryptogenic ($n$, %) | 4 (10) |
| Child A ($n$, %) | 15 (36) |
| Child B ($n$, %) | 23 (55) |
| Child C ($n$, %) | 4 (9) |

## 2. Materials and Methods

Forty-two patients with cirrhosis referred to a tertiary liver centre were included in this study. The diagnosis was established on the grounds of liver biopsy and/or typical clinical features and imaging studies. At the time of EUS the following demographic and laboratory data were collected: age, gender, etiology of liver disease, liver biochemistry, platelet count, and Child-Turcotte-Pugh score (CTP score).

All patients signed an informed consent form for the procedure. All examinations were done by two experienced endoscopists (AWK and PM), who had performed more than a thousand EUS procedures each. Endoscopy and EUS were performed as a single procedure using the GF-UMQ-130 echoendoscope (Olympus, Tokyo, Japan) at 7.5 and 12 MHz. Endoscopic features of portal hypertension were assessed first, followed by a detailed endosonographic examination of the stomach and oesophagus. The following data as part of the endoscopic examination were recorded: the presence and grade of oesophageal varices and the presence and grade of gastric varices. Oesophageal varices were graded as 0 = absent, small (<5 mm), and large (>5 mm) according to the most recent American Association for the Study of Liver Diseases (AASLD) guidelines. Gastric varices were graded as 0 = absent, 1 = small (<5 mm), or 2 = large (>5 mm).

The following data were collected during EUS examination: oesophageal and gastric varices and oesophageal and gastric collateral veins ("deep varices"). A grade scale of three proposed by us previously [3, 11] was used for the assessment of "deep" varices depending on their size: grade 0: absent, grade 1: small <5 mm, grade 2: large >5 mm. The diameter of the azygos vein was measured within 2 cm above the level of the Z line, and the thickness of the gastric wall was assessed in the gastric cardia region as already described [3].

Doppler ultrasound analysis was performed using the Acuson XP unit (Acuson Mountain view, Calif., US) with a curved array 3.5–5 MHz transducer, and gray scale and color Doppler images were obtained. During the color Doppler examinations a low-volume flow filter with a high degree of motion discrimination was applied. Diameter, patency, and flow direction in the portal and splenic vein were assessed. This analysis included minimal ($V_{min}$) and maximal ($V_{max}$) flow in both analyzed vessels as well as $T_{max}$ (time averaged maximum velocity).

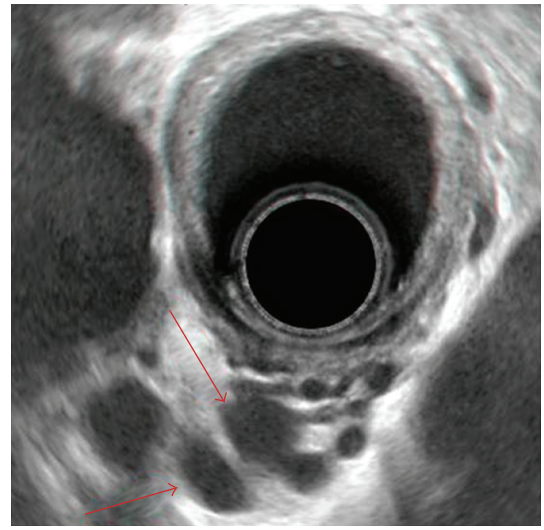


Figure 1: "Deep" oesophageal varices (red arrows) on endosonographic examination.

Statistical analysis was performed with ANOVA, chi-square, Yates, Fisher, and correlation coefficients using the StatView Program. $P$ values < 0.05 were considered to be statistically significant.

## 3. Results

Basic demographic and clinical data on study subjects are summarized in Table 1.

The size of the oesophageal varices exhibited a correlation with the diameter of the portal vein. In patients with grade 2 varices, this diameter was 13.6 ± 2.6 mm as compared to 11.1 ± 2.5 mm ($P = 0.008$) in subjects who had no varices, and 11.4±2.4 mm ($P = 0.04$) in subjects with grade 1 varices. No statistically significant correlation was seen between the size of oesophageal varices and $V_{min}$, $V_{max}$, Tamx of both portal and splenic veins. Regarding the gastric varices seen on endoscopy, upon comparison of patients with grade 2 and grade 0 varices, the size showed a correlation with $V_{min}$ (17.0 ± 8.7 mm versus 11.8 ± 4.4 mm, $P = 0.004$).

Data collected regarding the relationship between the grade of "deep" varices and the parameters of Doppler ultrasound are shown in Table 2. No statistically significant correlation between the size of "deep" oesophageal varices and the parameters recorded on Doppler ultrasound was seen. However, the size of "deep" gastric varices showed a correlation with $V_{min}$, $V_{max}$, and Tamx for the portal vein.

The correlation-coefficient analysis between the diameter of the azygous vein and the flow parameters in the portal and splenic veins showed no statistically significant correlation. Similarly, no significant correlation was seen between the thickness of the gastric wall and these parameters. These data are summarized in Table 3. A typical endosonographic image of large "deep" gastric varices is shown in Figure 1.

Table 2: Summary of Doppler ultrasound findings in relation to the size of "deep" oesophageal and gastric varices in the liver cirrhosis patients ($n = 42$). Data presented as mean ± SD. [a]$P = 0.05$; *$P < 0.05$; **$P < 0.01$ versus grade 0 varices.

| Doppler US | "Deep" oesophageal varices size | | | "Deep" gastric varices size | | |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 0 | 1 | 2 |
| $V_{min}$ portal | 12.7 ± 5.4 | 13 ± 6.3 | 14.1 ± 7.1 | 10.0 ± 3.0 | *16.1 ± 7.2 | 14.1 ± 6.8 |
| $V_{max}$ portal | 18.3 ± 5.3 | 20.6 ± 9.4 | 21.2 ± 10.2 | 14.8 ± 4.3 | **25.0 ± 9.7 | *21.3 ± 8.8 |
| $T_{max}$ portal | 14.8 ± 5.1 | 17.1 ± 9.0 | 17.7 ± 9.0 | 11.8 ± 3.2 | **20.6 ± 7.9 | *17.9 ± 9.0 |
| $V_{min}$ splenic | 14.6 ± 5.4 | 17.6 ± 9.6 | 16.9 ± 9.7 | 13.2 ± 5.7 | 17.7 ± 9.3 | 17.9 ± 9.5 |
| $V_{max}$ splenic | 21.8 ± 6.4 | 26.2 ± 14.4 | 25.1 ± 10.4 | 19.4 ± 5.8 | [a]27.6 ± 10.4 | [a]26.1 ± 12.3 |
| $T_{max}$ splenic | 17.3 ± 4.7 | 22.3 ± 11.0 | 20.1 ± 10.1 | 15.4 ± 5.0 | [a]22.2 ± 8.9 | [a]21.6 ± 10.7 |

Table 3: Correlation coefficient between the diameter of azygous vein/thickness of gastric wall and flow parameters examined in the patients with liver cirrhosis ($n = 42$).

| feature | Coefficient for correlation | $P$ value |
|---|---|---|
| Azygous vein diameter versus $V_{min}$ portal | 0.085 | 0.62 |
| Azygous vein diameter versus $V_{max}$ portal | 0.170 | 0.32 |
| Azygous vein diameter versus $T_{max}$ portal | 0.162 | 0.34 |
| Azygous vein diameter versus $V_{min}$ splenic | −0.026 | 0.88 |
| Azygous vein diameter versus $V_{max}$ splenic | 0.009 | 0.95 |
| Azygous vein diameter versus $T_{max}$ splenic | 0.022 | 0.89 |
| Gastric wall thickness versus $V_{min}$ portal | 0.030 | 0.85 |
| Gastric wall thickness versus $V_{max}$ portal | −0.86 | 0.59 |
| Gastric wall thickness versus $T_{max}$ portal | −0.49 | 0.76 |
| Gastric wall thickness versus $V_{min}$ splenic | −0.202 | 0.20 |
| Gastric wall thickness versus $V_{max}$ splenic | −0.163 | 0.31 |
| Gastric wall thickness versus $T_{max}$ splenic | −0.129 | 0.43 |

## 4. Discussion

Invasive angiographic technique such as HVPG (hepatic venous pressure gradient) measurement is frequently considered a gold standard in the study of the anatomy and pressures in patients with liver cirrhosis. Several groups have shown that patients with varices have a significantly higher HVPG than those without, but no clear correlation between HVPG and variceal size or bleeding risk has been firmly established [8]. Magnetic resonance (MR) imaging by means of time-of-flight or phase contrast angiography can both document the size and direction of the flow in studied vessels. Although this is a relatively easy method for the detection of spontaneous portosystemic collaterals, the pronounced variation within subjects raised reservation whether this technique will significantly contributes to the prediction of bleeding [8].

The advantage of EUS over upper gastrointestinal tract endoscopy in detection of features related to portal hypertension has been unequivocally shown in previous studies, demonstrating 92% sensitivity of EUS in the diagnosis of portal hypertension as compared to only 58% for upper GI endoscopy [1]. Despite this, EUS has not become a part of routine assessment for patients with liver cirrhosis, perhaps due to its limited availability and lack of properly designed prospective studies that utilize this modality for the assessment of patients with liver cirrhosis. EUS allows for visualisation of abnormal vessels belonging to intrinsic circulation, such as perioesophageal varices that are attached to the muscularis externa of the oesophagus and the paraoesophageal varices that are localized to the surrounding tissue [13]. Similarly, it allows for the detection of perigastric and paragastric varices [14]. They are often called "deep" varices and their presence is of prognostic value.

It has been previously demonstrated that patients with "deep" varices, a diameter exceeding 5 mm, are at higher risk of variceal recurrence after banding (93% versus 46%) and bleeding (43% versus 12%) [1, 15, 16]. In our previous study we have noted the presence of "deep" and potentially dangerous varices, which were undetected with routine endoscopy in a significant proportion of patients [3]. Thirty-three percent of subjects with large "deep" gastric varices showed no varices on endoscopy and 25% had only small ones [3]. Thus, identification of patients with large "deep" varices is of clinical importance. Also, an advanced hemodynamic study utilizing endoscopic color Doppler ultrasonography showed its potential usefulness in predicting recurrent variceal bleeding [17].

Abdominal Doppler ultrasound is a widely available, noninvasive tool that is a backbone in the assessment of patients with liver cirrhosis. The role of Doppler ultrasound in

the assessment of clinically relevant features of portal hypertension remains controversial. Pleština et al. suggested that Doppler ultrasound may be of use in the prediction of the risk for oesophageal variceal bleeding [18]. However, these findings are inconsistent with the results of other studies. For example, Berzigotti et al. found that color Doppler ultrasound played no role in predicting clinically significant portal hypertension and oesophageal varices [19]. Also, Cioni et al. demonstrated the lack of a relationship between the parameters of portal flow and the risk of bleeding [20], while Li et al. demonstrated that Doppler ultrasound parameters of the portal vein exhibited no correlation with the advancement of endoscopic abnormalities in patients with cirrhosis [12].

We have a long-lasting interest in applying endoscopic ultrasound for the study of features of portal hypertension in patients with liver cirrhosis [2, 3, 11, 21]. In this study we aimed to determine whether simple measurements routinely assessed during Doppler ultrasound and which include flow parameters in the portal and splenic vein show any correlation with the features of portal hypertension detected with endoscopy and EUS. To our best knowledge, this is the first study that searched for a potential relationship between Doppler and EUS findings in these patients.

We found that on endoscopy, the size of oesophageal varices correlated with the diameter but not with the flow parameters in the portal vein.

We observed no correlation between the Doppler ultrasound findings and EUS regarding "deep" oesophageal varices. Thus, Doppler ultrasound does not seem to be an alternative, noninvasive tool in this respect. However, we also found that there was a significant correlation between the size of "deep" gastric varices and the flow parameters in the portal vein and a correlation with the flow in splenic vein. Thus, at least in the context of "deep" gastric varices, Doppler ultrasound findings could be of importance. Lack of a universal correlation between portal flow and the presence/size of "deep" varices should be interpreted in the context of an important role of hyperdynamic circulation in liver cirrhosis. Structural changes in cirrhotic liver leading to increased portal pressure are no longer considered a sole underlying cause of portal hypertension. Indeed, hyperdynamic circulation with increased cardiac output and decreased peripheral resistance leading to increased vascular flow may be responsible for the limited correlation between Doppler ultrasound and EUS findings. Additionally, hyperkinetic circulation may exert a negative effect on the decrease of portal pressure related to the development of collaterals.

In summary, this study demonstrated that EUS provides important information on portal hypertension in patients with liver cirrhosis that show limited correlation with basic flow parameters detected by Doppler ultrasound.

## Acknowledgment

This study was a part of a Ministry of Science and Higher Education Project no. N 402 075 32/2455. A. Wiechowska-Kozłowska and P. Milkiewicz contributed equally to this work.

## References

[1] S. N. Sgouros, C. Bergele, and A. Avgerinos, "Endoscopic ultrasonography in the diagnosis and management of portal hypertension. Where are we next?" *Digestive and Liver Disease*, vol. 38, no. 5, pp. 289–295, 2006.

[2] A. Wiechowska-Kozłowska, A. Białek, and P. Milkiewicz, "Prevalence of "deep" rectal varices in patients with cirrhosis: an EUS-based study," *Liver International*, vol. 29, no. 8, pp. 1202–1205, 2009.

[3] A. Wiechowska-Kozłowska, A. Białek, J. Raszeja-Wyszomirska, T. Starzyńska, and P. Milkiewicz, "Ligation of oesophageal varices may increase formation of "deep" gastric collaterals," *Hepato-Gastroenterology*, vol. 57, no. 98, pp. 262–267, 2010.

[4] A. J. Sanyal, "The value of EUS in the management of portal hypertension," *Gastrointestinal Endoscopy*, vol. 52, no. 4, pp. 575–577, 2000.

[5] A. Kuramochi, H. Imazu, H. Kakutani, Y. Uchiyama, S. Hino, and M. Urashima, "Color Doppler endoscopic ultrasonography in identifying groups at a high-risk of recurrence of esophageal varices after endoscopic treatment," *Journal of Gastroenterology*, vol. 42, no. 3, pp. 219–224, 2007.

[6] H. Seno, Y. Konishi, M. Wada, H. Fukui, K. Okazaki, and T. Chiba, "Endoscopic ultrasonograph evaluation of vascular structures in the gastric cardia predicts esophageal variceal recurrence following endoscopic treatment," *Journal of Gastroenterology and Hepatology*, vol. 21, no. 1, pp. 227–231, 2006.

[7] G. C. Caletti, E. Brocchi, A. Ferrari, S. Fiorino, and L. Barbara, "Value of endoscopic ultrasonography in the management of portal hypertension," *Endoscopy*, vol. 24, no. 1, pp. 342–346, 1992.

[8] C. De Angelis, R. Pellicano, P. Carucci et al., "Endoscopic ultrasonography in hepatology: focus on portal hypertension," *Minerva Gastroenterologica e Dietologica*, vol. 54, no. 2, pp. 131–139, 2008.

[9] S. Hino, H. Kakutani, K. Ikeda et al., "Hemodynamic assessment of the left gastric vein in patients with esophageal varices with color Doppler EUS: factors affecting development of esophageal varices," *Gastrointestinal Endoscopy*, vol. 55, no. 4, pp. 512–517, 2002.

[10] P. J. McKiernan, K. Sharif, and G. L. Gupte, "The role of endoscopic ultrasound for evaluating portal hypertension in children being assessed for intestinal transplantation," *Transplantation*, vol. 86, no. 10, pp. 1470–1473, 2008.

[11] A. Wiechowska-Kozlowska, J. Raszeja-Wyszomirska, M. P. Wasilewicz et al., "Upper gastrointestinal endosonography in patients evaluated for liver transplantation," *Transplantation Proceedings*, vol. 41, no. 8, pp. 3082–3084, 2009.

[12] F. H. Li, J. Hao, J. G. Xia, H. L. Li, and H. Fang, "Hemodynamic analysis of esophageal varices in patients with liver cirrhosis using color Doppler ultrasound," *World Journal of Gastroenterology*, vol. 11, no. 29, pp. 4560–4565, 2005.

[13] G. C. Caletti, L. Bolondi, and L. Zani, "Detection of portal hypertension and esophageal varices by means of endoscopic ultrasonography," *Scandinavian Journal of Gastroenterology*, vol. 21, supplement 123, pp. 74–77, 1986.

[14] A. Irisawa, K. Obara, Y. Sato et al., "EUS analysis of collateral veins inside and outside the esophageal wall in portal hypertension," *Gastrointestinal Endoscopy*, vol. 50, no. 3, pp. 374–380, 1999.

[15] G. H. Lo, K. H. Lai, J. S. Cheng, R. L. Huang, S. J. Wang, and H. T. Chiang, "Prevalence of paraesophageal varices and gastric varices in patients achieving variceal obliteration by banding ligation and by injection sclerotherapy," *Gastrointestinal Endoscopy*, vol. 49, no. 4 I, pp. 428–436, 1999.

[16] D. O. Faigel, H. R. Rosen, A. Sasaki, K. Flora, and K. Benner, "EUS in cirrhotic patients with and without prior variceal hemorrhage in comparison with noncirrhotic control subjects," *Gastrointestinal Endoscopy*, vol. 52, no. 4, pp. 455–462, 2000.

[17] T. Sato, K. Yamazaki, J. Toyota, Y. Karino, T. Ohmura, and J. Akaike, "Endoscopic ultrasonographic evaluation of hemodynamics related to variceal relapse in esophageal variceal patients," *Hepatology Research*, vol. 39, no. 2, pp. 126–133, 2009.

[18] S. Pleština, R. Pulanić, M. Kralik, S. Pleština, and M. Samaržija, "Color Doppler ultrasonography is reliable in assessing the risk of esophageal variceal bleeding in patients with liver cirrhosis," *Wiener Klinische Wochenschrift*, vol. 117, no. 19-20, pp. 711–717, 2005.

[19] A. Berzigotti, R. Gilabert, J. G. Abraldes et al., "Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis," *American Journal of Gastroenterology*, vol. 103, no. 5, pp. 1159–1167, 2008.

[20] G. Cioni, E. Tincani, A. Cristani et al., "Does the measurement of portal flow velocity have any value in the identification of patients with cirrhosis at risk of digestive bleeding?" *Liver*, vol. 16, no. 2, pp. 84–87, 1996.

[21] A. Wiechowska-Koziowska, A. Biatek, M. Wójcicki, and P. Milkiewicz, ""Odd-looking" oesophageal varices," *Gut*, vol. 58, no. 4, pp. 519–559, 2009.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 147465, 8 pages
doi:10.1155/2012/147465

*Review Article*

# Epidemiology, Diagnosis, and Management of Cystic Lesions of the Pancreas

**Koen de Jong,[1] Marco J. Bruno,[2] and Paul Fockens[1]**

[1] *Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands*
[2] *Department of Gastroenterology and Hepatology, Erasmus Medical Center, 3000 CA, Rotterdam, The Netherlands*

Correspondence should be addressed to Paul Fockens, p.fockens@amc.nl

Received 2 June 2011; Accepted 25 July 2011

Academic Editor: Jose G. de la Mora-Levy

Copyright © 2012 Koen de Jong et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Although little is known on the true prevalence of pancreatic cysts, physicians are currently more frequently confronted with pancreatic cysts because of the increasing use of sophisticated cross-sectional abdominal imaging. Cystic lesions of the pancreas comprise of a heterogeneous group of diagnostic entities, some of which are benign such as inflammatory pseudocysts or serous cystadenomas and do not require resection when asymptomatic. Others like mucinous cysts or intraductal papillary mucinous neoplasms (IPMN) have a malignant potential and in these cases surgical resection is often indicated. For this reason an adequate distinction between the various cysts is crucial to optimize management strategy. Different diagnostic methods that could be of value in the differentiation include radiologic imaging techniques such as CT, MR, and endosonography. In addition, fluid aspiration for cytopathology, tumormarkers or molecular analysis is widely used. Different guidelines are available but so far no optimal diagnostic algorithm exists. We summarize the epidemiology, classification, clinical presentation, diagnostics, management, and future perspectives.

## 1. Introduction

As a result of the widespread use of cross-sectional imaging, clinicians are confronted with pancreatic cysts with increasing frequency [1]. The majority of these cysts are asymptomatic, and the decision whether or not to operate is not always straightforward. Although our knowledge of the pathophysiology and pathobiology of pancreatic cysts is increasing, relatively little is known about their natural history.

The apparent question is how to proceed after the detection of an asymptomatic pancreatic cyst choosing one of the following options: no further investigations, additional imaging ± fine needle aspiration (FNA), surveillance, or surgical/endoscopic treatment. Despite a spectacular improvement in diagnostic modalities in the past decades, differential diagnosis and hence management of pancreatic cysts remain controversial. Most centers have adopted a differential approach with follow up in case of absence of secondary features of malignancy and surgical resection in case of a high suspicion of malignancy. Multiple guidelines have appeared. In this paper we will attempt to provide a comprehensive overview of the epidemiology, diagnostic options, and management of pancreatic cysts.

## 2. Epidemiology

To date only a few studies have been performed investigating the true prevalence of pancreatic cysts. We have recently published a study in which 2803 magnetic resonance imaging (MRI) examinations were retrospectively reviewed in a group of mostly asymptomatic patients who decided to undergo a preventive screening abdominal MRI at their own initiative and costs without referral of a physician. Prevalence was 2.4% and increased with age [1]. A study by Laffan et al. reported a prevalence of 2.6% [2]. In retrospect, 2832 consecutive computed tomography (CT) scans were reviewed. Patients with known pancreatic disease or symptoms related to the pancreas were excluded. A prevalence of 13.5% was found in another recent retrospective study in 616 patients

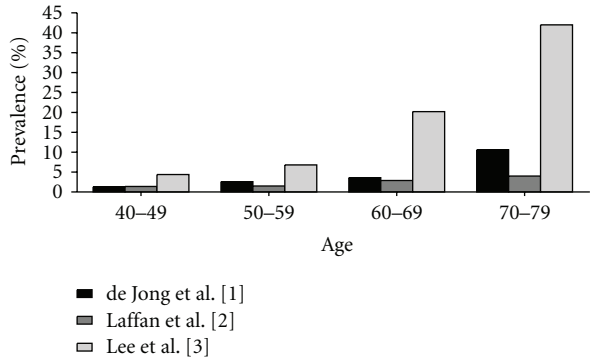



Figure 1: Prevalence of pancreatic cysts in relation to increasing age.

using MRI [3]. Patients were excluded from this study if they had a known or suspected history of pancreatic disease. In all these studies increasing age correlated with a higher prevalence of pancreatic cysts (Figure 1).

In an older Italian study reports of 24,039 MRI and CT scans were retrospectively reviewed with a computerized search. Pancreatic cysts were reported in 1.2% of which 58% (0.7% of total study population) did not have a history of pancreatitis [4]. The highest prevalence of pancreatic cysts using a radiologic imaging technique was found in a study by Zhang et al. [5]. Spin-echo MR images of 1444 patients were reviewed for pancreatic cysts by two radiologists, and pancreatic cysts were described in 19.6% of patients. Patients with known history of pancreatic disease were not excluded from this study.

In an autopsy study of 300 cases a stunning 24.3% were found to have pancreatic cysts [6]. It is of note that this study was performed in elderly patients (more than 80% were older than 65 years), and no information was provided of a possible history of pancreatic disease. The results of the described studies are summarized in Table 1. The broad range of prevalence values can be explained by the fact that studies differed in the selection of the study population, in-hospital or out-patient based and whether patients with potential pancreatic disease were excluded from analysis. Importantly, studies also differed in which imaging modality was employed with each technique having its distinct sensitivity and specificity for detecting cysts.

## 3. Classification of Pancreatic Cystic Lesions

*3.1. Nonneoplastic Pancreatic Cysts.* The most common nonneoplastic pancreatic cysts are serous cystadenomas and pancreatic pseudocysts, and these types are described in more detail in this paper. Rare nonneoplastic pancreatic cysts include true cysts, retention cysts, and lymphoepithelial cysts.

*3.1.1. Serous Cystadenoma.* Patients with serous cystadenomas (SCNs) are predominantly elderly women with a median age of approximately 60 years, and the cysts can arise in any region of the pancreas.

Classical features of a serous cystadenoma include microcystic morphology, a central area of calcification, and a watery, nonviscous fluid content. However a macrocystic variant of serous cystadenomas exists and can easily be confused with a pseudocyst or a mucinous cystadenoma [7–9]. Serous cystadenomas are lined by a glycogen-rich cuboidal epithelium which can be shown with cytopathological analysis [10]. Although a small number of cases of malignant serous cystadenocarcinomas have been described, it is generally believed that serous cystadenomas have virtually no malignant potential [11]. Serous cystadenomas can be treated conservatively if the patient is asymptomatic. Surgery is treatment of choice when a patient has symptoms or the distinction between a serous cystadenoma and a mucinous cystic neoplasm is not possible.

*3.1.2. Pseudocysts.* Pancreatic pseudocysts are fluid collections arising from leakage of the pancreatic duct lacking an epithelial lining. They usually occur following the course of an acute pancreatitis, chronic pancreatitis or secondary to an abdominal trauma [12]. The incidence of pseudocysts in the phase of an acute pancreatitis is 5.1% to 16% [13–15] whereas the incidence in chronic pancreatitis is higher with percentages varying from 20% to 40% [16–18].

Radiologic imaging of pseudocysts frequently shows a single cystic lesion, without septations or solid components. Aspirated fluid often has a low viscosity, high amylase, and cytology which is consistent with an inflammatory origin. The cysts are often filled with protease-free serous fluid if no connection to the pancreatic duct exists. Whereas size of >6 cm and duration of more than 6 weeks used to be main indicators for intervention, currently symptomatology is the main indicator for intervention.

*3.2. Neoplastic Pancreatic Cysts.* The majority of neoplastic cysts are represented by mucinous cystic neoplasms (MCNs) (10–49%) and intraductal papillary mucinous neoplasm (IPMN) (21–33%) [19, 20]. Solid pseudopapillary neoplasms are less common. Other rare neoplastic cystic lesions include cystic neuroendocrine tumors and acinar cell cystadenocarcinomas but these will not be discussed in this paper.

*3.2.1. Mucinous Cystic Neoplasm.* Patients with MCNs are almost exclusively middle-aged women [21, 22], and most of the MCNs appear in the body or tail of the pancreas although they occasionally may occur in the head. The average size of the cysts is larger than 5 cm at time of presentation [22–24]. MCNs are generally macrocystic, thick-walled cysts that typically lack communication with the ductal system [25, 26]. A microcystic MCN is rarely seen [27, 28]. They are either unilocular or multilocular with a small number of compartments [29]. Unique is the fact that MCNs contain a mucinous, dense ovarian stroma surrounding the epithelial cells, which is never seen in other cystic lesions. Therefore, ovariantype stroma is considered a requisite to distinguish MCNs from the other cystic neoplasms.

*3.2.2. Intraductal Papillary Mucinous Neoplasms.* IPMNs are slightly more often seen in male patients and they are usually

Table 1: Characteristics of studies on pancreatic cyst prevalence.

| Study | Number of patients | Prevalence (%) | Technique | Patients with known pancreatic disease excluded |
|---|---|---|---|---|
| de Jong et al. [1], 2010 | 2803 | 2.4 | MRI | Yes |
| Laffan et al. [2], 2008 | 2832 | 2.6 | CT | Yes |
| Lee et al. [3], 2010 | 616 | 13.5 | MRI | Yes |
| Spinelli et al. [4], 2004 | 24039 | 1.2 | MRI and CT | No |
| Zhang et al. [5], 2002 | 1444 | 19.6 | MRI | No |
| Kimura et al. [6], 1995 | 300 | 24.3 | autopsy | No |

Table 2: Characteristics of different pancreatic cysts.

| | MCN | IPMN | SPN | SCN | Pseudocyst |
|---|---|---|---|---|---|
| Sex distribution | F > M | M = F | F > M | F > M | F = M |
| Age | 40–60 | 60–70 | 20–30 | 60–70 | All ages |
| Average size of cyst | >3 cm | <3 cm | >3 cm | >3 cm | >3 cm |
| Morphologic characteristics | Septations thickened wall macrocystic | Dilatation of PD micro/macrocystic | Mixed solid and fluid with hemorrhage | Microcystic | Unilocular thick wall |
| Fluid | Viscous, clear | Viscous, clear | Thin, bloody | Thin, clear | Thin, dark |
| Malignant potential | Yes | Yes | Yes | No | No |

MCN: mucinous cystic neoplasm, IPMN: intraductal papillary mucinous neoplasm, SPN: solid pseudopapillary neoplasm, SCN: serous cystic neoplasm, PD: pancreatic duct.

older at presentation than patients with MCNs or serous cystadenomas. Most of the IPMNs arise in the head and uncinate process of the pancreas, and they are typically connected to the ductal system of the pancreas. IPMNs comprise lesions of the main pancreatic duct, side branches or a combination of these two. They have mixed features of microcystic and macrocystic lesions, and the main pancreatic duct is often dilated. IPMNs contain mucinous fluid which is sometimes extruding from the ampulla of Vater. An important difference in prevalence of malignancy exists for main-duct and side-branch IPMNs. The prevalence of malignancy for lesions of the main-duct IPMN is 57–92% whereas it is 6–46% for lesions of side-branch IPMN [30].

*3.2.3. Solid Pseudopapillary Neoplasms.* Solid pseudopapillary neoplasms (SPNs) are rare lesions which make up 1-2% of all pancreatic cystic neoplasms [31, 32]. They are almost exclusively found in young women with a median age of 30 years [33–35]. On the basis of the largest review [36], tumors ranged in size from 0.5 to 34.5 cm with a mean diameter of 6.08 cm.

They are equally distributed throughout the pancreas [36]. Solid pseudopapillary neoplasms often start as solid tumors and undergo degeneration giving it a cystic appearance on radiologic imaging [34]. On CT and MRI, the tumor is often well circumscribed, encapsulated, and heterogeneous with hemorrhagic and cystic degeneration [32]. Solid pseudopapillary neoplasms are tumors with relatively low malignant potential, with a reported incidence of malignant transformation of 15% [34]. Surgical resection of distant metastases is justified due to the excellent long-term prognosis in the presence of metastatic disease [37]. Characteristics of different pancreatic cysts are summarized in Table 2.

## 4. Clinical Presentation

Many patients with cystic lesions of the pancreas present without abdominal complaints [38]. Lesions are often detected when a radiologic examination is performed for another reason or when an individual decides to undergo preventive screening investigations. When the pancreatic cyst is symptomatic, patients may present with epigastric pain, postprandial fullness, palpable mass, gastric outlet obstruction, nausea, vomiting, diarrhoea, steatorrhea, and/or weight loss. Patients with IPMNs sometimes present with recurrent episodes of pancreatitis. Side-branch IPMNs are more often asymptomatic than main-duct IPMNs. MCNs and pseudopapillary neoplasms are frequently large at time of diagnosis and symptoms are more common in these patients. When an advanced cystic neoplasm exists, patients often present with complaints similar to pancreatic adenocarcinoma such as pain, weight loss, and jaundice [39].

## 5. Diagnostics

Diagnostic methods that can be valuable in the differentiation of pancreatic cysts include radiologic imaging techniques such as abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Endoscopic ultrasonography (EUS) and EUS-guided fine

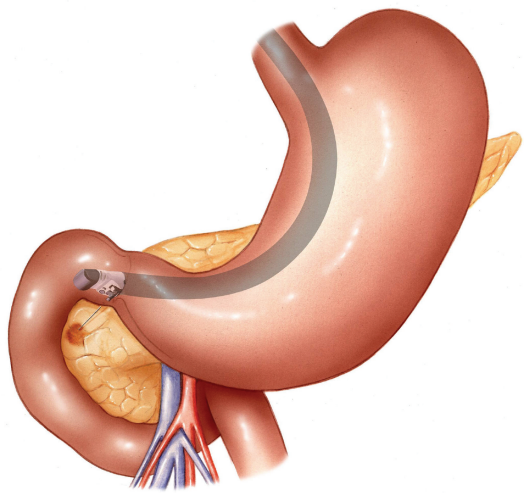
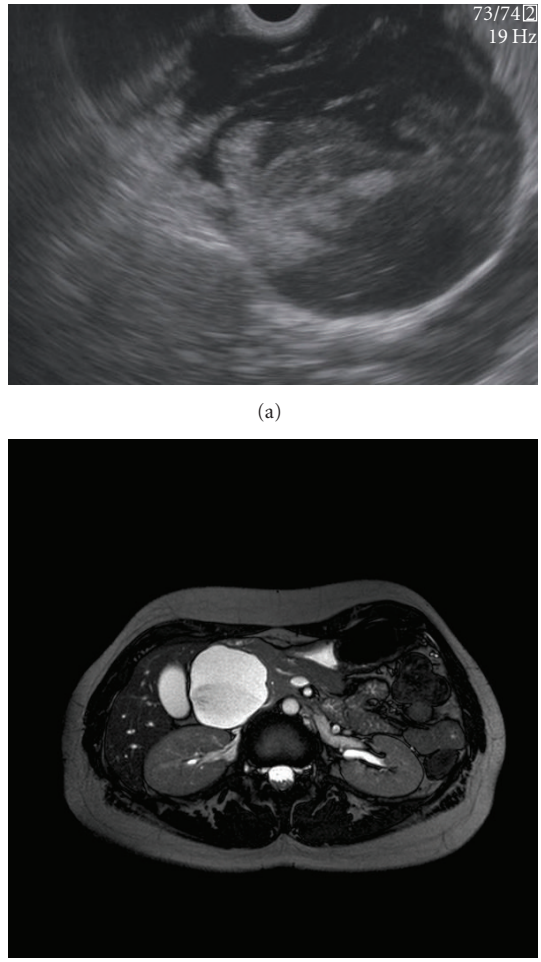


Figure 2: Cystic lesion in the pancreatic head is punctured using a linear array echo-endoscope.




(a)

(b)

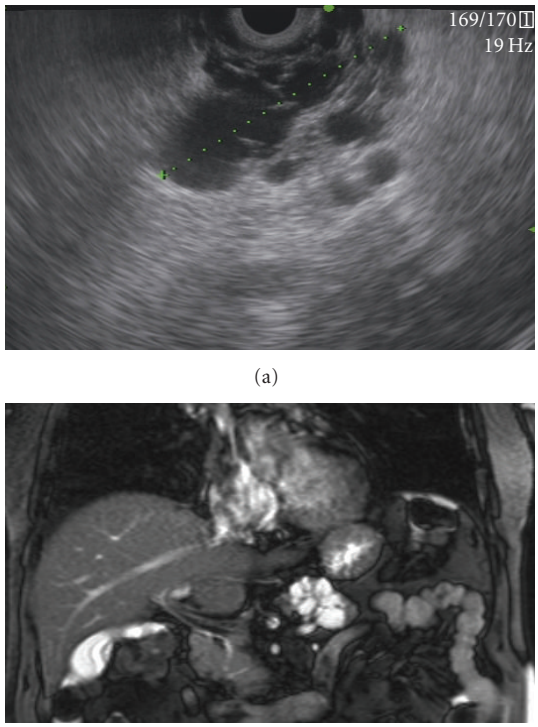
Figure 3: (a) EUS image of a malignant IPMN in the head of the pancreas. (b) MRI image of a malignant IPMN in the head of the pancreas.

needle aspiration (EUS-FNA) for cytopathologic examination, tumormarker determination, and molecular analysis are also widely used (Figures 2, 3, and 4).

Transabdominal ultrasonography is a safe imaging technique without radiation exposure which is helpful in the differentiation of solid and cystic lesions. It is currently widely used in the evaluation of abdominal complaints. As a result, cystic lesions are often initially detected with this modality. It is however not the imaging of first choice since it is difficult to visualize the complete pancreas due to overlying bowel or fat, and it is rather operator dependent. CT is often used in the diagnostic workup. It is a widely used imaging technique to visualize and differentiate pancreatic cysts based on morphologic features as size, microcystic/macrocystic aspect, presence of septations, nodules, and calcifications [40, 41]. MRI has the additional advantage to show a possible connection with the pancreatic duct which on T2-weighted image sequences is better visualized than with CT [42]. Another advantage of MRI, especially for follow up of the cysts, is the lack of radiation exposure.

EUS has emerged as a useful diagnostic technique in the evaluation of pancreatic cystic lesions, providing fine detail on the characteristics of the cyst because of the very high spatial resolution. It has therefore been suggested as an ideal imaging technique for pancreatic cysts [27, 43–45]. EUS can image characteristics of the cysts as well as the parenchymal changes and has a role in determining the resectability if malignancy is present [46]. Despite the fact that EUS is presently widely used for the differential diagnosis, a number of points of discussion still exist. Since EUS is invasive, technically difficult, and expensive, it is not available in all hospitals. Furthermore there is a substantial interobserver agreement between endosonographers. In a multicenter study 8 experienced endosonographers reviewed videotapes of 31 EUS procedures of pancreatic cysts. In this study there was only poor to moderate agreement for the diagnosis of neoplastic versus nonneoplastic, specific type, and EUS features [47]. An advantage of EUS is the possibility to perform FNA for analysis of the cyst fluid. EUS-FNA is considered a safe technique to obtain pancreatic cyst fluid with rare, mostly mild complications, but infection, pancreatitis, and intracystic haemorrhage have been reported [48, 49]. Infection of cysts after FNA is rare and, although common practice in most centers, data are lacking to support the use of prophylactic antibiotics. Furthermore, to minimize the risks of subsequent infection one should keep the number of punctures to a minimum and attempt to aspirate all fluid from the cyst whenever possible. Intracystic hemorrhage is a complication that occurred in 6% of all cases reported by Varadarajulu et al. but most of the complications were mild and did not need further medical intervention [50].

Cytological evaluation of pancreatic cyst fluid is widely used, and several studies report a sensitivity of approximately 50% for the differentiation of mucinous and nonmucinous pancreatic neoplasms [51–53]. However, other studies show less positive results since cytopathology is often nondiagnostic due to the low cellularity of the obtained cyst




(a)

(b)

Figure 4: (a) EUS image of a serous cystadenoma in the head of the pancreas. (b) MRI image of a serous cystadenoma in the head of the pancreas.

fluid [54, 55]. Biochemical analysis of cyst fluid and tumor markers have been evaluated for several years with the underlying thought that markers secreted into the cyst fluid identify the epithelial lining. Amylase is usually elevated in pseudocysts and IPMNs and low in MCNs and serous cystadenomas. Of the tumor markers, CEA is considered the best discriminant marker to differentiate between a mucinous and a nonmucinous cyst [54, 56]. A low CEA level (<5 ng/mL) has been shown to have a sensitivity between 50% and 100% and a specificity of 77–95% to differentiate between mucinous and nonmucinous cysts [51]. Pseudocysts and serous cystadenomas generally have a low CEA value. Currently, the most widely used cutoff for an elevated CEA is 192 ng/mL, which was established in a study by Brugge et al. as diagnostically sensitive in 75% and specific in 84% to discriminate between mucinous and nonmucinous cysts [54]. Altogether, the current yield of FNA is small, which can be caused by the microcystic aspect of a cyst, the high viscosity of the fluid or the minimum amount of fluid that is needed for certain examinations of the fluid. The standard use of a 19 G needle could be helpful to aspirate both larger cysts and cysts which contain fluid with a high viscosity.

## 6. Management (Guidelines)

The most recent guideline for the management of pancreatic cyst was published in 2007 by Khalid and Brugge [57]. In this guideline the authors advice to thoroughly evaluate each incidental pancreatic cyst since many cysts are premalignant (MCN and IPMN). The initial imaging test proposed is a contrast-enhanced triphasic multidetector CT scan, which may be followed by EUS-FNA in particular cases when FNA is needed for CEA level or to puncture a solid component. Resection is recommended in all MCNs and main-duct IPMNs. Firm recommendations for the management of branch-duct IPMNs are not provided. Serous cystadenomas should only be resected if symptomatic or if the diagnosis remains in doubt. All pseudopapillary neoplasms should be considered for resection. No general guidelines are provided for the interval of follow up when surgery is not undertaken. The authors state that this decision depends on the kind of lesion and the reason why surgery was not performed.

The American Society for Gastrointestinal Endoscopy issued a guideline on the use of EUS in the management of pancreatic cysts [58]. Cystic lesions of the pancreas require diagnostic evaluation regardless of size, and EUS alone is considered not accurate enough to definitively diagnose the type of cystic lesion or to determine its malignant potential. Furthermore, FNA is advised with a low sensitivity of cytologic analysis but a high specificity for MCN and malignancies. Biochemical analysis may provide clinically useful information but cannot provide a definitive diagnosis or determine whether the lesion is malignant. In this guideline it is stated that there are currently no accepted endoscopic therapies for cystic neoplasms of the pancreas, and there is a role for endoscopic drainage of inflammatory pancreatic fluid collections.

In 2005 international consensus guidelines for the management of IPMNs and MCNs were published in which a list of clinically relevant questions and answers is provided [30]. The recommendation is to resect all main-duct and mixed variant IPMNs regardless of size as long as the patient is a good surgical candidate. Asymptomatic side-branch IPMNs can be followed with CT or MRI as long as there are no mural nodes, dilatation of the main duct or growth in size. The authors do not explicitly state that all branch-duct IPMNs >3 cm should be resected. More data based on branch-duct IPMNs >3 cm without main-duct dilatation or mural nodules are needed to determine if all branch-duct IPMNs >3 cm should be resected immediately. The authors state that MCNs should always be resected unless there are contraindications for surgery.

## 7. Future Developments

New methods to improve the yield of FNA are urgently required. Existing tumor markers have only limited value, and more sensitive biomarkers need to be identified. New techniques including proteomics and molecular analysis may be helpful for the differential diagnosis of pancreatic cysts [59].

Also the development of new techniques to minimize the fluid needed for examinations may well be useful. Furthermore, the development of new techniques to increase the cellularity of the obtained fluid could be helpful. Three reports have been recently published, studying a new type of brush

(EchoBrush, Cook Medical) to improve the yield of cytologic examination [60–62]. These studies suggest that this relatively new technique improves the yield, but larger randomized trials are necessary to confirm these results and to define the safety profile of this more aggressive approach.

Currently, no accepted endoscopic treatment option for neoplastic cystic lesions is available but a few experimental studies have been performed to determine the safety and effectiveness of EUS-guided ethanol lavage with paclitaxel to treat pancreatic cysts [63–65]. The first studies report that this technique is a safe and feasible but larger studies with longer follow up are necessary.

## 8. Conclusion

Patients presenting with pancreatic cysts have to be thoroughly evaluated. Cross-sectional imaging should be used for the morphological characterization, and EUS-FNA for fluid and tissue sampling could be used in particular cases to discriminate between mucinous and nonmucinous cysts. Management should be based upon on carefully weighting the malignant potential of a pancreatic cystic lesions and the risk of surgery. Larger prospective studies with longer follow up are needed to increase the knowledge of the natural history of pancreatic cysts.

## References


[1] K. de Jong, C. Y. Nio, J. J. Hermans et al., "High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations," *Clinical Gastroenterology and Hepatology*, vol. 8, no. 9, pp. 806–811, 2010.

[2] T. A. Laffan, K. M. Horton, A. P. Klein et al., "Prevalence of unsuspected pancreatic cysts on MDCT," *American Journal of Roentgenology*, vol. 191, no. 3, pp. 802–807, 2008.

[3] K. S. Lee, A. Sekhar, N. M. Rofsky, and I. Pedrosa, "Prevalence of incidental pancreatic cysts in the adult population on MR imaging," *American Journal of Gastroenterology*, vol. 105, no. 9, pp. 2079–2084, 2010.

[4] K. S. Spinelli, T. E. Fromwiller, R. A. Daniel et al., "Cystic pancreatic neoplasms: observe or operate," *Annals of Surgery*, vol. 239, no. 5, pp. 651–659, 2004.

[5] X. M. Zhang, D. G. Mitchell, M. Dohke, G. A. Holland, and L. Parker, "Pancreatic cysts: depiction on single-shot fast spin-echo MR images," *Radiology*, vol. 223, no. 2, pp. 547–553, 2002.

[6] W. Kimura, H. Nagai, A. Kuroda, T. Muto, and Y. Esaki, "Analysis of small cystic lesions of the pancreas," *International Journal of Pancreatology*, vol. 18, no. 3, pp. 197–206, 1995.

[7] D. Chatelain, P. Hammel, D. O'Toole et al., "Macrocystic form of serous pancreatic cystadenoma," *American Journal of Gastroenterology*, vol. 97, no. 10, pp. 2566–2571, 2002.

[8] B. Khurana, K. J. Mortele, J. Glickman, S. G. Silverman, and P. R. Ros, "Macrocystic serous adenoma of the pancreas: radiologic-pathologic correlation," *American Journal of Roentgenology*, vol. 181, no. 1, pp. 119–123, 2003.

[9] K. Lewandrowski, A. Warshaw, and C. Compton, "Macrocystic serous cystadenoma of the pancreas: a morphologic variant differing from microcystic adenoma," *Human Pathology*, vol. 23, no. 8, pp. 871–875, 1992.

[10] J. L. Frossard, P. Amouyal, G. Amouyal et al., "Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions," *American Journal of Gastroenterology*, vol. 98, no. 7, pp. 1516–1524, 2003.

[11] T. Matsumoto, S. Hirano, K. Yada et al., "Malignant serous cystic neoplasm of the pancreas: report of a case and review of the literature," *Journal of Clinical Gastroenterology*, vol. 39, no. 3, pp. 253–256, 2005.

[12] A. L. Warshaw, "Pancreatic cysts and pseudocysts: new rules for a new game," *British Journal of Surgery*, vol. 76, no. 6, pp. 533–534, 1989.

[13] E. L. Bradley, A. C. Gonzalez, and J. L. Clements Jr., "Acute pancreatic pseudocysts: incidence and implications," *Annals of Surgery*, vol. 184, no. 6, pp. 734–737, 1976.

[14] A. Maringhini, G. Uomo, R. Patti et al., "Pseudocysts in acute nonalcoholic pancreatitis: incidence and natural history," *Digestive Diseases and Sciences*, vol. 44, no. 8, pp. 1669–1673, 1999.

[15] N. J. London, J. P. Neoptolemos, J. Lavelle, I. Bailey, and D. James, "Serial computed tomography scanning in acute pancreatitis: a prospective study," *Gut*, vol. 30, no. 3, pp. 397–403, 1989.

[16] M. Barthet, M. Bugallo, L. S. Moreira, C. Bastid, B. Sastre, and J. Sahel, "Management of cysts and pseudocysts complicating chronic pancreatitis. A retrospective study of 143 patients," *Gastroenterologie Clinique et Biologique*, vol. 17, no. 4, pp. 270–276, 1993.

[17] R. W. Ammann, A. Akovbiantz, F. Largiader, and G. Schueler, "Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients," *Gastroenterology*, vol. 86, no. 5, pp. 820–828, 1984.

[18] D. W. Elliott, "Pancreatic pseudocysts," *Surgical Clinics of North America*, vol. 55, no. 3, pp. 339–362, 1975.

[19] C. C. Fernandez-del Castillo, J. Targarona, S. P. Thayer, D. W. Rattner, W. R. Brugge, and A. L. Warshaw, "Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients," *Archives of Surgery*, vol. 138, no. 4, pp. 427–434, 2003.

[20] N. V. Adsay, D. S. Klimstra, and C. C. Compton, "Cystic lesions of the pancreas. Introduction," *Seminars in Diagnostic Pathology*, vol. 17, no. 1, pp. 1–6, 2000.

[21] M. G. Sarr, H. A. Carpenter, L. P. Prabhakar et al., "Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant (or premalignant) neoplasms?" *Annals of Surgery*, vol. 231, no. 2, pp. 205–212, 2000.

[22] S. Crippa, R. Salvia, A. L. Warshaw et al., "Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients," *Annals of Surgery*, vol. 247, no. 4, pp. 571–579, 2008.

[23] G. H. Sakorafas and M. G. Sarr, "Cystic neoplasms of the pancreas; what a clinician should know," *Cancer Treatment Reviews*, vol. 31, no. 7, pp. 507–535, 2005.

[24] A. L. Mulkeen, P. S. Yoo, and C. Cha, "Less common neoplasms of the pancreas," *World Journal of Gastroenterology*, vol. 12, no. 20, pp. 3180–3185, 2006.

[25] R. Salvia, L. Festa, G. Butturini et al., "Pancreatic cystic tumors," *Minerva Chirurgica*, vol. 59, no. 2, pp. 185–207, 2004.

[26] F. Campbell and B. Azadeh, "Cystic neoplasms of the exocrine pancreas," *Histopathology*, vol. 52, no. 5, pp. 539–551, 2008.

[27] W. R. Brugge, "The role of EUS in the diagnosis of cystic lesions of the pancreas," *Gastrointestinal Endoscopy*, vol. 52, supplement 6, pp. S18–S22, 2000.

[28] W. R. Brugge, "Evaluation of pancreatic cystic lesions with EUS," *Gastrointestinal Endoscopy*, vol. 59, no. 6, pp. 698–707, 2004.

[29] N. C. Balci and R. C. Semelka, "Radiologic features of cystic, endocrine and other pancreatic neoplasms," *European Journal of Radiology*, vol. 38, no. 2, pp. 113–119, 2001.

[30] M. Tanaka, S. Chari, V. Adsay et al., "International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas," *Pancreatology*, vol. 6, no. 1-2, pp. 17–32, 2006.

[31] R. C. Martin, D. S. Klimstra, M. F. Brennan, and K. C. Conlon, "Solid-pseudopapillary tumor of the pancreas: a surgical enigma?" *Annals of Surgical Oncology*, vol. 9, no. 1, pp. 35–40, 2002.

[32] D. S. Klimstra, B. M. Wenig, and C. S. Heffess, "Solid-pseudopapillary tumor of the pancreas: a typically cystic carcinoma of low malignant potential," *Seminars in Diagnostic Pathology*, vol. 17, no. 1, pp. 66–80, 2000.

[33] C. Mao, M. Guvendi, D. R. Domenico, K. Kim, N. R. Thomford, and J. M. Howard, "Papillary cystic and solid tumors of the pancreas: a pancreatic embryonic tumor? Studies of three cases and cumulative review of the world's literature," *Surgery*, vol. 118, no. 5, pp. 821–828, 1995.

[34] S. G. Tipton, T. C. Smyrk, M. G. Sarr, and G. B. Thompson, "Malignant potential of solid pseudopapillary neoplasm of the pancreas," *British Journal of Surgery*, vol. 93, no. 6, pp. 733–737, 2006.

[35] E. Panieri, J. E. Krige, P. C. Bornman, S. M. Graham, J. Terblanche, and J. P. Cruse, "Operative management of papillary cystic neoplasms of the pancreas," *Journal of the American College of Surgeons*, vol. 186, no. 3, pp. 319–324, 1998.

[36] T. Papavramidis and S. Papavramidis, "Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in english literature," *Journal of the American College of Surgeons*, vol. 200, no. 6, pp. 965–972, 2005.

[37] S. M. de Castro, D. Singhal, D. C. Aronson et al., "Management of solid-pseudopapillary neoplasms of the pancreas: a comparison with standard pancreatic neoplasms.," *World Journal of Surgery*, vol. 31, no. 5, pp. 1130–1135, 2007.

[38] C. Bassi, R. Salvia, E. Molinari, C. Biasutti, M. Falconi, and P. Pederzoli, "Management of 100 consecutive cases of pancreatic serous cystadenoma: wait for symptoms and see at imaging or vice versa?" *World Journal of Surgery*, vol. 27, no. 3, pp. 319–323, 2003.

[39] D. L. Kerlin, C. F. Frey, B. I. Bodai, P. L. Twomey, and B. Ruebner, "Cystic neoplasms of the pancreas," *Surgery Gynecology and Obstetrics*, vol. 165, no. 6, pp. 475–478, 1987.

[40] C. A. Curry, J. Eng, K. M. Horton et al., "CT of primary cystic pancreatic neoplasms: can CT be used for patient triage and treatment?" *American Journal of Roentgenology*, vol. 175, no. 1, pp. 99–103, 2000.

[41] M. Minami, Y. Itai, K. Ohtomo, H. Yoshida, K. Yoshikawa, and M. Iio, "Cystic neoplasms of the pancreas: comparison of MR imaging with CT," *Radiology*, vol. 171, no. 1, pp. 53–56, 1989.

[42] K. Koito, T. Namieno, T. Ichimura et al., "Mucin-producing pancreatic tumors: comparison of MR cholangiopancreatography with endoscopic retrograde cholangiopancreatography," *Radiology*, vol. 208, no. 1, pp. 231–237, 1998.

[43] J. F. Tseng, A. L. Warshaw, D. V. Sahani et al., "Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment," *Annals of Surgery*, vol. 242, no. 3, pp. 413–421, 2005.

[44] K. Yamaguchi and M. Tanaka, "Radiologic imagings of cystic neoplasms of the pancreas," *Pancreatology*, vol. 1, no. 6, pp. 633–636, 2001.

[45] J. Ariyama, M. Suyama, K. Satoh, and K. Wakabayashi, "Endoscopic ultrasound and intraductal ultrasound in the diagnosis of small pancreatic tumors," *Abdominal Imaging*, vol. 23, no. 4, pp. 380–386, 1998.

[46] S. L. Brandwein, J. J. Farrell, B. A. Centeno, and W. R. Brugge, "Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS," *Gastrointestinal Endoscopy*, vol. 53, no. 7, pp. 722–727, 2001.

[47] N. A. Ahmad, M. L. Kochman, C. Brensinger et al., "Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions," *Gastrointestinal Endoscopy*, vol. 58, no. 1, pp. 59–64, 2003.

[48] L. S. Lee, J. R. Saltzman, B. C. Bounds, J. M. Poneros, W. R. Brugge, and C. C. Thompson, "EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors," *Clinical Gastroenterology and Hepatology*, vol. 3, no. 3, pp. 231–236, 2005.

[49] D. O'Toole, L. Palazzo, R. Arotcarena et al., "Assessment of complications of EUS-guided fine-needle aspiration," *Gastrointestinal Endoscopy*, vol. 53, no. 4, pp. 470–474, 2001.

[50] S. Varadarajulu and M. A. Eloubeidi, "Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas," *Gastrointestinal Endoscopy*, vol. 60, no. 4, pp. 631–635, 2004.

[51] L. A. van der Waaij, H. M. van Dullemen, and R. J. Porte, "Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis," *Gastrointestinal Endoscopy*, vol. 62, no. 3, pp. 383–389, 2005.

[52] R. M. Walsh, J. M. Henderson, D. P. Vogt et al., "Prospective preoperative determination of mucinous pancreatic cystic neoplasms," *Surgery*, vol. 132, no. 4, pp. 628–634, 2002.

[53] H. C. Oh, M. H. Kim, C. Y. Hwang et al., "Cystic lesions of the pancreas: challenging issues in clinical practice," *American Journal of Gastroenterology*, vol. 103, no. 1, pp. 229–239, 2008.

[54] W. R. Brugge, K. Lewandrowski, E. Lee-Lewandrowski et al., "Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study," *Gastroenterology*, vol. 126, no. 5, pp. 1330–1336, 2004.

[55] B. A. Centeno, A. L. Warshaw, W. Mayo-Smith, J. F. Southern, and K. Lewandrowski, "Cytologic diagnosis of pancreatic cystic lesions: a prospective study of 28 percutaneous aspirates," *Acta Cytologica*, vol. 41, no. 4, pp. 972–980, 1997.

[56] K. B. Lewandrowski, J. F. Southern, M. R. Pins, C. C. Compton, and A. L. Warshaw, "Cyst fluid analysis in the differential diagnosis of pancreatic cysts: a comparison of pseudocysts, serous cystadenomas, mucinous cystic neoplasms, and mucinous cystadenocarcinoma," *Annals of Surgery*, vol. 217, no. 1, pp. 41–47, 1993.

[57] A. Khalid and W. Brugge, "ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts," *American Journal of Gastroenterology*, vol. 102, no. 10, pp. 2339–2349, 2007.

[58] B. C. Jacobson, T. H. Baron, D. G. Adler et al., "ASGE guideline: the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas," *Gastrointestinal Endoscopy*, vol. 61, no. 3, pp. 363–370, 2005.

[59] E. Ke, B. B. Patel, T. Liu et al., "Proteomic analyses of pancreatic cyst fluids," *Pancreas*, vol. 38, no. 2, pp. e33–e42, 2009.

[60] M. Al-Haddad, M. Raimondo, T. Woodward et al., "Safety and efficacy of cytology brushings versus standard FNA in

evaluating cystic lesions of the pancreas: a pilot study," *Gastrointestinal Endoscopy*, vol. 65, no. 6, pp. 894–898, 2007.

[61] M. Al-Haddad, K. R. Gill, M. Raimondo et al., "Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study," *Endoscopy*, vol. 42, no. 2, pp. 127–132, 2010.

[62] M. Bruno, M. Bosco, P. Carucci et al., "Preliminary experience with a new cytology brush in EUS-guided FNA," *Gastrointestinal Endoscopy*, vol. 70, no. 6, pp. 1220–1224, 2009.

[63] H. C. Oh, D. W. Seo, T. J. Song et al., "Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts," *Gastroenterology*, vol. 140, no. 1, pp. 172–179, 2011.

[64] J. DeWitt, K. McGreevy, C. M. Schmidt, and W. R. Brugge, "EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study," *Gastrointestinal Endoscopy*, vol. 70, no. 4, pp. 710–723, 2009.

[65] S. I. Gan, C. C. Thompson, G. Y. Lauwers, B. C. Bounds, and W. R. Brugge, "Ethanol lavage of pancreatic cystic lesions: initial pilot study," *Gastrointestinal Endoscopy*, vol. 61, no. 6, pp. 746–752, 2005.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 348719, 5 pages
doi:10.1155/2012/348719

*Review Article*

# EUS-Guided Biliary Drainage

**Marc Giovannini and Erwan Bories**

*Endoscopic Unit, Paoli-Calmettes Institute, 232 Boulevard St-Marguerite, 13273 Marseille Cedex 9, France*

Correspondence should be addressed to Marc Giovannini, giovanninim@wanadoo.fr

Received 24 April 2011; Accepted 29 May 2011

Academic Editor: Fauze Maluf-Filho

Copyright © 2012 M. Giovannini and E. Bories. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The echoendoscopic biliary drainage is an option to treat obstructive jaundices when ERCP drainage fails. These procedures compose alternative methods to the side of surgery and percutaneous transhepatic biliary drainage, and it was only possible by the continuous development and improvement of echoendoscopes and accessories. The development of linear setorial array echoendoscopes in early 1990 brought a new approach to diagnostic and therapeutic dimenion on echoendoscopy capabilities, opening the possibility to perform punction over direct ultrasonographic view. Despite of the high success rate and low morbidity of biliary drainage obtained by ERCP, difficulty could be found at the presence of stent tumor ingrown, tumor gut compression, periampulary diverticula, and anatomic variation. The echoendoscopic technique starts performing punction and contrast of the left biliary tree. When performed from gastric wall, the access is made through hepatic segment III. From duodenum, direct common bile duct punction. Dilatation is required before stent introduction, and a plastic or metallic stent is introduced. This phrase should be replaced by: diathermic dilatation of the puncturing tract is required using a 6F cystostome. The technical success of hepaticogastrostomy is near 98%, and complications are present in 36%: pneumoperitoneum, choleperitoneum, infection, and stent disfunction. To prevent bile leakage, we have used the 2 stent techniques, the first stent introduced was a long uncovered metallic stent (8 or 10 cm), and inside this first stent a second fully covered stent of 6 cm was delivered to bridge the bile duct and the stomach. Choledochoduodenostomy overall success rate is 92% and described complications include, in frequency order, pneumoperitoneum and focal bile peritonitis, present in 19%. By the last 10 years, the technique was especially performed in reference centers, by ERCP experienced groups, and this seems to be a general guideline to safer procedure execution.

## 1. Introduction

Endoscopic biliary stenting is the most common method to treat obstructive jaundice. But in 3–12% of cases, selective cannulation of the major papilla failed and surgery or percutaneous biliary drainage is required. But percutaneous drainage needed dilated intrahepatic biliary ducts and the rate of complications reaches 25–30% of cases including peritoneal bleeding. A new technique of biliary drainage using EUS and EUS-guided puncture of the bile duct (common bile duct or left hepatic duct) is now possible.

Using EUS guidance and dedicated accessories it's now possible to create biliodigestive anastomosis.

The aim of this paper is:

(1) to describe the material needed for such procedures,

(2) to describe the technique of biliary drainage under EUS guidance,

(3) to describe the place today of these techniques in comparison with ERCP.

## 2. Material

*2.1. Interventional Echoendoscopes.* Around 1990, the Pentax-Corporation developed an electronic convex curved linear array echoendoscope (FG32UA) with an imaging plane in the long axis of the device that overlaps with the instrumentation plane. This echoendoscope, equipped with a 2.0 mm working channel, enabled fine-needle biopsy under EUS guidance. However, the relatively small working channel of the FG 32UA was a drawback for pseudocyst drainage since it necessitated the exchange of the echoendoscope for a therapeutic duodenoscope to insert either a stent or nasocystic drain. To enable stent placement using an echoendoscope, the EUS interventional echoendoscopes (FG

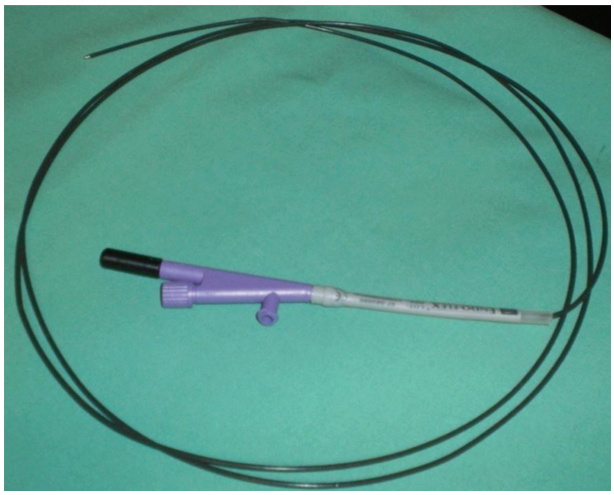


Figure 1: 6F cystostome (Endoflex company).

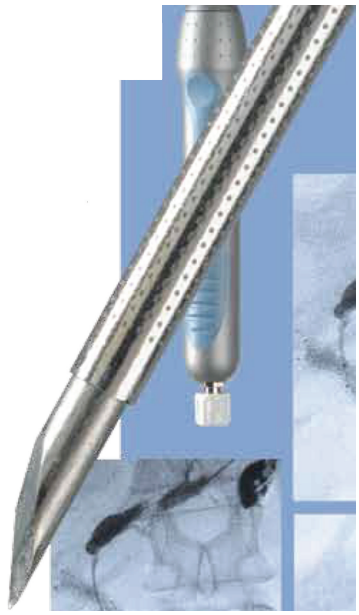


Figure 2: Echotip "ACCESS NEEDLE" Cook company.

38X, EG 38UT, and EG 3870UTK) were developed by Pentax-Hitachi. The FG 38X has a working channel of 3.2 mm, which allows the insertion of a 8.5F stent or nasocystic drain and the EG38UT and EG3870UTK have a larger working channel of 3.8 mm with an elevator allowing the placement of a 10F stent [1, 2].

The Olympus Corporation has also developed convex array echoendoscopes. The GF UC 30P has a biopsy channel of 2.8 mm, which enables the placement of a 7-french stent or nasocystic catheter, and the instrument is equipped with an elevator. A new prototype, the GF UCT 30, has a larger working-channel of 3.7 mm allowing the placement of 10-french stent. The main drawback of convex linear array echoendoscopes is the more limited imaging field (120° using the Pentax and 180° using the Olympus) produced by an electronic transducer. These instruments are coupled with the Aloka processor or with a smaller processor (Suzie).

*2.2. Needles and Accessories for Drainage.* Some authors have used needle knife catheters, but the needle can be difficult to visualize endosonographically. The "Zimmon" needle-knife (Wilson-Cook Corporation, Winston Salem, NC, USA) has a large gauge needle that is easier to visualize. Diathermy is usually required to penetrate the cyst [3] (Figure 1).

A standard endosonography fine needle aspiration (FNA) needle is well visualized sonographically and can be used for pseudocyst puncture. The drawback of this needle is the small caliber (22 or 23 G) that will accept only a 0.018-inch guidewire. Using a 19 G FNA needle (Wilson-Cook Corporation), a 0.0035-inch guidewire can be inserted through the needle into the dilated bile duct. Wilson Cook Corporation has recently developed a "new access needle"; However, one of the main problems during these new techniques of hepaticogastrostomy, is the difficulty manipulating the wire guide through the 19-gauge EUS needle. The main trouble was the "stripping" of the coating of the wire, which in turn created a risk of leaving a part of the wire coating in the patient and also the impossibility to continue the procedure and to insert the stent. To solve this problem, we worked with Cook Medical to design a special needle called the EchoTip Access Needle* (Figure 2). This needle is original because the stylet is sharp and it is relatively easy to insert the needle into the bile duct or the pancreatic duct or a pseudocyst. When the stylet is withdrawn, the needle left in place is smooth and the manipulation of the wire guide is easy and the device is designed to decrease the possibility of the wire stripping.

## 3. EUS-Guided Rendez-Vous Technique

After puncture of the left hepatic biliary system (see above) using a 19-gauges needle (Echo−1−19; Cook Endoscopy), a 0.035-inch hydrophilic guidewire (Tracer Metro Direct, Cook Endoscopy or Jagwire, Boston scientific, Paris, France) was inserted into the biliary duct and then rolled up inside the duodenum. Then, echoendoscope was gently withdrawn leaving the guidewire in place. Afterwards, a duodenoscope was inserted in parallel of the guidewire and placed in the third duodenum, allowing retrograde approach. Guidewire was then catched with standard snare through the working channel and after over-the-wire biliary sphincteromy, stones removal or stent placement could be achieve as usually.

## 4. EUS-Choledocoduodenostomy

A 19-G needle (EchoTip; Wilson-Cook) is inserted trans-duodenally into the bile duct under EUS guidance. Bile is aspirated and contrast medium is injected into the bile duct for cholangiography. A 450-cm long, 0.035-inch guidewire is inserted into through the 19-G needle into the bile duct. The choledochoduodenal fistula is dilated using a biliary catheter for dilation (Soehendra biliary dilator; Wilson-Cook), or a

6F cystostome (Endoflex, company). A 7 Fr to 10 Fr biliary plastic stent or a covered self-expandable metallic stent is placed through the choledochoduodenostomy site into the extrahepatic bile duct.

## 5. Technique of Left Hepaticogastrostomy under EUS Guidance (HGE) (Figure 3)

EUS-guided hepaticogastrostomy was first reported by Burmester [4] in 2003. The technique is also basically similar to EUS-guided drainage of pancreatic pseudocysts. By using an interventional echoendoscope, the dilated left hepatic duct (segment III) was well visualized. HGE was then performed under combined fluoroscopic and ultrasound guidance, with the tip of the echoendoscope positioned such that the inflated balloon was in the middle part of the small curvature of the stomach. A needle (19 G, EchoTip Access Needle, Cook Ireland Ltd., Limerick, Ireland) was inserted transgastrically into the distal part of the left hepatic duct and contrast medium was injected. Opacification demonstrated a dilated biliary ducts to the complete obstruction. The needle was exchanged over a guidewire (0.02-inch diameter, Terumo Europe, Leuven, Belgium) for a 6.5F diathermic sheath (prototype Cysto-Gastro set, EndoFlex, Voerde, Germany), which was then used to enlarge the channel between the stomach and the left hepatic duct. The sheath was introduced by using cutting current. After exchange over a guidewire (TFE-coated 0.035-inch diameter, Cook Europe, Bjaeverskov, Denmark), a 8.5F, 8-cm—long hepatico-gastric stent) or a covered metallic expandable stent (Boston-scientific, 8 cm length) was positioned.As observed by fluoroscopy, contrast emptied from the stent into the stomach. To prevent bile leakage you can leave through the metallic stent a 6 or 7F naso-biliary drain in aspiration during 48 hours. More recently we decided to combine an uncovered stent and a covered stent inserted into. Among these, hepaticogastrostomy was sometimes combined with placement of an additional metallic stent bridging the distal stricture.

## 6. Place of the Bilio-Digestive Anastomosis Guided by EUS in Comparison with ERCP

ERCP is still today the Gold Standard technique for the drainage of an obstructive jaundice due to a pancreatic cancer. Success rate of biliary stenting using ERCP is around 80–85% but sometime ERCP failed to cannulate selectively the papilla or failed to reach the papilla in case of duodenal obstruction. These new techniques of biliary drainage using EUS guidance could be an alternative to percutaneous procedures or to Surgery.

The problem with the percutaneous techniques of biliary drainage is the high rate of complication (bleeding, peritoneal bile leakage) around 20–30% of the cases and the morbidity and the mortality of Surgery for such palliative procedures are, respectively, of 35–50% and 10–15%.

For probably, these new techniques of biliary drainages will be in the future an alternative to Surgery and percutaneous biliary drainage.

To date, 120 patients with EUS-guided bile duct drainage have been reported in thirteen studies (Table 1). 19-gauge or 22-gauge fine needles or fine needles followed by needle knife or cystotome were used for puncturing intrahepatic bile ducts in all of the patients. Hepaticogastrostomy was successful in all but two cases (49/51, 96%). Various types of stents, including plastic stents, uncovered MS, and covered MS were used for the drainage. Once the stents were placed, all but one patient (48/49, 98%) had successful resolution of obstructive jaundice. The rate of procedurerelated early complications was 19% (5 mild and 5 severe) with one death: 1 case of ileus probably due to the use of morphine during anesthesia, 1 case of bilioma, and 2 cases of cholangitis. Stent migration has been reported as a late complication in one case. Kahaleh et al. described that the advantages of EUS-guided hepaticogastrostomy over percutaneous transhepatic drainage included puncture of the biliary tree with real-time US when using color-Doppler information to limit the possibility of vascular injury, the lack of ascites in the interventional field when present in the peritoneum, and the lack of an external drain. And based on their experience, they also pointed out the extrahepatic approach has a greater chance of complication than the intrahepatic approach. Itoi et al. reported the limitations of this technique as follows, (i) nonapposed gastric wall and the left liver lobe, with a certain displacement between the puncture site of the gastric wall and intrahepatic bile duct, resulting in possibility of procedure failure. (ii) risk of mediastinitis with a transesophageal approach, (iii) difficulty of puncture in case of liver cirrhosis, (iv) risk of injuring the portal vein and (v) necessitating the use of small-caliber stents or MS with a small-diameter delivery device [17].

From a clinical standpoint, however, the most relevant technical choice appears to be the type of stent. As detailed in Table 1, 7 to 8.5 plastic stents were placed in 46% of cases, whereas uncovered, partially covered or fully covered SEMS were placed initially in 54%. It is difficult to draw significant conclusions from the published reports, since no formal comparisons have been made between the two types of stents. SEMS are appealing for three reasons. First, upon full expansion SEMS effectively seal the puncture/dilation tract, which would in theory prevent leakage. Secondly, their larger diameter provides better long-term patency, which would decrease the need for stent revisions. Finally, if dysfunction by ingrowth or clogging occurs, management is somewhat less challenging than with plastic stents, since a new stent (plastic or SEMS) can easily be inserted through the occluded SEMS in place. In contrast, exchanging a clogged plastic transmural stent usually requires over-the-wire replacement, because free-hand removal involves the risk of track disruption with subsequent guidewire passage into the peritoneum, hence requiring repeat EUSBD if drainage is to be reestablished [18]. These presumed advantages of SEMS must be balanced against the fact that transmural SEMS insertion and deployment are somewhat more demanding than they are at ERCP. In particular, the serious risk of foreshortening and bile peritonitis should be prevented with careful attention to details [15].

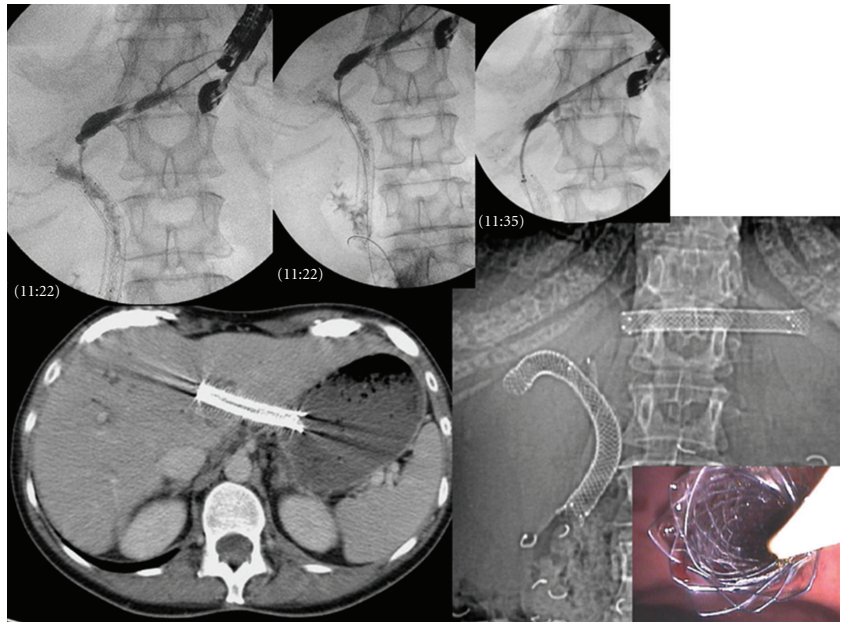



Figure 3: Hepaticogastrostomy performed after ERCP failed to drain the left hepatic lobe in patient with a Klatskin Tumor.

Table 1: Summary of the published literature on EUS-HG and related transmural intrahepatic EUSBD.

| Author/year/ref | *n* Total | *n* IH-transmural | | Success | | Complications | | Initial stent | |
|---|---|---|---|---|---|---|---|---|---|
| | EUSBD | EUSHG | nonHG | technical | Clinical | *n* | Type | Plastic | SEMS |
| Burmester et al. [4] 2003 | 4 | 1 | 1 | 2 | 2 | 0 | — | 2 | 0 |
| Püspök et al. [5] 2005 | 6 | 0 | 1 | 1 | 1 | 0 | — | 1 | 0 |
| Artifon et al. [6] 2007 | 1 | 1 | 0 | 1 | 1 | 0 | — | 0 | 1 |
| Bories et al. [7] 2007 | 11 | 11 | 0 | 10 | 10 | 4 | 2 cholangitis, 1 ileus, 1 biloma | 7 | 3 |
| Will et al. [8] 2007 | 8 | 4 | 4 | 7 | 6 | 2 | 1 cholangitis, 1 pain | 2 | 5 |
| Chopin-Laly et al. [9] 2004 | 1 | 1 | 0 | 1 | 1 | 0 | — | 0 | 1 |
| Iglesias-García et al. [10] 2008 | 1 | 1 | 0 | 1 | 1 | 0 | — | NS | NS |
| Horaguchi et al. [11] 2009 | 16 | 5 | 2 | 7 | 6 | 1 | Cholangitis | 7 | 0 |
| Maranki et al. [12] 2009 | 49 | 3 | 0 | 3 | 3 | 0 | — | 3 | 0 |
| Park et al. [13] 2009 | 14 | 8 | 1 | 9 | 9 | 2 | Pneumo | 0 | 9 |
| Park et al. [14] 2010 | 5 | 5 | 0 | 5 | 5 | 0 | — | 0 | 5 |
| Martins et al. [15] 2010 | 1 | 1 | 0 | 1 | 0 | 1 | Peritonitis and death | 0 | 1 |
| Eum et al. [16] 2010 | 3 | 1 | 0 | 1 | 1 | 0 | — | 0 | 1 |
| Total | 120 | 42 | 9 | 49 | 46 | 10 | 5 mild/5 severe | 22 | 26 |

We reported recently our experience on 38 patients [19] (F = 20, Mean age = 66.5 yrs, (38–93 yrs)) were referred for management of biliary disorders: benign disease in 11 (iatrogenic stenosis = 8, chronic pancreatitis = 1, fistula = 1, bile duct dilation = 1) and malignant in 27 (pancreatic cancer = 10, cholangiocarcinoma = 10, other = 7). EUS approach was chosen after failure of ERCP ($n = 9$), impossibility to reach papilla (duodenal strictures = 6, post-surgical anatomy = 9) or incomplete left bile duct drainage ($n = 14$). All procedures were realized using therapeutic echoendoscope, and fluoroscopic guidance. EUS procedures were performed using transgastric approach. Stents were placed transpapillary (transpapillary stent insertion), between the stomach and the left liver lobe to keep the fistula open (hepaticogastrostomy) or both. 41 EUS-guided biliary procedures were realized. Choleperitoneum occurred in 1 casen treated medically. 36 transgastric approaches were performed in 35 patients with technical success in 97%. All stents placed under EUS guidance were clinically efficient. Complications occurred in 25% ($n = 9$, choleperitoneum = 5,

stent migration = 3, liver abscess = 1). All complications were managed conservatively. 1 patient died secondary to severe choleperitoneum.

## 7. Conclusion

EUS-guided biliary management is useful in case of failure of ERCP with a high rate of technical success and clinical efficacy. Morbidity rate is high during biliary drainage requiring experienced team. In summary. EUS-guided biliary procedure open a new way to achieve biliary drainage, complementary to percutaneous approach. Hepaticogastrostomy is feasible providing high success rate. Nevertheless morbidity rate is still elevated. Further technical improvements are therefore mandatory to reduces a number of adverse events.

## References


[1] M. Giovannini, C. Pesenti, E. Bories, and F. Caillol, "Interventional EUS: difficult pancreaticobiliary access," *Endoscopy*, vol. 38, supplement 1, pp. S93–S95, 2006.

[2] M. Kahaleh, "EUS-guided cholangio drainage and rendezvous techniques," *Techniques in Gastrointestinal Endoscopy*, vol. 9, no. 1, pp. 39–45, 2007.

[3] H. Grimm, K. F. Binmoeller, and N. Soehendra, "Endosonography-guided drainage of a pancreatic pseudocyst," *Gastrointestinal Endoscopy*, vol. 38, no. 2, pp. 170–171, 1992.

[4] E. Burmester, J. Niehaus, T. Leineweber, and T. Huetteroth, "EUS-cholangio-drainage of the bile duct: report of 4 cases," *Gastrointestinal Endoscopy*, vol. 57, no. 2, pp. 246–251, 2003.

[5] A. Püspök, F. Lomoschitz, C. Dejaco, M. Hejna, T. Sautner, and A. Gangl, "Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series," *American Journal of Gastroenterology*, vol. 100, no. 8, pp. 1743–1747, 2005.

[6] E. L. Artifon, D. M. Chaves, S. Ishioka, T. F. Souza, S. E. Matuguma, and P. Sakai, "Echoguided hepatico-gastrostomy: a case report," *Clinics*, vol. 62, no. 6, pp. 799–802, 2007.

[7] E. Bories, C. Pesenti, F. Caillol, C. Lopes, and M. Giovanni, "Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study," *Endoscopy*, vol. 39, no. 4, pp. 287–291, 2007.

[8] U. Will, A. Thieme, F. Fueldner, R. Gerlach, I. Wanzar, and F. Meyer, "Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage," *Endoscopy*, vol. 39, no. 4, pp. 292–295, 2007.

[9] X. Chopin-Laly, T. Ponchon, A. Guibal, and M. Adham, "Endoscopic biliogastric stenting: a salvage procedure," *Surgery*, vol. 145, no. 1, p. 123, 2009.

[10] J. Iglesias-García, J. Lariño-Noia, S. Seijo-Ríos, and J. E. Domínguez-Muñoz, "Endoscopic ultrasound for cholangiocarcinoma re-evaluation after Wallstent placement," *Revista Espanola de Enfermedades Digestivas*, vol. 100, no. 4, pp. 236–237, 2008.

[11] J. Horaguchi, N. Fujita, Y. Noda et al., "Endosonography-guided biliary drainage in cases with difficult transpapillary endoscopic biliary drainage: original article," *Digestive Endoscopy*, vol. 21, no. 4, pp. 239–244, 2009.

[12] J. Maranki, A. J. Hernandez, B. Arslan et al., "Interventional endoscopic ultrasound-guided cholangiography: long-term experience of an emerging alternative to percutaneous transhepatic cholangiography," *Endoskopie Heute*, vol. 41, pp. 532–538, 2009.

[13] D. H. Park, J. E. Koo, J. Oh et al., "EUS-guided biliary drainage with one-step placement of a fully covered metal stent for malignant biliary obstruction: a prospective feasibility study," *American Journal of Gastroenterology*, vol. 104, no. 9, pp. 2168–2174, 2009.

[14] D. H. Park, T. J. Song, J. Eum et al., "EUS-guided hepaticogastrostomy with a fully covered metal stent as the biliary diversion technique for an occluded biliary metal stent after a failed ERCP (with videos)," *Gastrointestinal Endoscopy*, vol. 71, no. 2, pp. 413–419, 2010.

[15] F. P. Martins, L. G. B. Rossini, and A. P. Ferrari, "Migration of a covered metallic stent following endoscopic ultrasound-guided hepaticogastrostomy: fatal complication," *Endoscopy*, vol. 42, no. 2, pp. E126–E127, 2010.

[16] J. Eum, D. H. Park, C. H. Ryu et al., "EUS-guided biliary drainage with a fully covered metal stent as a novel route for natural orifice transluminal endoscopic biliary interventions: a pilot study (with videos)," *Gastrointestinal Endoscopy*, vol. 72, no. 6, pp. 1279–1284, 2010.

[17] M. Perez-Miranda, C. De la Serna, P. Diez-Redondo, and J. Vila, "Endosonography-guided cholangiopancreatography as a salvage drainage procedure for obstructed biliary and pancreatic ducts," *The World Journal of Gastrointestinal Endoscopy*, vol. 2, pp. 212–222, 2010.

[18] N. Fujita, T. Sugawara, Y. Noda et al., "Snare-over-the-wire technique for safe exchange of a stent following endosonography-guided biliary drainage," *Digestive Endoscopy*, vol. 21, no. 1, pp. 48–52, 2009.

[19] J. A. Wilson, B. Hoffman, R. H. Hawes, and J. Romagnuolo, "EUS in patients with surgically altered upper GI anatomy," *Gastrointestinal Endoscopy*, vol. 72, no. 5, pp. 947–953, 2010.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 796751, 12 pages
doi:10.1155/2012/796751

*Review Article*

# Prevention of Post-ERCP Pancreatitis

**F. Donnellan and Michael F. Byrne**

*Department of Gastroenterology, Division of Medicine, Vancouver General Hospital, Vancouver, BC, Canada V5Z 1M9*

Correspondence should be addressed to F. Donnellan, fdonnellan77@hotmail.com

Received 31 May 2011; Accepted 13 June 2011

Academic Editor: Fauze Maluf-Filho

Copyright © 2012 F. Donnellan and M. F. Byrne. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Pancreatitis is the most common complication of ERCP. It can be associated with substantial morbidity. Hence, the minimization of both the incidence and severity of post-ERCP pancreatitis is paramount. Considerable efforts have been made to identify factors that may be associated with an increased risk of this complication. In addition, both procedure- and pharmacological-related interventions have been proposed that may prevent this complication. This paper outlines these interventions and presents the evidence to support their use in the prevention of post-ERCP pancreatitis.

## 1. Introduction

The prediction of post-ERCP pancreatitis is difficult. However, a number of factors have been identified that place patients at a relatively higher risk. These include both patient and procedure-related factors. A number of procedure-related interventions have been proposed that may reduce the risk of pancreatitis. Furthermore, identification of the mechanism of injury and the subsequent cascade of events leading to the clinical manifestation of pancreatitis has also resulted in the use of pharmacological interventions to reduce the risk of this complication.

This paper describes both the procedure- and pharmacological-related interventions currently being proposed for use in the prevention of post-ERCP pancreatitis.

## 2. Diagnosis of Post-ERCP Pancreatitis

Post-ERCP pancreatitis is defined as acute pancreatitis that has developed de novo following ERCP and, based on consensus guidelines proposed by Cotton et al. in 1991, is the presence of new pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase concentration occurring 24 hours after an ERCP, with pain severe enough to require admission to the hospital or to extend an admitted patient's length of stay [1].

The severity of post-ERCP pancreatitis is mainly based on the length of hospitalization: mild post-ERCP pancreatitis is defined as need for hospital admission or prolongation of planned admission up to 3 days, moderate post-ERCP pancreatitis as need for hospitalization of 4–10 days, and severe post-ERCP pancreatitis as hospitalization for more than 10 days, or hemorrhagic pancreatitis, pancreatic necrosis, or pseudocyst, or need for percutaneous drainage or surgical intervention.

## 3. Incidence of Post-ERCP Pancreatitis

Most studies reporting ERCP complications have specifically analyzed the risk associated with sphincterotomy. Freeman et al. demonstrated an overall incidence of post-ERCP pancreatitis of 5.4% following endoscopic biliary sphincterotomy in a multicentre prospective study of 2347 patients involving 17 centers, [2]. Based on consensus guidelines previously discussed [1], pancreatitis was graded as mild in 42%, moderate in 51%, and severe in 7% with a mortality rate of 0.8%. Pancreatitis was also found to be the most frequent complication occurring in 3.5% of cases in a systematic review of 21 studies involving 16,885 patients undergoing unselected ERCP (both diagnostic and therapeutic). It was graded as mild in 45%, moderate in 44%, and severe in 11% of cases with a mortality rate of 3% [3].

Table 1: Risk factors associated with the development of post-ERCP pancreatitis. Risk factors, apart from ampullectomy, are significant by multivariate analyses in prospective multicenter studies and by meta-analysis [3–6]. Ampullectomy is generally accepted to be a risk factor for pancreatitis. SOD: sphincter of Oddi dysfunction.

| Patient-related factors | Procedure-related factors | Operator-related factors |
|---|---|---|
| Female | Precut sphincterotomy | Trainee involvement |
| SOD | Pancreatic duct injection | |
| Previous pancreatitis | Balloon dilation of intact sphincter | |
| Chronic pancreatitis absent | Pancreatic sphincterotomy | |
| Younger age (<60 years) | Difficult cannulation | |
| Normal bilirubin | Minor papilla sphincterotomy | |
| | Pain during ERCP | |
| | Ampullectomy | |

## 4. Mechanisms of Post-ERCP Pancreatitis

sA number of mechanisms have been proposed as potential triggering factors in the development post-ERCP pancreatitis. Mechanical injury to both the papilla and pancreatic duct may occur in response to instrumental manipulation resulting in impaired drainage from the pancreas. Thermal injury may develop following application of electrosurgical current during biliary or pancreatic sphincterotomy. Chemical injury may result following injection of contrast medium into the pancreatic duct. Hydrostatic injury may result following injection of contrast medium into the pancreatic duct or from infusion of water or saline solution during sphincter manometry. Irrespective of the mechanism, the initial injury leads to a cascade of event resulting in the premature activation of proteolytic enzymes, autodigestion, and impaired acinar secretion with subsequent clinical manifestations of local and systemic effects of pancreatitis. Most approaches to the prevention of post-ERCP pancreatitis are aimed at interruption of one of the points in this cascade.

## 5. Risk Factors for Post-ERCP Pancreatitis

It is important to identify cases in which there is a relatively higher risk of pancreatitis so that preventive measures such as pancreatic stenting or pharmacological prophylaxis may be considered. Assessment of both patient- and procedure-related factors is important to determine such high-risk cases (Table 1). Masci et al. in a meta-analysis of 15 studies identified three patient-related and two procedure-related factors associated with a definite risk of post-ERCP pancreatitis. The patient-related factors included suspected sphincter of Oddi dysfunction (relative risk (RR) 4.09, 95% CI 3.37–4.96; $P < 0.001$), female gender (RR 2.23, 95% CI 1.75–2.84; $P < 0.001$), and previous pancreatitis (RR 2.46, 95% CI 1.93–3.12; $P < 0.001$). The procedure-related factors included precut sphincterotomy (RR 2.71, 95% CI 2.02–3.63; $P < 0.001$) and pancreatic injection (RR 2.2, 95% CI 1.6–3.01; $P < 0.001$) [4].

Additionally, multiple attempts (greater than 10 attempts) at cannulation (odds ratio (OR) 14.9, 95% CI 10.50–21.26; $P < 0.001$), pain during ERCP (OR 1.9, 95% CI 1.113–3.438; $P = 0.01$) [5], minor papilla sphincterotomy (OR 3.82, 95% CI 2.003–7.106; $P < 0.0001$), age < 60 years (OR 1.61, 95% CI 1.33–2.402; $P = 0.04$), $\geqslant$2 contrast injections into the pancreatic duct (OR 1.5, 95% CI 1.046–2.103; $P = 0.03$), trainee involvement (OR 1.5, 95% CI 1.029–2.057; $P = 0.03$) [6], moderate to difficult cannulation (6 to greater than 15 attempts) (OR 3.41, 95% CI 2.13–5.47; $P = 0.0001$), pancreatic sphincterotomy (OR 3.07, 95% CI 1.64–5.75; $P = 0.0001$), a normal serum bilirubin (OR 1.89, 95% CI 1.22–2.93; $P = 0.0023$), and absence of chronic pancreatitis (OR 1.87, 95% CI 1.00–3.48; $P = 0.0471$) [7] have all been shown by multivariate analysis to be risk factors for post-ERCP pancreatitis. Furthermore, risk factors are likely to be cumulative so that patients with multiple factors are at an extremely high risk of developing pancreatitis [7].

## 6. Prevention of Post-ERCP Pancreatitis

### 6.1. The Endoscopist

*6.1.1. Case Volume.* The indications for ERCP are likely to be different in low volume compared with high-volume centers and hence might impact on the reported rates of pancreatitis. High-volume centers have been shown to perform a significantly larger number of more difficult procedures in patients at an increased risk of pancreatitis [5].

However, there is no evidence that ERCP case volume influences the rate of post-ERCP pancreatitis. Both Williams et al. [8] and Testoni et al. [5] demonstrated in prospective multicentre studies that the risk of pancreatitis was not associated with either the case volume of the single endoscopist or the center. In contrast, trainee participation has been shown to be a significant risk factor for the development of post-ERCP pancreatitis [6].

*The incidence of post-ERCP pancreatitis is not dependent on the case volume of the endoscopist or the center.*

### 6.2. ERCP Techniques

*6.2.1. Standard Cannulation.* The standard method of biliary cannulation at ERCP utilizes a catheter device with or without a soft tip guidewire. Contrast injection through the catheter can also facilitate deep cannulation of the common

bile duct. However, inadvertent contrast injection of the pancreatic duct may occur. In contrast, with guidewire cannulation, entry into either the bile or pancreatic duct is determined by fluoroscopy obviating the need for contrast injection and possible pancreatic duct filling.

While a large randomized controlled trial by Bailey et al. involving 413 patients failed to show a difference in pancreatitis between the two approaches (7.9% in the guidewire group versus 6.2% in the contrast group; $P = 0.48$) [9], a number of studies, with similarly large patient sizes, demonstrated a lower rate with guidewire cannulation (8.6% versus 16.6%; $P = 0.037$ [10], 2.0% versus 11.3%; $P = 0.001$ [11]).

Furthermore, Cheung et al. concluded from a systematic review of 7 randomized controlled trials totaling 2132 patients that guidewire cannulation significantly reduced the risk of pancreatitis compared with contrast injection (3.2% versus 8.7%; RR 0.38, 95% CI 0.19–0.76) [12].

*The wire-guided technique is recommended for biliary cannulation.*

*6.2.2. Pancreatic Duct Injection.* Pancreatic duct injection and in particular multiple injections are a risk factor for post-ERCP pancreatitis development [13]. As already mentioned, Cheng et al. found in a prospective multicentre study involving 15 US centers and 1115 patients that two or more contrast injections of the pancreatic duct were significantly associated with the development of pancreatitis [6]. Furthermore, Cheon et al. demonstrated in a retrospective study that a higher rate of pancreatitis was associated with any pancreatic duct opacification compared with bile duct opacification alone (6.9% versus 0.8%, $P = 0.001$) and an increased extent of duct opacification (head only versus head and body versus head, body, and tail) (3.6% versus 4.5% versus 8.6%) [14]. ERCP is being increasingly used in the diagnosis of pancreatic cystic neoplasms, in particular, to determine communication of the cyst with ductal system. If a pancreatogram is required in such circumstances, or indeed occurs inadvertently, it is recommended to keep the number of injections and the volume injected to a minimum [15].The mechanism by which contrast injection can cause pancreatitis remains controversial. The osmolality of the contrast media used has been proposed as a possible contributing factor. Low-osmolality is thought to be safer than high-osmolality contrast media as it is associated with less osmotically driven fluid shifts and subsequent lower increases in intraductal pressure. While the results from a number of randomized trials have been contradictory [16, 17], the meta-analysis by George et al. showed that there was no significant difference between high- and low-osmolality contrast media with respect to the development of pancreatitis [18].

*Pancreatic duct injection, if occurs inadvertently or required, should be kept to a minimum.*

*6.2.3. Pancreatic Guidewire-Assisted Biliary Cannulation.* Pancreatic guidewire placement can be effectively used to facilitate biliary access, by straightening the ampulla and preventing pancreatic duct cannulation. This technique has been used in selected cases of difficult biliary cannulation where the pancreatic duct is unintentionally cannulated repeatedly and relatively easily [19]. Two randomized controlled studies comparing this technique with continuing standard cannulation have produced conflicting results regarding the development of post-ERCP pancreatitis. In the study by Maeda et al., no cases of pancreatitis were identified in 53 randomized patients. Furthermore, no pancreatic stents were placed [20]. In contrast, Herreros de Tejada et al. demonstrated a nonstatistically significant higher rate of pancreatitis in the pancreatic guidewire group (97 patients) compared with the standard cannulation group (91 patients) (17% versus 8%; $P = 0.079$) [21]. 12 out of 97 patients in the pancreatic guidewire group in this latter study underwent pancreatic stenting. The question of whether pancreatic stenting is required subsequent to guidewire placement was addressed in a randomized controlled study by Ito et al. They found a significantly lower risk of pancreatitis in 35 patients in whom a pancreatic stent (5 French 4 cm single pigtail) was inserted following guidewire placement compared to the same number of patients in whom no stent was inserted (2.9% versus 23%; RR 0.13, CI 0.016–0.95) [22].

*Pancreatic duct stenting after guidewire placement for achieving selective biliary cannulation is recommended to reduce the incidence of post-ERCP pancreatitis.*

*6.2.4. Pancreatic Duct Stenting.* Impaired drainage of the pancreatic duct, resulting from papillary edema or spasm of the sphincter of Oddi, has been proposed as a cause or a risk factor for the development of post-ERCP pancreatitis. This has resulted in placement of pancreatic duct stents in high-risk cases in an effort to prevent post-ERCP pancreatitis. However, there is no consensus as to exactly which cases merit stent placement.

A number of prospective randomized trials have demonstrated the benefit of pancreatic stent insertion in reducing both the rate and severity of post-ERCP pancreatitis after difficult cannulation, needle-knife precut, biliary sphincterotomy for sphincter of Oddi dysfunction (SOD) and manometry, pancreatic sphincterotomy, and endoscopic balloon dilation [23–31] (Table 2). The recent meta-analysis by Choudhary et al. further confirmed these results demonstrating that prophylactic pancreatic stent placement significantly decreased the odds of post-ERCP pancreatitis (OR, 0.22; 95% CI, 0.12–0.38; $P = 0.01$) [32].

Pancreatic stents are not without problems. Follow-up evaluation is necessary to ensure passage or removal. In addition, placement can be technically difficult. Smithline et al. and Aizawa and Ueno found that stent placement was unsuccessful in 5 out of 48 patients (10.4%) and 2 out of 40 patients (5%), respectively [23, 28]. Furthermore, unsuccessful stent placement can itself be associated with a risk of pancreatitis. A prospective study of 225 high risk ERCPs by Freeman demonstrated that pancreatitis developed in 2 out of 3 patients (66.7%) in whom pancreatic stenting failed, compared to 32 out of 222 (14.4%) in whom stenting was successful ($P = 0.06$). Interestingly, stent placement was unsuccessful in 3 of the 93 cases in which conventional deep guidewire insertion into the pancreatic duct was used compared with none of the 132 cases in which a modified

Table 2: Studies demonstrating effect of pancreatic stenting on post-ERCP pancreatitis. Difficult cannulation was defined as that requiring greater than 30 minutes of manipulation to achieve successful cannulation.

| Study | Study no. | Rate of pancreatitis | | $P$ value | Indications for pancreatic stent placement | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No-stent group | Stent group | | SOD | Precut | Difficult cannulation | Balloon dilation | Pancreatic sphincterotomy |
| Smithline et al. [23] | 93 | 18% | 14% | 0.60 | + | + | | | |
| Sherman et al. [24] | 104 | 21% | 2% | 0.004 | | + | | | |
| Elton et al. [25] | 164 | 12.5% | 0.7% | 0.003 | | | | | + |
| Tarnasky et al. [26] | 80 | 26% | 7% | 0.03 | + | | | | |
| Patel et al. [27] | 36 | 33% | 11% | <0.05 | + | | | | |
| Aizawa and Ueno [28] | 130 | 6% | 0% | 0.11 | | | | + | |
| Fazel et al. [29] | 74 | 28% | 5% | 0.009 | + | | + | | |
| Sofuni et al. [30] | 211 | 13.6% | 3.2% | 0.019 | All consecutive ERCPs irrespective of specific risk factors | | | | |
| Tsuchiya et al. [31] | 64 | 12.5% | 3.1% | >0.05 | All consecutive ERCPs irrespective of specific risk factors | | | | |

technique involving an 0.018-inch guidewire, passed as little as 1 to 2 cm beyond the pancreatic sphincter, was used [33].

There is wide variation in both the guidewire and the type of stent used for prophylaxis of post-ERCP pancreatitis. Brackbill et al. found in a survey of biliary endoscopists that 33% used straight stents, 30% used pigtail stents, and 35% used a combination. In addition, the survey found that internal flanges were always used in 14%, never used in 54%, and sometimes used in 32% [34]. Two randomized controlled prospective studies have compared the outcomes of a short straight 5 French stent without an inner flange with an unflanged long single pigtail 3 French stent. The study by Guda et al., published only in abstract form, found a higher placement failure rate in the 3 French group of 36 patients, a higher spontaneous dislodgement rate in the 5 French group of 43 patients, and a similar pancreatitis rate [35]. Meanwhile, Chahal et al. demonstrated a significantly higher placement failure rate (8.3% versus 0%; $P = 0.0003$), a nonsignificant higher pancreatitis rate (14% versus 9%; $P = 0.3$), and a lower spontaneous stent dislodgement rate (88% versus 98%; $P = 0.0001$) in the 3 French group of 133 patients compared with the 5 French group of 116 patients [36].

There is little data on the duration a pancreatic stent should remain in place to reduce the risk of pancreatitis. Sherman et al. found a significantly higher rate of pancreatitis in 46 patients in whom the pancreatic stent was removed immediately following needle-knife precut compared to 47 patients in whom the stent remained in-placed for 7–10 days (2.2% versus 21.3%; $P = 0.004$). Furthermore, pancreatitis developed in 13.8% of the 58 patients in whom the precut was performed without stent placement [24]. The optimal duration however is not known. One expert recommendation suggests that pancreatic stenting for a minimum of 24 hours in high-risk cases such as SOD should suffice. In contrast, pancreatic stenting for a few hours should be satisfactory in lower-risk cases such as those where biliary access is difficult [33].

*With regard to pancreatic stenting, pancreatic stent placement reduces the rate of post-ERCP pancreatitis in high-risk cases. Short 5 French stents are easier to deploy and more likely to migrate spontaneously compared with long 3 French stents. However, they do not confer a benefit in terms of pancreatitis risk reduction. The optimal duration for stents to remain in place is unknown.*

*6.2.5. Endoscopic Sphincterotomy.* Thermal injury following application of electrosurgical current during biliary or pancreatic sphincterotomy has been implicated in the pathogenesis of post-ERCP pancreatitis [7, 37]. This is likely related to impaired drainage of the pancreatic duct from the resulting edema of the ampullary tissue. Pure current, in comparison to blended or "endocut" current, provides superior tissue cutting capability and, in theory, should be associated with less edema and a lower risk of pancreatitis. However, the incidence of bleeding is significantly higher when pure-cut current is used [38]. The type of current used for sphincterotomy and its association with pancreatitis have produced conflicting results.

In a randomized controlled study involving 170 patients, Elta et al. demonstrated that the use of pure-cut current was associated with a lower incidence of pancreatitis compared with blended current (3% versus 12%; $P < 0.05$) [39]. This was further supported by randomized controlled trial by Stefanidis et al. (3.2% versus 12.9%; $P = 0.048$) [40]. In contrast, both MacIntosh et al. and Norton et al. reported in randomized controlled trials of 246 and 267 patients, respectively, no significant difference in the rate of pancreatitis between pure-cut and blended current (7.8% versus 6.1%; $P = 0.62$ [41], 0.7% versus 2.3%; $P > 0.05$ [42]). A subsequent meta-analysis of these 4 trials by Verma et al. found no significant difference in the pancreatitis rates between pure-cut and blended current (3.8% versus 7.9%) [38].

*There is no consensus on the type of current to be utilized during sphincterotomy to minimize the risk of post-ERCP pancreatitis.*

*6.2.6. Balloon Sphincteroplasty (Endoscopic Papillary Balloon Dilation).* Balloon sphincteroplasty or endoscopic papillary balloon dilation is a technique to use for biliary stone extraction used as an alternative to, or in conjunction with, endoscopic sphincterotomy. It has the advantage of

preserving sphincter of Oddi function in younger patients [43], of lower bleeding rates compared with sphincterotomy [44], and of removing stones in Billroth II cases when sphincterotomy can be technically very challenging [45]. However, a multicentre randomized controlled trial found a significantly higher morbidity rate including pancreatitis following balloon sphincteroplasty in 117 patients compared to endoscopic sphincterotomy performed in 120 patients (15.4% versus 0.8%; $P < 0.001$) [46]. Indeed, there were 2 deaths due to pancreatitis following balloon sphincteroplasty and none following sphincterotomy. Furthermore, Baron and Harewood demonstrated in a meta-analysis of eight prospective randomized trials that post-ERCP pancreatitis occurred more commonly in the balloon dilation group (7.4% versus 4.3%, $P = 0.05$), leading the authors to conclude that it should be avoided in routine practice [44].

However, since the study by Baron and Harewood [44], a number of studies have demonstrated that balloon dilation following sphincterotomy can be used effectively and safely to extract bile duct stones. Maydeo and Bhandari demonstrated in a prospective study involving 60 patients that large diameter (12–15 mm) balloon dilation following endoscopic sphincterotomy did not result in any cases of postprocedure pancreatitis [47]. Furthermore, Heo et al. found no difference in the rate of pancreatitis in a prospective trial of 200 patients, equally randomized to either balloon dilation (12–20 mm) following sphincterotomy or sphincterotomy alone (4.0% in both groups) [48]. The safety of the combined procedure may be related to the force of the balloon exerted in the direction of the biliary sphincterotomy and away from the pancreatic orifice.

*Endoscopic papillary balloon dilation alone is associated with an unacceptably high risk of pancreatitis. This does not appear to be the case when it is performed in conjunction with endoscopic sphincterotomy.*

*6.2.7. Needle-Knife Precut.* Precutting with a needle knife is typically used for access to the biliary system when standard cannulation techniques have been unsuccessful. This technique has been shown to be an independent risk factor for pancreatitis [4, 49]. However, the risk may be related more to the multiple cannulation attempts or pancreatic duct injections rather than the precut technique itself. This issue has been addressed in a number of randomized prospective trials. Manes et al. randomized 151 patients to either needle-knife precut (fistulotomy) or persistence with standard cannulation in cases of difficult biliary cannulation defined as unsuccessful cannulation after 10 minutes. The pancreatitis rate was significantly lower in the precut group (2.6 versus 14.9%; $P = 0.008$) [50]. A further study by Cennamo et al., where patients were randomized to either precutting (needle knife papillotomy) or persistence with standard cannulation after 5 minutes, found a similarly lower rate of pancreatitis in the precut group (3% versus 5%) [51]. A subsequent meta-analysis involving 6 studies demonstrated that early precut implementation significantly reduced the risk of post-ERCP pancreatitis when compared with standard cannulation (2.5% versus 5.3%, OR 0.47, 95% CI 0.24–0.91) [52].

There are a number of different approaches to performing needle-knife precut. The most widely performed precut techniques include needle-knife papillotomy, where the precut starts at the papillary orifice, and needle-knife fistulotomy, where the precut is superior to and separate from the papillary orifice. However, there is little high level evidence on the optimal needle-knife technique to use. Mavrogiannis et al. found in a randomized prospective study a lower rate of pancreatitis in 74 patients who underwent needle-knife fistulotomy compared to 79 patients who underwent needle-knife precut papillotomy (0% versus 7.59%, $P < 0.05$) [53]. Abu-Hamda et al. demonstrated a similar lower rate of pancreatitis in a retrospective series comparing the fistulotomy technique in 44 patients with the papillotomy technique in 47 patients (0% versus 12.8%; $P = 0.03$). While the authors comment on the retrospective nature and small sample size of the study, they highlight the post-ERCP pancreatitis can be best minimized by completely avoiding the papillary orifice [54].

*Early needle-knife precut implementation in cases of difficult biliary cannulation is associated with a lower risk of post-ERCP pancreatitis compared with persistence with standard cannulation techniques. Needle-knife fistulotomy technique may be superior to needle-knife papillotomy.*

*6.2.8. Sphincter of Oddi Manometry (SOM) and Sphincter of Oddi Dysfunction (SOD).* Sphincter of Oddi manometry (SOM) is the gold standard diagnostic test for sphincter of Oddi dysfunction (SOD). It is generally accepted to be associated with a relatively higher risk of pancreatitis. There are a number of methods that have been shown to reduce this risk. Early manometry was performed using continuous perfusion compared with more recent manometry which involves continuous aspiration of the perfused fluid, in theory reducing the risk of perfusion-related hydrostatic ductal injury. Sherman et al. found in a randomized controlled trial involving 76 patients a significant reduction in pancreatitis when manometry was performed with an aspirating catheter compared with a standard perfusion catheter (3.0% versus 23.5%; $P = 0.01$) [55]. Specific manometry of either the bile or pancreatic sphincter may also be an important contributory factor to pancreatitis development. Rolny et al. reported acute pancreatitis in 11% of patients who had pancreatic manometry alone compared with 1% who had biliary manometry alone [56]. Indeed, Sherman et al., in a further study, found no difference in pancreatitis rates in 36 patients randomized to biliary manometry with either an aspirating or a standard catheter, suggesting that perfusion injury may only be a problem when pancreatic manometry is performed [57]. Prophylactic pancreatic stent placement has also been shown to be of benefit in reducing pancreatitis in cases of SOD and following manometry. The initial randomized controlled trial of 80 patients with SOD documented by positive manometry demonstrated that stenting significantly reduced the rate of pancreatitis following biliary sphincterotomy compared with controls (7% versus 26%; $P = 0.03$) [24]. A subsequent study by Fazel et al. of 76 high-risk patients defined as having difficult cannulation, or undergoing manometry or endoscopic sphincterotomy,

Table 3: Pharmacological agents that have been used in the prevention of post-ERCP pancreatitis.

| |
|---|
| *Agents with proven efficacy* |
| Non steroidal anti-inflammatory drugs |
| Diclofenac |
| *Agents with possible efficacy* |
| Ceftazidime |
| Glyceryl trinitrate |
| Octreotide |
| Protease inhibitors |
| Ulinastatin |
| Nafamostat |
| Somatostatin |
| *Agents with proven inefficacy* |
| Allopurinol |
| Corticosteroids |
| Heparin |
| N-acetylcysteine |
| Protease inhibitor |
| Gabexate |

found a significantly lower frequency of pancreatitis in those who underwent pancreatic stenting compared to those who did not (5% versus 28%; $P > 0.05$) [29].

There is some evidence to support that the risk of pancreatitis may be more likely related to the underlying SOD and not the manometry per se. Firstly, the rates of pancreatitis in the manometry studies performed with an aspirating catheter by Sherman et al. [55, 57] are similar to those for ERCP in general. Furthermore, the multicentre study by Freeman et al. found a similar rate of pancreatitis between those who underwent biliary sphincterotomy with suspected SOD and those who underwent sphincterotomy in conjunction with manometry (20.3% versus 17.9%). Interestingly, severe pancreatitis was more common in patients who underwent sphincterotomy without manometry (3.6% versus 0.8%) [2]. In addition, a retrospective review of 100 consecutive patients demonstrated a significantly lower rate of pancreatitis in patients who had manometry only compared to those who had undergone both manometry and ERCP (9.3% versus 26.1%). Performance of sphincterotomy did not increase the risk beyond that associated with ERCP [58].

*Potential methods for reducing the rate of pancreatitis associated with sphincter manometry include performing pancreatic manometry with an aspirating catheter, performing biliary manometry alone in cases of suspected biliary disease, and placing prophylactic pancreatic stents. However, it should not be assumed that avoiding manometry in suspected SOD will reduce the risk of post-ERCP pancreatitis.*

*6.2.9. Endoscopic Ampullectomy.* Endoscopic snare removal of the major duodenal papilla (endoscopic ampullectomy) has been advocated as a treatment for both adenomas that occur sporadically and in association with familial adenomatous polyposis [59].

*Postprocedure Pancreatitis .* A number of studies suggest that placement of a pancreatic stent reduces this risk. However, high-level evidence is lacking.

In a retrospective series of 16 patients by Zádorová et al., postampullectomy pancreatitis was reported in 0% and 20% of patients with and without a pancreatic stent, respectively [60]. Cheng et al. demonstrated in a further retrospective series of 55 patients that pancreatic stenting was associated with a lower, but not statistically significant, rate of pancreatitis (9.6% versus 25%; $P = 0.33$) [61]. In addition, a prospective trial by Harewood et al. found a significantly higher rate of pancreatitis in the 9 patients who did not undergo pancreatic stenting compared to the 10 patients who did (33% versus 0%; $P = 0.02$) [62]. However, this trial was stopped prematurely because of concerns of the risk of pancreatitis and did not reach the study's power calculation of 25 patients in each group.

*Although high-level evidence is not available, pancreatic stenting following endoscopic ampullectomy is recommended to reduce postprocedure pancreatitis.*

*6.3. Pharmacological Agents.* The ideal pharmacological agent should be highly effective in reducing post-ERCP pancreatitis, have a short administration time, be well tolerated with a low side-effect profile and cost-effective. Several agents have shown promise. However, the vast majority have fallen short of these goals (Table 3).

*6.3.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).* NSAIDs are potent inhibitors of a number of inflammatory mediators including prostaglandins and phospholipase-A2, and both of which may play a role in the pathophysiology of acute pancreatitis [63]. Elmunzer et al. demonstrated in a meta-analysis, from four randomized controlled trials involving 912 patients, that prophylactic rectal NSAIDs were effective in reducing pancreatitis, with a pooled relative risk after administration of 0.36 (95% CI 0.22–0.60) [64]. In addition, no adverse events attributable to NSAIDs were reported. Two of the trials evaluated rectal diclofenac immediately after procedure, while the other two evaluated rectal indomethacin immediately preprocedure, and all four found a positive result in post-ERCP pancreatitis reduction. Interestingly, the randomized prospective trial by Cheon et al. found no difference in the 105 patients who received oral diclofenac compared with the 102 patients who received placebo (16.2% versus 16.7%; $P$ = NS) [65]. Possible explanations for this difference may relate to peak plasma NSAID concentrations, which occur within 30 minutes with rectal administration in contrast to 2 hours with oral administration. Furthermore, bioavailability is reduced with oral administration because of first pass metabolism [66]. NSAIDs are relatively inexpensive and easy to administer as a once-off dose in comparison to other potentially promising agents which require continuous infusions and may not be readily available. Although routine rectal administration of 100 mg of diclofenac or indomethacin, immediately before

or after ERCP, is recommended in the guidelines published by the European Society of Gastrointestinal Endoscopy, this practice has not yet been widely adopted [15].

*6.3.2. Glyceryl Trinitrate.* Glyceryl trinitrate (GTN) is a smooth muscle relaxant which can lower basal pressure in the Sphincter of Oddi. It is most easily administered either by sublingual spray or transdermal patch. The results from single center prospective controlled trials of its effect on the reduction of post-ERCP pancreatitis are conflicting. Kaffes et al. found no benefit with the transdermal patch compared with placebo in 318 patients (7.7% versus 7.4%; $P$ = NS) [67], while Moretó et al. found a significant reduction in pancreatitis in 144 patients (15% versus 4.2%; $P < 0.05$) [68]. The conclusions drawn from a number of meta-analyses are similar. Bai et al. found, from 8 randomized controlled trials involving 1920 patients, that the incidence of pancreatitis was significantly reduced by GTN treatment compared with placebo (5.9% versus 9.8%; $P = 0.002$) [69]. In contrast, both meta-analyses by Bang et al. and Shao et al. did not show an overall significant reduction in post-ERCP pancreatitis [70, 71]. In addition to a benefit of GTN shown in some studies in the prophylaxis of post-ERCP pancreatitis, it is inexpensive, easy to administer, and has few major side effects. However, the optimal dose, timing, and route of administration require further clarification. Currently, it is not recommended for routine use in ERCP [15].

*6.3.3. Ceftazidime.* There is only one study which has evaluated a possible role for antibiotics in the prevention of post-ERCP pancreatitis. This prospective randomized controlled trial demonstrated that 2 g of the cephalosporin, ceftazidime administered intravenously 30 minutes before ERCP, significantly reduced the incidence of post-ERCP pancreatitis in the control group of 160 patients compared with the antibiotic group of 155 patients (9.4% versus 2.6%; $P = 0.009$) [72]. However, the quality of the study is questionable as the control group received no antibiotics rather than placebo. There have been no confirmatory studies on the use of antibiotics.

*6.3.4. Somatostatin and Octreotide.* Both somatostatin and its synthetic analogue, octreotide, are potent inhibitors of exocrine secretion of the pancreas, which play an important role in the pathogenesis of acute pancreatitis by causing autodigestion of the organ [73].

Two meta-analyses analyzed the efficacy of somatostatin for the prophylactic management of post-ERCP pancreatitis. Andriulli et al. included results from 9 studies and found a nonsignificant effect of somatostatin on pancreatitis (7.3% of controls versus 5.3% of treated patients; OR 0.73; 95% CI 0.54–1.006). Furthermore, this meta-analysis produced nonbeneficial results for both short- (<6 hours) and long-term (≥12 hours) somatostatin infusions (6.4% in controls versus 8.5% in treated patients; OR 1.361, 95% CI 0.886–2.091, 6.4% in controls versus 3.0% in treated patients; OR 0.447, 95% CI 0.133–1.508, resp.) [74]. Rudin et al. also demonstrated in a meta-analysis involving 3,130 patients from 7 studies that a short-term infusion (<12 hours) was not beneficial. However, this meta-analysis yielded a significant risk reduction of 7.7% for long-term somatostatin infusion (≥12 hours) [75].

Both meta-analyses included the same studies that looked at bolus administration of somatostatin prior to ERCP and found a significant reduction in post-ERCP pancreatitis rates (11.3% in controls versus 3.0% in treated patients; OR 0.271, 95% CI 0.138–0.536). However, the pancreatitis rate of the control patients in the bolus group was twice that of the control patients in both the short- and long-term infusion groups (11.3% versus 6.4% and 6.4%, resp.). This led the authors to conclude that caution should be applied when bolus administration of somatostatin is being considered [74].

Octreotide is a synthetic analogue with a longer half-life than somatostatin.The results from studies have produced conflicting results. Thomopoulos et al. demonstrated a significant reduction in the incidence of pancreatitis between octreotide (1.5 mg subcutaneously in three divided doses) 24 hours prior to ERCP and placebo in a multicentre randomized controlled trial involving 202 patients (2.0% versus 8.9%; $P = 0.03$) [76]. In contrast, Testoni et al. demonstrated no difference in 114 patients randomized to either octreotide (0.6 mg subcutaneously in three divided doses) 24 hours prior to ERCP or placebo (12.0% versus 14.3%; $P$ = NS) [77]. A subsequent meta-analysis of 15 studies found that octreotide was not beneficial in the prevention of post-ERCP pancreatitis [78]. However, a more recent meta-analysis involving 18 studies demonstrated that octreotide used at a dose of at least 0.5 mg significantly reduced the rate of post-ERCP pancreatitis compared with controls (3.4% versus 7.5%; $P = 0.001$). No benefit was identified when it was used at a lower dose (7.2% versus 6.0%; $P = 0.35$) [79]. The authors also concluded that there were insufficient data on the optimal timing and route of administration. Furthermore, the ESGE guidelines do not recommend octreotide for the prophylaxis of post-ERCP pancreatitis but comment that future studies should evaluate its efficacy at 0.5 mg or higher [15].

*6.3.5. Protease Inhibitors.* One of the initial events in the development of acute pancreatitis is intracellular activation of trypsin. Protease inhibitors prevent activation of trypsin and have been used for both the treatment of acute pancreatitis and for the prevention of post-ERCP pancreatitis. These include gabexate, ulinastatin, and nafamostat mesylate. The published evidence on a potential benefit of these agents in post-ERCP pancreatitis comes from high-level randomized controlled trials but has produced conflicting results.

Two such prospective randomized controlled trials have shown a benefit for the use of gabexate in the reduction of post-ERCP pancreatitis. Xiong et al. demonstrated a significant reduction in 97 patients treated with gabexate, commencing 30 minutes prior to ERCP and continuing for 4 hours after, compared to 96 patients treated with placebo (3.1% versus 10.5%; $P = 0.40$) [80]. Manes et al. found a similar reduction regardless of whether gabexate was administered pre- or post-ERCP (3.9% in group given gabexate 1 hour pre, versus 3.4% in group given gabexate

1 hour post, versus 9.4% in placebo group; $P < 0.01$) [81]. In contrast, Andriulli et al. demonstrated in two separate large multicentre trials that both short (2 hours) and long term administration (>6.5 hours) of gabexate was ineffective at reducing post-ERCP pancreatitis compared with placebo (6.5% versus 8.1%; $P$ = NS, 4.8% versus 5.8%; $P$ = NS) [82, 83]. A subsequent meta-analysis incorporating 5 studies reported that gabexate was ineffective for the prevention of post-ERCP pancreatitis [74].

One of the major drawbacks associated with gabexate is its short half-life of 55 seconds and hence the need for an infusion over several hours. In contrast, ulinastatin has a longer half-life of 35 minutes and can be given as a bolus injection [84]. Tsujino et al. found in a randomized, prospective trial, involving 406 patients, that ulinastatin (150,000 U) administered prior to ERCP significantly reduced the incidence of post-ERCP pancreatitis compared with placebo (2.9% versus 7.4%, $P = 0.041$) [85]. However, routine prophylactic use of ulinastatin prior to ERCP is unlikely to be cost-effective because the frequency of post-ERCP pancreatitis is low and the majority of cases are mild. With this in mind, Yoo et al. randomized 227 patients, identified during the ERCP to be at high risk of post-ERCP pancreatitis development, to either ulinastatin (100,000 U) or placebo immediately after the procedure and found no significant reduction in the treatment group (5.6% versus 6.7%; $P = 0.715$) [86]. This study was included in a recent meta-analysis of 7 randomized trials which demonstrated that ulinastatin reduced the incidence of post-ERCP pancreatitis (OR 0.53; 95% CI 0.31–0.89; $P = 0.02$) and subsequently concluded that ulinastatin was of value when administered prior to ERCP at a dose not less than 150,000 U to patients at average risk of developing pancreatitis [87].

To date, two prospective randomized controlled single-center trials have shown the benefit of nafamostat in the prevention off post-ERCP pancreatitis [88, 89]. Choi et al. demonstrated a post-ERCP pancreatitis rate of 3.3% in the 354 patients treated with nafamostat compared with 7.4% in the 350 patients treated with placebo, commencing 1 hour before and continuing for 24 hours after ERCP ($P = 0.018$). Similarly, Yoo et al. found a significant reduction in the 286 patients equally randomized to either nafamostat or placebo, commenced 60 minutes prior to and continuing for hours after ERCP (2.8% versus 9.1%; $P = 0.03$). Despite these positive results, the length of infusion and routine prophylactic use are impractical. Further studies are required to determine if bolus injection and post-procedural administration in high-risk patients produce a similar risk reduction.

Protease inhibitors have shown some promise. However, they are costly and may require hospital admission because of duration of administration postprocedure, and, as a recent meta-analysis shows, the numbers needed to treat to prevent a single episode of post-ERCP pancreatitis are extremely high (gabexate = 33.3 and ulinastatin = 28.6) [90].

## 7. Allopurinol

Capillary endothelial injury, mediated by oxygen-derived free radicals, may be involved in the pathogenesis of acute pancreatitis [91, 92]. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, which generates oxygen-derived free radicals.

Allopurinol is a xanthine oxidase inhibitor. Marks et al. initially demonstrated in an animal model that pretreatment with oral allopurinol decreased the incidence of ERCP-induced pancreatitis [93]. The results from subsequent human studies have been conflicting. Both Katsinelos et al. and Martinez-Torres et al. demonstrated, in prospective placebo-controlled trials of 243 and 170 patients, respectively, a benefit for its use in the prevention of post-ERCP pancreatitis [94, 95]. In the former, patients received 600 mg dose at 15 and 3 hours prior to ERCP with a subsequent significant reduction in post-ERCP pancreatitis compared with placebo (3.2% versus 17.8%; $P < 0.001$), while in the latter, patients received 300 mg at the same timing with a similar significant reduction compared with placebo (2.3% versus 9.4%; $P = 0.04$). In contrast, Mosler et al. found in a prospective randomized trial of 701 patients no difference between allopurinol and placebo administered at 4 hours and 1 hour preprocedure (12.96% versus 12.14%; $P = 0.52$) [96]. In addition, Romagnuolo et al. did not demonstrate a significant reduction in post-ERCP pancreatitis rates in 586 patients randomized to either 300 mg allopurinol or placebo 1 hour prior to ERCP (5.5% versus 4.1%; $P = 0.44$) [97]. The conflicting results from these studies may suggest that both the dose and timing of administration of allopurinol may influence the development of post-ERCP pancreatitis. However, a subsequent meta-analysis incorporating 6 randomized controlled trials and 1554 patients demonstrated that prophylactic allopurinol did not reduce the frequency or severity of post-ERCP pancreatitis and led the authors to conclude that allopurinol should not be recommended for the prophylactic prevention of post-ERCP pancreatitis [98].

*7.1. Corticosteroids.* In a prospective randomized controlled multicentre study of 1115 patients, prophylaxis with 40 mg of oral prednisone did not alter either the frequency (16.6% in the prednisone group versus 13.6% in the placebo group; $P = 0.19$) or the severity of pancreatitis compared with placebo [99].

*7.2. Heparin.* Heparin has an inhibitory effect on proteases in both plasma and pancreatic tissue and also improves pancreatic microcirculation during experimental pancreatitis [100]. It has been suggested as a potential treatment in the prevention of post-ERCP pancreatitis. However, a prospective randomized controlled multicentre study demonstrated that subcutaneous low molecular weight heparin in 221 patients offered no benefit compared to placebo in 227 patients in terms of reduction of pancreatitis (8.1% versus 8.8%; $P = 0.87$) [101].

*7.3. N-Acetylcysteine.* N-acetylcysteine is a free radical scavenger and has been shown to decrease the incidence and severity of experimental pancreatitis [102]. However, two randomized controlled trials have not shown its benefit in the prevention of post-ERCP pancreatitis. Both Katsinelos et al. [103] and Milewski et al. [104] found no difference

in pancreatitis rates in 249 patients (12.1% versus 9.6%; $P > 0.05$) and 106 patients (7.3% versus 11.8%; $P$ = NS) randomized to N-acetylcysteine or placebo, respectively.

*While a number of agents have shown promise in clinical trials, there is currently no accepted pharmacologic intervention to prevent post-ERCP pancreatitis. However, this continues to be an active area of research.*

## 8. Conclusions

Awareness of both patient- and procedure-related factors for the development of post-ERCP pancreatitis can be used to risk stratify patients in particular to identify those in which pharmacological or procedural interventions should be considered.

ERCP should be avoided in unnecessary or low yield cases especially when multiple patient-related risk factors for the development of pancreatitis are present. A number of pharmacological agents, in particular rectal NSAIDs, have also shown promise, but none are currently being consistently used. The procedural interventions that have been demonstrated to reduce the incidence of post-ERCP pancreatitis including guide-wire cannulation rather than contrast injection, and pancreatic stent placement in high-risk cases.

## References


[1] P. B. Cotton, G. Lehman, J. Vennes et al., "Endoscopic sphincterotomy complications and their management: an attempt at consensus," *Gastrointestinal Endoscopy*, vol. 37, no. 3, pp. 383–393, 1991.

[2] M. L. Freeman, D. B. Nelson, S. Sherman et al., "Complications of endoscopic biliary sphincterotomy," *The New England Journal of Medicine*, vol. 335, no. 13, pp. 909–918, 1996.

[3] A. Andriulli, S. Loperfido, G. Napolitano et al., "Incidence rates of post-ERCP complications: a systematic survey of prospective studies," *The American Journal of Gastroenterology*, vol. 102, no. 8, pp. 1781–1788, 2007.

[4] E. Masci, A. Mariani, S. Curioni, and P. A. Testoni, "Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis," *Endoscopy*, vol. 35, no. 10, pp. 830–834, 2003.

[5] P. A. Testoni, A. Mariani, and A. Giussani, "Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study," *The The American Journal of Gastroenterology*, vol. 105, no. 8, pp. 1753–1761, 2010.

[6] C. L. Cheng, S. Sherman, J. L. Watkins et al., "Risk factors for post-ERCP pancreatitis: a prospective multicenter study," *The American Journal of Gastroenterology*, vol. 101, no. 1, pp. 139–147, 2006.

[7] M. L. Freeman, J. A. DiSario, D. B. Nelson et al., "Risk factors for post-ERCP pancreatitis: a prospective, multicenter study," *Gastrointestinal Endoscopy*, vol. 54, no. 4, pp. 425–434, 2001.

[8] E. J. Williams, S. Taylor, P. Fairclough et al., "Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study," *Endoscopy*, vol. 39, no. 9, pp. 793–801, 2007.

[9] A. A. Bailey, M. J. Bourke, S. J. Williams et al., "A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis," *Endoscopy*, vol. 40, no. 4, pp. 296–301, 2008.

[10] E. L. A. Artifon, P. Sakai, J. E. M. Cunha, B. Halwan, S. Ishioka, and A. Kumar, "Guidewire cannulation reduces risk of post-ERCP pancreatitis and facilitates bile duct cannulation," *The American Journal of Gastroenterology*, vol. 102, no. 10, pp. 2147–2153, 2007.

[11] T. H. Lee, D. H. Park, J. Y. Park et al., "Can wire-guided cannulation prevent post-ERCP pancreatitis? A prospective randomized trial," *Gastrointestinal Endoscopy*, vol. 69, no. 3, pp. 444–449, 2009.

[12] J. Cheung, K. K. Tsoi, W. L. Quan, J. Y. W. Lau, and J. J. Y. Sung, "Guidewire versus conventional contrast cannulation of the common bile duct for the prevention of post-ERCP pancreatitis: a systematic review and meta-analysis," *Gastrointestinal Endoscopy*, vol. 70, no. 6, pp. 1211–1219, 2009.

[13] J. Vandervoort, R. M. Soetikno, T. C. K. Tham et al., "Risk factors for complications after performance of ERCP," *Gastrointestinal Endoscopy*, vol. 56, no. 5, pp. 652–656, 2002.

[14] Y. K. Cheon, K. B. Cho, J. L. Watkins et al., "Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacificationA figure is presented," *Gastrointestinal Endoscopy*, vol. 65, no. 3, pp. 385–393, 2007.

[15] J. M. Dumonceau, A. Andriulli, J. Deviere et al., "European Society of Gastrointestinal Endoscopy (ESGE)Guideline: prophylaxis of post-ERCP pancreatitis," *Endoscopy*, vol. 42, no. 6, pp. 503–515, 2010.

[16] J. S. Barkin, G. L. Casal, D. K. Reiner, R. I. Goldberg, R. S. Phillips, and S. Kaplan, "A comparative study of contrast agents for endoscopic retrograde pancreatography," *The American Journal of Gastroenterology*, vol. 86, no. 10, pp. 1437–1441, 1991.

[17] G. K. Johnson, J. E. Geenen, R. A. Bedford et al., "A comparision of nonionic versus ionic contrast media: results of a prospective multicenter study," *Gastrointestinal Endoscopy*, vol. 42, no. 4, pp. 312–316, 1995.

[18] S. George, A. A. Kulkarni, G. Stevens, C. E. Forsmark, and P. Draganov, "Role of osmolality of contrast media in the development of post-ERCP pancreatitis: a metanalysis," *Digestive Diseases and Sciences*, vol. 49, no. 3, pp. 503–508, 2004.

[19] J. M. Dumonceau, J. Deviere, and M. Cremer, "A new method of achieving deep cannulation of the common bile duct during endoscopic retrograde cholangiopancreatography," *Endoscopy*, vol. 30, no. 7, p. S80, 1998.

[20] S. Maeda, H. Hayashi, O. Hosokawa et al., "Prospective randomized pilot trial of selective biliary cannulation using pancreatic guide-wire placement," *Endoscopy*, vol. 35, no. 9, pp. 721–724, 2003.

[21] A. Herreros de Tejada, J. L. Calleja, G. Díaz et al., "Double-guidewire technique for difficult bile duct cannulation: a multicenter randomized, controlled trial," *Gastrointestinal Endoscopy*, vol. 70, no. 4, pp. 700–709, 2009.

[22] K. Ito, N. Fujita, Y. Noda et al., "Can pancreatic duct stenting prevent post-ERCP pancreatitis in patients who undergo pancreatic duct guidewire placement for achieving selective biliary cannulation? A prospective randomized controlled trial," *Journal of Gastroenterology*, vol. 45, no. 11, pp. 1183–1191, 2010.

[23] A. Smithline, W. Silverman, D. Rogers et al., "Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in

high-risk patients," *Gastrointestinal Endoscopy*, vol. 39, no. 5, pp. 652–657, 1993.

[24] S. Sherman, D. T. Earle, L. Bucksot et al., "Does leaving a main pancreatic duct stent in place reduce the incidence of precut biliary sphincterotomy (ES)-induced pancreatitis? A final analysis of a randomized prospective study," *Gastrointestinal Endoscopy*, vol. 43, p. A486, 1996.

[25] E. Elton, D. A. Howell, W. G. Parsons, T. Qaseem, and B. L. Hanson, "Endoscopic pancreatic sphincterotomy: indications, outcome, and a safe stentless technique," *Gastrointestinal Endoscopy*, vol. 47, no. 3, pp. 240–249, 1998.

[26] P. R. Tarnasky, Y. Y. Palesch, J. T. Cunningham, P. D. Mauldin, P. B. Cotton, and R. H. Hawes, "Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction," *Gastroenterology*, vol. 115, no. 6, pp. 1518–1524, 1998.

[27] R. Patel, P. Tarnasky, W. S. Hennessy et al., "Does stenting after pancreatic sphincterotomy reduce post-ERCP pancreatitis in patients with prior biliary sphincterotomy? Preliminary results of a prospective randomized controlled trial," *Gastrointestinal Endoscopy*, vol. 49, p. AB80, 1999.

[28] T. Aizawa and N. Ueno, "Stent placement in the pancreatic duct prevents pancreatitis after endoscopic sphincter dilation for removal of bile duct stones," *Gastrointestinal Endoscopy*, vol. 54, no. 2, pp. 209–213, 2001.

[29] A. Fazel, A. Quadri, M. F. Catalano, S. M. Meyerson, and J. E. Geenen, "Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study," *Gastrointestinal Endoscopy*, vol. 57, no. 3, pp. 291–294, 2003.

[30] A. Sofuni, H. Maguchi, T. Itoi et al., "Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent," *Clinical Gastroenterology and Hepatology*, vol. 5, no. 11, pp. 1339–1346, 2007.

[31] T. Tsuchiya, T. Itoi, A. Sofuni et al., "Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 14, no. 3, pp. 302–307, 2007.

[32] A. Choudhary, M. L. Bechtold, M. Arif et al., "Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review," *Gastrointestinal Endoscopy*, vol. 73, no. 2, pp. 275–282, 2011.

[33] M. L. Freeman, "Pancreatic Stents for Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis," *Clinical Gastroenterology and Hepatology*, vol. 5, no. 11, pp. 1354–1365, 2007.

[34] S. Brackbill, S. Young, P. Schoenfeld, and G. Elta, "A survey of physician practices on prophylactic pancreatic stents," *Gastrointestinal Endoscopy*, vol. 64, no. 1, pp. 45–52, 2006.

[35] N. M. Guda, M. F. Catalano, and J. E. Geenen, "Post ERCP pancreatitis: differences in outcomes between 3 Fr long Pigtail and modified short 5 Fr Geenen stents: a randomized controlled trial," *Gastrointestinal Endoscopy*, vol. 65, p. AB113, 2007.

[36] P. Chahal, P. R. Tarnasky, B. T. Petersen et al., "Short 5Fr vs Long 3Fr Pancreatic Stents in Patients at Risk for Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis," *Clinical Gastroenterology and Hepatology*, vol. 7, no. 8, pp. 834–839, 2009.

[37] M. L. Freeman, "Complications of endoscopic biliary sphincterotomy: a review," *Endoscopy*, vol. 29, no. 4, pp. 288–297, 1997.

[38] D. Verma, A. Kapadia, and D. G. Adler, "Pure versus mixed electrosurgical current for endoscopic biliary sphincterotomy: a meta-analysis of adverse outcomes," *Gastrointestinal Endoscopy*, vol. 66, no. 2, pp. 283–290, 2007.

[39] G. H. Elta, J. L. Barnett, R. T. Wille, K. A. Brown, W. D. Chey, and J. M. Scheiman, "Pure cut electrocautery current for sphincterotomy causes less post- procedure pancreatitis than blended current," *Gastrointestinal Endoscopy*, vol. 47, no. 2, pp. 149–153, 1998.

[40] G. Stefanidis, G. Karamanolis, N. Viazis et al., "A comparative study of postendoscopic sphincterotomy complications with various types of electrosurgical current in patients with choledocholithiasis," *Gastrointestinal Endoscopy*, vol. 57, no. 2, pp. 192–197, 2003.

[41] D. G. MacIntosh, J. Love, and N. S. Abraham, "Endoscopic sphincterotomy by using pure-cut electrosurgical current and the risk of post-ERCP pancreatitis: a prospective randomized trial," *Gastrointestinal Endoscopy*, vol. 60, no. 4, pp. 551–556, 2004.

[42] I. D. Norton, B. T. Petersen, J. Bosco et al., "A randomized trial of endoscopic biliary sphincterotomy using pure-cut versus combined cut and coagulation waveforms," *Clinical Gastroenterology and Hepatology*, vol. 3, no. 10, pp. 1029–1033, 2005.

[43] I. Yasuda, E. Tomita, M. Enya, T. Kato, and H. Moriwaki, "Can endoscopic papillary balloon dilation really preserve sphincter of oddi function?" *Gut*, vol. 49, no. 5, pp. 686–691, 2001.

[44] T. H. Baron and G. C. Harewood, "Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials," *The American Journal of Gastroenterology*, vol. 99, no. 8, pp. 1455–1460, 2004.

[45] J. J. G. H. M. Bergman, A. M. Van Berkel, M. J. Bruno et al., "A randomized trial of endoscopic balloon dilation and endoscopic sphincterotomy for removal of bile duct stones in patients with a prior Billroth II gastrectomy," *Gastrointestinal Endoscopy*, vol. 53, no. 1, pp. 19–26, 2001.

[46] J. A. Disario, M. L. Freeman, D. J. Bjorkman et al., "Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones," *Gastroenterology*, vol. 127, no. 5, pp. 1291–1299, 2004.

[47] A. Maydeo and S. Bhandari, "Balloon sphincteroplasty for removing difficult bile duct stones," *Endoscopy*, vol. 39, no. 11, pp. 958–961, 2007.

[48] J. H. Heo, D. H. Kang, H. J. Jung et al., "Endoscopic sphincterotomy plus large-balloon dilation versus endoscopic sphincterotomy for removal of bile-duct stones," *Gastrointestinal Endoscopy*, vol. 66, no. 4, pp. 720–726, 2007.

[49] S. Loperfido, G. Angelini, G. Benedetti et al., "Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study," *Gastrointestinal Endoscopy*, vol. 48, no. 1, pp. 1–10, 1998.

[50] G. Manes, P. Di Giorgio, A. Repici, G. MacArri, S. Ardizzone, and G. B. Porro, "An analysis of the factors associated with the development of complications in patients undergoing precut sphincterotomy: a prospective, controlled, randomized, multicenter study," *The American Journal of Gastroenterology*, vol. 104, no. 10, pp. 2412–2417, 2009.

[51] V. Cennamo, L. Fuccio, A. Repici et al., "Timing of precut procedure does not influence success rate and complications of ERCP procedure: a prospective randomized comparative

study," *Gastrointestinal Endoscopy*, vol. 69, no. 3, pp. 473–479, 2009.

[52] V. Cennamo, L. Fuccio, R. M. Zagari et al., "Can early precut implementation reduce endoscopic retrograde cholangiopancreatography-related complication risk? Meta-analysis of randomized controlled trials," *Endoscopy*, vol. 42, no. 5, pp. 381–388, 2010.

[53] C. Mavrogiannis, C. Liatsos, A. Romanos, C. Petoumenos, A. Nakos, and G. Karvountzis, "Needle-knife fistulotomy versus needle-knife precut papillotomy for the treatment of common bile duct stones," *Gastrointestinal Endoscopy*, vol. 50, pp. 334–339, 1999.

[54] E. M. Abu-Hamda, T. H. Baron, D. T. Simmons, and B. T. Petersen, "A retrospective comparison of outcomes using three different precut needle knife techniques for biliary cannulation," *Journal of Clinical Gastroenterology*, vol. 39, no. 8, pp. 717–721, 2005.

[55] S. Sherman, F. P. Troiano, R. H. Hawes, and G. A. Lehman, "Sphincter of Oddi manometry: decreased risk of clinical pancreatitis with use of a modified aspirating catheter," *Gastrointestinal Endoscopy*, vol. 36, no. 5, pp. 462–466, 1990.

[56] P. Rolny, B. Anderberg, I. Ihse, E. Lindstrom, G. Olaison, and A. Arvill, "Pancreatitis after sphincter of Oddi manometry," *Gut*, vol. 31, no. 7, pp. 821–824, 1990.

[57] S. Sherman, R. H. Hawes, F. P. Troiano, and G. A. Lehman, "Pancreatitis following bile duct sphincter of Oddi manometry: utility of the aspirating catheter," *Gastrointestinal Endoscopy*, vol. 38, no. 3, pp. 347–350, 1992.

[58] M. E. Maldonado, P. G. Brady, J. J. Mamel, and B. Robinson, "Incidence of pancreatitis in patients undergoing sphincter of Oddi manometry (SOM)," *The American Journal of Gastroenterology*, vol. 94, no. 2, pp. 387–390, 1999.

[59] K. F. Binmoeller, S. Boaventura, K. Ramsperger, and N. Soehendra, "Endoscopic snare excision of benign adenomas of the papilla of Vater," *Gastrointestinal Endoscopy*, vol. 39, no. 2, pp. 127–131, 1993.

[60] Z. Zádorová, M. Dvořák, and J. Hajer, "Endoscopic therapy of benign tumors of the papilla of Vater," *Endoscopy*, vol. 33, no. 4, pp. 345–347, 2001.

[61] C. L. Cheng, S. Sherman, E. L. Fogel et al., "Endoscopic snare papillectomy for tumors of the duodenal papillae," *Gastrointestinal Endoscopy*, vol. 60, no. 5, pp. 757–764, 2004.

[62] G. C. Harewood, N. L. Pochron, and C. J. Gostout, "Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla," *Gastrointestinal Endoscopy*, vol. 62, no. 3, pp. 367–370, 2005.

[63] J. A. Viedma, M. Perez-Mateo, J. Agullo, J. E. Dominguez, and F. Carballo, "Inflammatory response in the early prediction of severity in human acute pancreatitis," *Gut*, vol. 35, no. 6, pp. 822–827, 1994.

[64] B. J. Elmunzer, A. K. Waljee, G. H. Elta, J. R. Taylor, S. M. A. Fehmi, and P. D. R. Higgins, "A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis," *Gut*, vol. 57, no. 9, pp. 1262–1267, 2008.

[65] Y. K. Cheon, K. B. Cho, J. L. Watkins et al., "Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial," *Gastrointestinal Endoscopy*, vol. 66, no. 6, pp. 1126–1132, 2007.

[66] N. M. Davies and K. E. Andersen, "Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls," *Clinical Pharmacokinetics*, vol. 33, no. 3, pp. 184–213, 1997.

[67] A. J. Kaffes, M. J. Bourke, S. Ding, A. Alrubaie, V. Kwan, and S. J. Williams, "A prospective, randomized, placebo-controlled trial of transdermal glyceryl trinitrate in ERCP: effects on technical success and post-ERCP pancreatitis," *Gastrointestinal Endoscopy*, vol. 64, no. 3, pp. 351–357, 2006.

[68] M. Moretó, M. Zaballa, I. Casado et al., "Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: a randomized double-blind trial," *Gastrointestinal Endoscopy*, vol. 57, no. 1, pp. 1–7, 2003.

[69] Y. Bai, C. Xu, X. Yang, J. Gao, D. W. Zou, and Z. S. Li, "Glyceryl trinitrate for prevention of pancreatitis after endoscopic retrograde cholangiopancreatography: a meta-analysis of randomized, double-blind, placebo-controlled trials," *Endoscopy*, vol. 41, no. 8, pp. 690–695, 2009.

[70] U. C. Bang, C. Nojgaard, P. K. Andersen, and P. Matzen, "Meta-analysis: nitroglycerin for prevention of post-ERCP pancreatitis," *Alimentary Pharmacology & Therapeutics*, vol. 29, pp. 1078–1085, 2009.

[71] L. M. Shao, Q. Y. Chen, M. Y. Chen, and J. T. Cai, "Nitroglycerin in the prevention of post-ERCP pancreatitis: a meta-analysis," *Digestive Diseases and Sciences*, vol. 55, no. 1, pp. 1–7, 2010.

[72] S. Räty, J. Sand, M. Pulkkinen, M. Matikainen, and I. Nordback, "Post-ERCP pancreatitis: reduction by routine antibiotics," *Journal of Gastrointestinal Surgery*, vol. 5, no. 4, pp. 339–345, 2001.

[73] Z. Tulassay and J. Papp, "The effect of long-acting somatostatin analogue on enzyme changes after endoscopic pancreatography," *Gastrointestinal Endoscopy*, vol. 37, no. 1, pp. 48–50, 1991.

[74] A. Andriulli, G. Leandro, T. Federici et al., "Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis," *Gastrointestinal Endoscopy*, vol. 65, no. 4, pp. 624–632, 2007.

[75] D. Rudin, A. Kiss, R. V. Wetz, and V. M. Sottile, "Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials," *Journal of Gastroenterology and Hepatology*, vol. 22, no. 7, pp. 977–983, 2007.

[76] K. C. Thomopoulos, N. A. Pagoni, K. A. Vagenas, V. G. Margaritis, G. I. Theocharis, and V. N. Nikolopoulou, "Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis," *Gastrointestinal Endoscopy*, vol. 64, no. 5, pp. 726–731, 2006.

[77] P. A. Testoni, F. Bagnolo, A. Andriulli et al., "Octreotide 24-h prophylaxis in patients at high risk for post-ERCP pancreatitis: results of a multicenter, randomized, controlled trial," *Alimentary Pharmacology & Therapeutics*, vol. 15, no. 7, pp. 965–972, 2001.

[78] Y. Bai, J. Gao, D. W. Zou, and Z. S. Li, "Prophylactic octreotide administration does not prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials," *Pancreas*, vol. 37, no. 3, pp. 241–246, 2008.

[79] Y. Zhang, Q. B. Chen, Z. Y. Gao, and W. F. Xie, "Meta-analysis: octreotide prevents post-ERCP pancreatitis, but only at sufficient doses," *Alimentary Pharmacology & Therapeutics*, vol. 29, no. 11, pp. 1155–1164, 2009.

[80] G. S. Xiong, S. M. Wu, X. W. Zhang, and Z. Z. Ge, "Clinical trial of gabexate in the prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis," *Brazilian Journal of Medical and Biological Research*, vol. 39, no. 1, pp. 85–90, 2006.

[81] G. Manes, S. Ardizzone, G. Lombardi, G. Uomo, O. Pieramico, and G. B. Porro, "Efficacy of postprocedure administration of gabexate mesylate in the prevention of post-ERCP pancreatitis: a randomized, controlled, multicenter study," *Gastrointestinal Endoscopy*, vol. 65, no. 7, pp. 982–987, 2007.

[82] A. Andriulli, R. Clemente, L. Solmi et al., "Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial," *Gastrointestinal Endoscopy*, vol. 56, no. 4, pp. 488–495, 2002.

[83] A. Andriulli, L. Solmi, S. Loperfido et al., "Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate," *Clinical Gastroenterology and Hepatology*, vol. 2, no. 8, pp. 713–718, 2004.

[84] B. M. Jonsson-Berling and K. Ohlsson, "Distribution and elimination of intravenously injected urinary trypsin inhibitor," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 51, no. 6, pp. 549–557, 1991.

[85] T. Tsujino, Y. Komatsu, H. Isayama et al., "Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial," *Clinical Gastroenterology and Hepatology*, vol. 3, no. 4, pp. 376–383, 2005.

[86] J. W. Yoo, J. K. Ryu, S. H. Lee et al., "Preventive effects of ulinastatin on post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients: a prospective, randomized, placebo-controlled trial," *Pancreas*, vol. 37, no. 4, pp. 366–370, 2008.

[87] S. Chen, H. Shi, X. Zou, and H. Luo, "Role of ulinastatin in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: the Emperor's new clothes or Aladdin's magic lamp?" *Pancreas*, vol. 39, no. 8, pp. 1231–1237, 2010.

[88] C. W. Choi, D. H. Kang, G. H. Kim et al., "Nafamostat mesylate in the prevention of post-ERCP pancreatitis and risk factors for post-ERCP pancreatitis," *Gastrointestinal Endoscopy*, vol. 69, no. 4, pp. e11–e18, 2009.

[89] K. S. Yoo, K. R. Huh, Y. J. Kim et al., "Nafamostat mesilate for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized, double-blind, controlled trial," *Pancreas*, vol. 40, no. 2, pp. 181–186, 2011.

[90] T. Seta and Y. Noguchi, "Protease inhibitors for preventing complications associated with ERCP: an updated meta-analysis," *Gastrointestinal Endoscopy*, vol. 73, no. 4, pp. 700–706, 2011.

[91] H. Sanfey and J. L. Cameron, "Increased capillary permeability: an early lesion in acute pancreatitis," *Surgery*, vol. 96, no. 3, pp. 485–491, 1984.

[92] H. Sanfey, G. B. Bulkley, and J. L. Cameron, "The role of oxygen-derived free radicals in the pathogenesis of acute pancreatitis," *Annals of Surgery*, vol. 200, no. 4, pp. 405–413, 1984.

[93] J. M. Marks, B. J. Dunkin, B. L. Shillingstad et al., "Pretreatment with allopurinol diminishes pancreatography-induced pancreatitis in a canine model," *Gastrointestinal Endoscopy*, vol. 48, no. 2, pp. 180–183, 1998.

[94] P. Katsinelos, J. Kountouras, J. Chatzis et al., "High-dose allopurinol for prevention of post-ERCP pancreatitis: a prospective randomized double-blind controlled trial," *Gastrointestinal Endoscopy*, vol. 61, no. 3, pp. 407–415, 2005.

[95] H. Martinez-Torres, X. Rodriguez-Lomeli, C. Davalos-Cobian et al., "Oral allopurinol to prevent hyperamylasemia and acute pancreatitis after endoscopic retrograde cholangiopancreatography," *World Journal of Gastroenterology*, vol. 15, no. 13, pp. 1600–1606, 2009.

[96] P. Mosler, S. Sherman, J. Marks et al., "Oral allopurinol does not prevent the frequency or the severity of post-ERCP pancreatitis," *Gastrointestinal Endoscopy*, vol. 62, no. 2, pp. 245–250, 2005.

[97] J. Romagnuolo, R. Hilsden, G. S. Sandha et al., "Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized placebo-controlled trial," *Clinical Gastroenterology and Hepatology*, vol. 6, no. 4, pp. 465–471, 2008.

[98] M. Zheng, Y. Chen, J. Bai, Y. Xin, X. Pan, and L. Zhao, "Meta-analysis of prophylactic allopurinol use in post-endoscopic retrograde cholangiopancreatography pancreatitis," *Pancreas*, vol. 37, no. 3, pp. 247–253, 2008.

[99] S. Sherman, U. Blaut, J. L. Watkins et al., "Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study," *Gastrointestinal Endoscopy*, vol. 58, no. 1, pp. 23–29, 2003.

[100] P. Toulon, G. Chadeuf, J. L. Bouillot et al., "Involvement of heparin cofactor II in chymotrypsin neutralization and in the pancreatic proteinase-antiproteinase interaction during acute pancreatitis in man," *European Journal of Clinical Investigation*, vol. 21, no. 3, pp. 303–309, 1991.

[101] T. Rabenstein, B. Fischer, V. Wiessner et al., "Low-molecular-weight heparin does not prevent acute post-ERCP pancreatitis," *Gastrointestinal Endoscopy*, vol. 59, no. 6, pp. 606–613, 2004.

[102] G. Yagci, H. Gul, A. Simsek et al., "Beneficial effects of N-acetylcysteine on sodium taurocholate-induced pancreatitis in rats," *Journal of Gastroenterology*, vol. 39, no. 3, pp. 268–276, 2004.

[103] P. Katsinelos, J. Kountouras, G. Paroutoglou, A. Beltsis, K. Mimidis, and C. Zavos, "Intravenous N-acetylcysteine does not prevent post-ERCP pancreatitis," *Gastrointestinal Endoscopy*, vol. 62, pp. 105–111, 2005.

[104] J. Milewski, G. Rydzewska, M. Degowska, M. Kierzkiewicz, and A. Rydzewski, "N-acetylcysteine does not prevent post-endoscopic retrograde cholangiopancreatography hyperamylasemia and acute pancreatitis," *World Journal of Gastroenterology*, vol. 12, no. 23, pp. 3751–3755, 2006.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2012, Article ID 190708, 8 pages
doi:10.1155/2012/190708

*Clinical Study*

# Combination of Conservative and Interventional Therapy Strategies for Intra- and Extrahepatic Cholangiocellular Carcinoma: A Retrospective Survival Analysis

**M. Knüppel,[1] S. Kubicka,[2] A. Vogel,[2] N. P. Malek,[2] M. Schneider,[3] F. Papendorf,[4] T. Greten,[5] J. Wedemeyer,[2] and A. Schneider[2]**

[1] *Departement of Anesthesiology and Intensive Care Medicine, Hannover Medical School, 30625 Hannover, Germany*
[2] *Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, 30625 Hannover, Germany*
[3] *Centre for Biometry, Medical Informatics and Medical Technology, Institute for Biometry, Hannover Medical School, 30625 Hannover, Germany*
[4] *Tumour Centre Hannover, Hannover Medical School, 30625 Hannover, Germany*
[5] *Gastrointestinal Malignancies, National Cancer Institute, Bethesda, MD 20892-8322, USA*

Correspondence should be addressed to M. Knüppel, m.knueppel@me.com

Received 4 December 2010; Revised 26 January 2011; Accepted 21 March 2011

Academic Editor: Jose G. de la Mora-Levy

Copyright © 2012 M. Knüppel et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Background*. Due to the predominantly advanced stage at the time of diagnosis treatment of cholangiocarcinoma is difficult. Apart from surgical resection, interventional treatment strategies are increasingly used in advanced stage tumours. The aim of the study was a retrospective comparison of the effect of the various forms of treatment on morbidity and mortality. *Method*. A total of 195 patients, received either chemotherapy or a combination of photodynamic therapy (PDT) or transarterial chemoembolization (TACE) and chemotherapy. *Results*. The median survival rate for all patients was 15.6 months, 50.8% were still alive 1 year after diagnosis. Patients, who had previously undergone surgery, survived 17.1 months longer than those without surgical treatment ($P < .01$). Chemotherapy prolonged the survival by 9.2 months ($P = .47$). Palliative patients under combination of chemotherapy and PDT survived on average 1.8 months longer ($P = .28$), with chemotherapy and TACE 9.8 months longer ($P = .04$) compared to chemotherapy alone. *Conclusions*. It appears that surgical treatment and chemotherapy combined with PDT or TACE may prolong survival.

## 1. Introduction

Carcinomas of the bile tract, a malignant neoplasia spreading from the bile duct epithelia, were described for the first time as tumours of the common hepatic duct by Durand-Fardel in 1840.

20–25% of all tumours are located intrahepatic, 50–60% perihilar, and 20–25% extrahepatic [1, 2]. The classification by Bismuth et al. [3] groups perihilar tumours located in the main branches of the biliary tree into four different categories. Type I tumours are limited to the common bile duct and are located more than 2 cm away from the confluence of right and left hepatic ducts while type II tumours involve the confluence. Type III tumours involve either the right (IIIa) or left (IIIb) hepatic duct while type IV tumours extend to both ducts or are located multifocally. "Klatskin" tumours are those with involvement of the hepatic duct bifurcation [4]. Today, cholangiocarcinoma is the second most frequent primary tumour disease of the liver, nevertheless, the prevalence rate is relatively low (2-3/100,000) compared with other tumours of the gastrointestinal tract [5, 6].

Due to the predominantly advanced tumour stage at the time of diagnosis, therapy of cholangiocarcinoma and gallbladder carcinoma remains difficult [7]. Currently, the only curative treatment is R0 resection [8]. However, in the majority of cases advanced tumour spread and lymph node involvement require a palliative approach. Surgical therapy

of perihilar Klatskin tumours depends on the Bismuth classification. Tumour of types I and II are treated with en-bloc resection of the extrahepatic bile ducts and the gallbladder, regional lymphadenectomy, and Roux-Y hepaticojejunostomy. In case of type III tumours an additional left or right hemihepatectomy is performed, whereas type IV tumours necessitate additional extended hemihepatectomy. The survival rate of patients with intrahepatic tumours is 18–24 months depending on the hilar infiltration [9].

Unresectable bile duct and gallbladder tumours are associated with a very poor prognosis. Apart from the recommendation for best supportive care, adequate drainage of the bile ducts with plastic or metal stent via endoscopic retrograde cholangiography (ERC) is an important element of the mainly palliative therapy [8, 10].

Bile duct tumours as well as gallbladder tumours are moderately chemotherapy-sensitive tumours. So far there is no standard protocol, thus patients in good general condition or with tumour-associated symptoms should be included in clinical trials evaluating palliative chemotherapy. For example, prolonged survival (4 months) and higher quality of life are reported for a small prospective randomised trial evaluating the combination of 5-FU/Leucovorin and Etoposide versus "best supportive care"; however these data are without significance [11]. Other study protocols cover treatment with gemcitabine or 5-FU as monotherapy as well as in combination with cisplatin and the combination of capecitabine with cisplatin/5-FU. The available data worldwide show that there might be a possibility to document the benefit of certain substances in trials with sufficiently large numbers of patients. Apart from the application of chemotherapeutic drugs interventional procedures applied and evaluated, for example transarterial chemoembolisation (TACE) [12, 13].

Another procedure is photodynamic therapy (PDT), whereby patients are given a photosensitizing agent (for example photofrin), which increasingly accumulates in malignant cells. Thereafter, transpapillary or percutaneous radiation with light of a specific wave length activates the sensitizing agent and generates reactive oxygen radicals. This leads to destruction of the tumour cells. In the early 1990's McCaughan reported on the first successful application of photodynamic therapy in the treatment of bile duct carcinoma [14]. A prospective study by Ortner et al. in the late 1990's showed a significant positive effect of PDT with Photofrin in combination with biliary stenting compared to drainage alone [15]. There are other studies confirming this tendency [16–21].

To date no comparative data are available on patients, who received chemotherapy alone or a combination of PDT or TACE and chemotherapy.

The aim of this retrospective study was to explore and compare data of a selective patient group with bile duct tumours treated with various forms of therapy regarding their effect on morbidity and mortality. All patients were treated in the Gastroenterological Day Clinic of Medizinische Hochschule Hannover (MHH).

## 2. Material and Methods

*2.1. Data Collection.* All patients undergoing treatment for a malignant bile duct tumour in the Gastroenterological Day Clinic of MHH between 1999 and 2005 were included in a retrospective analysis. The followup covered the period from diagnosis to death or last contact with the day clinic. Patient data were obtained from the MHH documentation system ALIDA and the H.I.T. data bank of the MHH Tumour Centre and entered into an individual own data bank (Microsoft Excel 2003, Germany).

The following data were collected: gender, date of birth, date of diagnosis and death, or date of last contact with the patient, height, body weight, BMI, localisation of the tumour, histology, histological/cytological confirmation, presence of various risk factors and symptoms, UICC/TNM classification, tumour markers CEA and CA 19-9, laboratory parameter (bilirubin, Quick, albumin, cholinesterase, GGT, ALT, and AST), previous operations and R-classification, and reason of death.

The patients were divided into two subgroups according to tumour localisation (ICD) and therapy distinguishing between patients with malignant tumours of the intrahepatic (C22.1) and extrahepatic bile ducts (C24.0), particularly Klatskin tumours of the hepatic duct bifurcation according to Bismuth.

*2.2. Therapy.* Generally, the patients received gemcitabine i.v. as chemotherapeutic drug. Alternatively, a combination of gemcitabine and cisplatin, gemcitabine, and oxaliplatin, 5-FU or 5-FU and oxaliplatin was applied.

Photodynamic therapy was performed in 3 sessions at 6 week intervals via ERC or PTCD according to the procedure established by Ortner/Berr et al. All patients received the photosensitizing agent Photofrin.

TACE was performed in the Radiological Department of MHH. After fasting a catheter was inserted into the patients' femoral artery and under radiological control an embolizing agent was injected into the blood vessel supplying the tumour.

*2.3. Statistics.* The Kaplan-Meier survival curves were produced using PASW 18.0.2 (SPSS, *Somers/NY*, USA), and the prognosis in the subgroups compared using log rank test. The patients were divided into two subgroups (surgery versus palliation) and uni- and multivariate analysis of hazard ratios was performed using Cox regression. A $P$-value $< .05$ showed significancy. Because of the small numbers of patients in each subgroup it was difficult to show a valid differentiated and stable multivariate analysis. The complete followup was surveyed, and in view of the known short life expectancy after diagnosis a 3-year survival rate was also determined and the remaining patients were censored.

## 3. Results

As Table 1 shows a total of 195 patients were included in the study, 84 females (43.1%) and 111 males (56.9%). At the time

Table 1: Age, localisation, therapies, and results of all patients with diagnosis of cholangiocarcinoma.

| Variables | Total | ($n$) ($n = 195$) | Women | ($n$) ($n = 84$) | Men | ($n$) ($n = 111$) |
|---|---|---|---|---|---|---|
| *Median age at point of diagnosis* | 58.47 (±12.28) | | 56.83 (±10.74) | | 59.70 (±13.24) | |
| *Median age at point of death* | 59.62 (±11.97) | | 58.12 (±11.03) | | 60.71 (±12.57) | |
| *Localisation* | | | | | | |
| C22.1 | 111 (56.9%) | | 48 (57.1%) | | 63 (56.8%) | |
| C24.0 | 84 (43.1%) | | 36 (42.9%) | | 48 (43.2%) | |
| *Therapy* | | | | | | |
| OP | 63 (34.1%) | ($n = 185$) | 28 (35.4%) | ($n = 79$) | 35 (33.0%) | ($n = 106$) |
| adjuvant chemotherapy | 15 (8.2%) | ($n = 183$) | 7 (9.0%) | ($n = 78$) | 8 (7.6%) | ($n = 105$) |
| photodynamic therapy | 14 (7.7%) | ($n = 183$) | 6 (7.6%) | ($n = 79$) | 8 (7.7%) | ($n = 104$) |
| TACE | 18 (9.8%) | ($n = 183$) | 12 (15.2%) | ($n = 79$) | 6 (5.8%) | ($n = 104$) |
| chemotherapy | 137 (80.6%) | ($n = 170$) | 60 (83.3%) | ($n = 72$) | 77 (78.6%) | ($n = 98$) |
| *Results of therapy* | | ($n = 184$) | | ($n = 81$) | | ($n = 103$) |
| no tumor | 11 (6.0%) | | 7 (8.6%) | | 4 (3.9%) | |
| complete remission | 6 (3.3%) | | 4 (4.9%) | | 2 (1.9%) | |
| partial remission | 4 (2.2%) | | 1 (1.2%) | | 3 (2.9%) | |
| Reduction of tumor mass without def. Rem. | 6 (3.3%) | | 1 (1.2%) | | 5 (4.9%) | |
| unchanged | 8 (4.3%) | | 2 (2.5%) | | 6 (5.8%) | |
| progress | 140 (76.1%) | | 62 (76.5%) | | 78 (75.7%) | |
| no result of primary therapy | 9 (4.9%) | | 4 (4.9%) | | 5 (4.9%) | |
| *Survival after* | | ($n = 195$) | | ($n = 84$) | | ($n = 111$) |
| 3 months | 165 (84.6%) | | 74 (88.1%) | | 91 (82.0%) | |
| 6 months | 140 (71.8%) | | 65 (77.4%) | | 75 (67.6%) | |
| 12 months | 99 (50.8%) | | 47 (56.0%) | | 52 (46.8%) | |
| *Event of death* | 154 (80.6%) | ($n = 191$) | 65 (80.2%) | ($n = 81$) | 89 (80.9%) | ($n = 110$) |

of diagnosis the median age was 58.47 years (females: 56.82 years, males: 59.7 years.); at the time of death the median age was 59.62 years (females 58.12 years, males 60.71 years).

111 patients (56.9%) suffered from a tumour of the intrahepatic bile ducts (ICD C22.1) and 84 patients (43.1%) had an extrahepatic tumour (ICD C 24.0), for example, at the hepatic bifurcation (according to Bismuth).

Initially 3.7% (females 5.6%, males 2.2%) were at UICC stage IA, 14.6% (females: 19.4%, males: 10.9%) at stage IB, 19.5% (females: 19.4%, males: 19.6%) at stage IIA, 20.7% (females: 19.4%, males: 21.7%) at stage IIB, 11.0% (females: 13.9%, males: 8.7%) at stage III, and finally 30.5% (females: 22.2%, males: 37.0%) at stage IV.

The average survival after diagnosis was 15.6 months (females: 17.43 months, males: 14.43 months). Three months after commencement of treatment, 165 (84.6%) of the 195 patients had survived (88.1% of females, 82.0% of males). After 6 months the surviving number of patients was reduced to 140 (71.8% females of 77.4%; males 67.6%), and after 1 year only half of all patients (50.8% females of 56.0; males 46.8%) surveyed since commencement of treatment had survived.

Around a quarter (26.5%) of the male patients and a third (33.8%) of the female patients suffered from a preexisting cholelithiasis. 11.8% of the males and 6.8% of the females suffered from primary sclerosing cholangitis and 5.8% of the males and 4.1% of the females suffered from ulcerative colitis. Liver cirrhosis was diagnosed in 15.5% of the males and in 8.0% of the females. 1.0% of the males and 4.1% of the females suffered from primary biliary cirrhosis. During the course of the treatment mild or moderate ascites was diagnosed in 17.5% of the males and 14.2% of the females. Thrombosis of the portal vein was seen in 6.2% of male patients and 12.7% of female patients.

In the majority of patients serum concentrations of bilirubin, cholinesterase, and coagulation parameters were within normal; the albumin concentration was reduced in one third (31.5%) of the females and a quarter (25.9%) of the males. The mean value determined for CEA was 21 $\mu$g/L (standard deviation ±84 $\mu$g/L) and CA 19-9 1521 U/L (standard deviation 3588 U/L) in males. For females the value determined for CEA was 8 $\mu$g/L (standard deviation 27 $\mu$g/L) and 13161 U/L (standard deviation 84518 U/L) for CA 19-9. Transaminases and GGT were elevated in all patients.

63 (34.1%) patients had previously undergone surgery, 15 (8.2%) patients received additional perioperative adjuvant chemotherapy.

137 (80.6%) patients (60 females, 77 males) received chemotherapy in the Gastroenterological Day Clinic. 14 (7.7%) patients (6 females, 8 males) were treated with photodynamic therapy (PDT), and 18 (9.8%) patients (12 females. 6 males) were treated with transarterial chemoembolization. PDT was performed in 2 sessions (median, range 1–4 sessions).

However, at the end of the observation period, the result in the vast majority of patients (76.1%) was progression of the tumour disease. In 6% of the patients (approximately twice as many females as males) the tumour was no longer visible. Complete remission could be assumed in 3.3% and partial remission in 2.2% of the patients. In 3.3% a reduction of the tumour mass without defined remission could be assumed. In 4.9% no effect of the primary treatment was observed.

At the end of the observation period 80.6% of patients had died independent of gender.

93.5% (females 95.4%, males 92.2%) of all patients died by progression of the tumour's disease while only 1.9% (females: 0%, males: 3.3%) died by cardiovascular diseases (e.g., heart attack, stroke etc.). 4.5% (females 4.6%, males 4.4%) died by other diseases like sudden death of unknown reason, infection, liver failure, and so forth.

If death was caused by tumour progression 42.9% (females: 40.0%, males: 44.4%) of all patients being evaluated by UICC—classification was at UICC stage IV ((IA 3.6% (females: 5.0%, males: 2.8%), IB 7,1% (females: 10.0%, males: 5.6%), IIA 23.2% (females: 25.0%, males: 22.2%), IIB 16.1% (females: 10.0%, males: 19.4%), III 7.1% (females: 10.0%, males: 5.6%)). The Cox regression analysis showed a higher hazard ratio for patients with UICC stage IIa and more. The risk was significantly higher after univariate analysis ($P = .008$) and insignificantly higher after multivariate analysis ($P = .18$).

The median survival time of patients, who had undergone surgery was 27.1 months, that is, the survival time was 17.1 months longer compared to those patients without primary surgical treatment ($P < .01$). Cox regression analysis additionally showed the hazard ratio was minimized significantly by this treatment (univariate $P < .0001$/multivariate $P = .029$). With adjuvant chemotherapy a median survival time of 33.4 months ($P < .49$) could be achieved, however, this was statistically insignificant (Table 2). The hazard ratio was significantly lower in univariate but not in multivariate analysis ($P = .005/P = .18$) (Figure 3).

A comparison of all patients (operated or palliative care) who were treated with chemotherapy in the Gastroenterological Day Clinic and patients without chemotherapy (Table 2) revealed that chemotherapy prolonged survival by a median of 9.2 months, which was statistically insignificant ($P = .47$). Univariate Cox regression showed a reduction of hazard ratio but without significancy ($P = .47$) while multivariate analysis showed a higher risk for patients undergoing chemotherapy which was also insignificant ($P = .25$) (Figure 3). As in the majority of cases patients with gastrointestinal tumours were treated with gemcitabine and the number of patients treated with an alternative substance was low, the Kaplan-Meier analysis distinguished only these two subgroups. First-line chemotherapy with gemcitabine revealed no advantage compared to other substances. In fact, there were statistically significant advantages for patients treated with alternative substances ($P < .05$).

Concerning the interventional therapy groups it was noted that patients, who underwent photodynamic therapy survived 19.3 months compared to 15.5 months without photodynamic treatment. Again, there was no statistical significance ($P = .49$). Uni- and multivariate analysis showed a risk reduction which was not significant ($P = .49/P = .52$). In the group treated with transarterial chemoembolization survival was insignificantly prolonged by 7.5 months ($P = .19$) (Table 2) and the hazard ratio was also insignificantly lowered ($P = .19/P = .25$) (Figure 3).

Table 2: Median 3-year survival (IQR) under conservative versus interventional therapies including all patients with cholangiocarcinoma.

| Therapy | Total ($n$) | Median survival (months) | Significance ($P$) |
|---|---|---|---|
| OP | 61 | 27.1 (14.9) | |
| No OP | 121 | 10.0 (15.1) | <.001 |
| Adjuvant chemotherapy | 14 | 33.4 (27.1) | |
| No adj. chemo | 47 | 26.6 (14.9) | .49 |
| Chemotherapy | 136 | 17.4 (20.4) | |
| No chemotherapy | 33 | 8.2 (3) | .466 |
| PDT | 14 | 19.3 (19.4) | |
| No PDT | 166 | 15.5 (27.3) | .488 |
| TACE | 18 | 22.0 (16.7) | |
| No TACE | 162 | 14.5 (22.8) | .190 |

When looking at the various factors, which could have an influence on the average 3-year survival rate, marked formation of ascites ($P < .001$), previously present cholelithiasis (<.05), metastases ($P < .001$), reduced albumin concentration ($P < .05$), and reduced concentration of cholinesterase (<.05), elevated GGT ($P < .01$) and CEA ($P < .05$) were identified. The Cox regression analysis showed the hazard ratio was insignificantly higher for patients at an age of >60 years ($P = .062/P = .62$) but insignificantly lower for women ($P = .2/P = .5$)

As several studies dealing with the treatment of CCC patients with photodynamic therapy and stenting, but there are few data available on a combination of chemotherapy and photodynamic therapy or TACE, these patients were analysed separately in a "palliation only group" ($n = 95$). Patients under chemotherapy had a lower risk both in univariate and multivariate Cox regression ($P < .001/P < .05$) (Table 3). Median survival was 11.7 months longer than without chemotherapy ($P < .05$). Patients treated with a combination of chemo- and photodynamic therapy survived 1.8 months longer than those treated with chemotherapy alone (Table 3). However, there was no statistical significant difference ($P = .28$) (Figure 1) both in Kaplan-Meier-analysis and Cox regression (univariate/multivariate $P = .23$). The result for patients treated with a combination of TACE and chemotherapy was similar (Figure 2). Additional transarterial chemoembolization prolonged the survival time by 9.8 months, which has statistical significance ($P < .05$) in Kaplan-Meier-analysis (Table 3) and univariate Cox regression ($P < .05$) but not in multivariate analysis ($P = .06$).

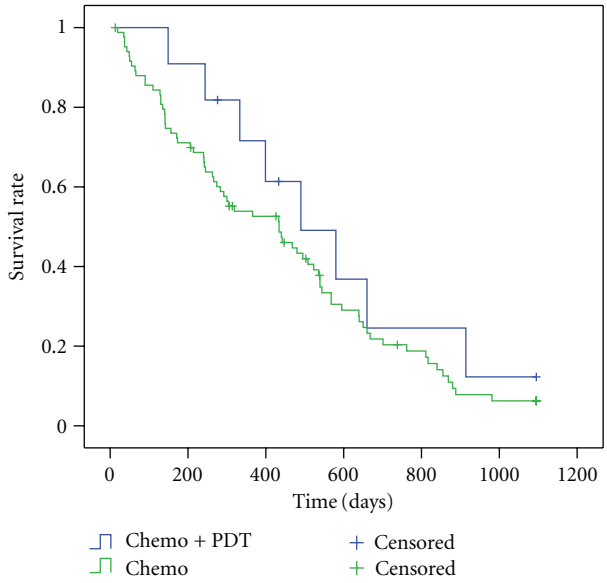



Figure 1: 3-years-Kaplan-Meier estimate for chemo versus photodynamic therapy ($P = .28$) in patients with cholangiocarcinoma (palliation group).

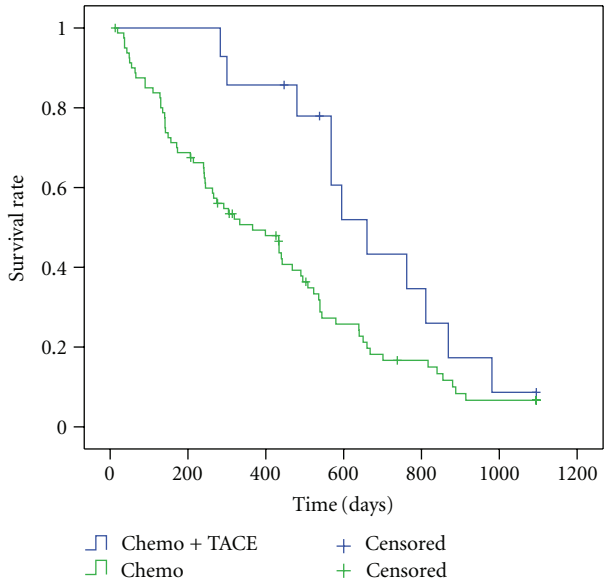



Figure 2: 3-years-Kaplan-Meier estimate for chemo versus transarterial chemoembolisation ($P = .04$) in patients with cholangiocarcinoma (palliation group).

## 4. Discussion

To date no standard therapy has been established for patients with malignant tumours of the bile ducts. As this is a disease with a low but increasing incidence rate, the majority of patients are treated in clinical trials with protocols which vary considerably. In the majority of cases the disease is not diagnosed in the advanced stage. This complicates planning the therapy, which subsequently is palliative in most cases.

Table 3: Median 3-year-survival (IQR) of patients with cholangiocarcinoma undergoing stand-alone chemotherapy versus combination of chemotherapy and interventional therapies (palliation group).

| Therapy | Total ($n$) | Median survival (months) | significance ($P$) |
|---|---|---|---|
| Chemo + PDT | 11 | 16.3 (10.9) | |
| Chemo | 84 | 14.5 (16.9) | .283 |
| Chemo + TACE | 14 | 22.0 (10) | |
| Chemo | 81 | 12.2(16.6) | .039 |

Our results partially correspond with those reported in numerous publications. The short survival time of 1 year and 3 months from diagnosis to death correlates with the survival times reported in known studies [22–24]. The high mortality rate with 50% within 1 year after diagnosis emphasises the great malignity of these tumours, and the currently mostly futile therapeutic efforts to achieve long-term remission or cure.

The association of significantly elevated or reduced values for cholinesterase, albumin GGT, and CEA with a shorter survival time can be explained by the severely impaired organ function in the advanced stage of the disease. Marked ascites and metastases are to be seen in the same context as uni- and multivariate analysis of the UICC stages additionally show. The survival was significantly reduced in patients, who suffered from cholelithiasis prior to the diagnosis of CCC. The predominant opinion is that chronic inflammatory stimulation of the cells caused by the permanent effect of bile acid is to be considered potentially malignant and influence the development of CCC [23, 25, 26].

Surgical treatment significantly improved the survival rate of patients treated at MHH. Kahn et al. [23], Yamamoto et al. [27], and Chen et al. [28] could already show similar results in three studies on surgical resection of CCC. Therefore, surgical resection remains to present the only sensible therapeutic measure with a curative approach at present. Adjuvant chemotherapy prolonged the survival time by approximately 6 months, which is contrary to various reports [22]. Takada et al. [29] could not see any advantages of adjuvant chemotherapy in his frequently cited work. The most likely reason for our differing result could be the small case number ($n = 63$), particularly as the data were statistically significant ($P < .05$) only in univariate Cox regression analysis but insignificant in Kaplan-Meier ($P = .49$) and multivariate analysis ($P = .18$).

There were only a small number of patients in our observation group suffering from liver cirrhosis additionally (15.5% of males, 8.0% of females). Since all patients could be classified as Child-Pugh-Score A, and today liver transplantation seems to be an option for patients with cholangiocarcinoma only in experimental settings [30] we treated them like all different.

On average the survival time of patients, who in view of the hopeless prognosis underwent primary chemotherapy with gemcitabine or alternative substances in a palliative approach, was prolonged by approximately 12 months.

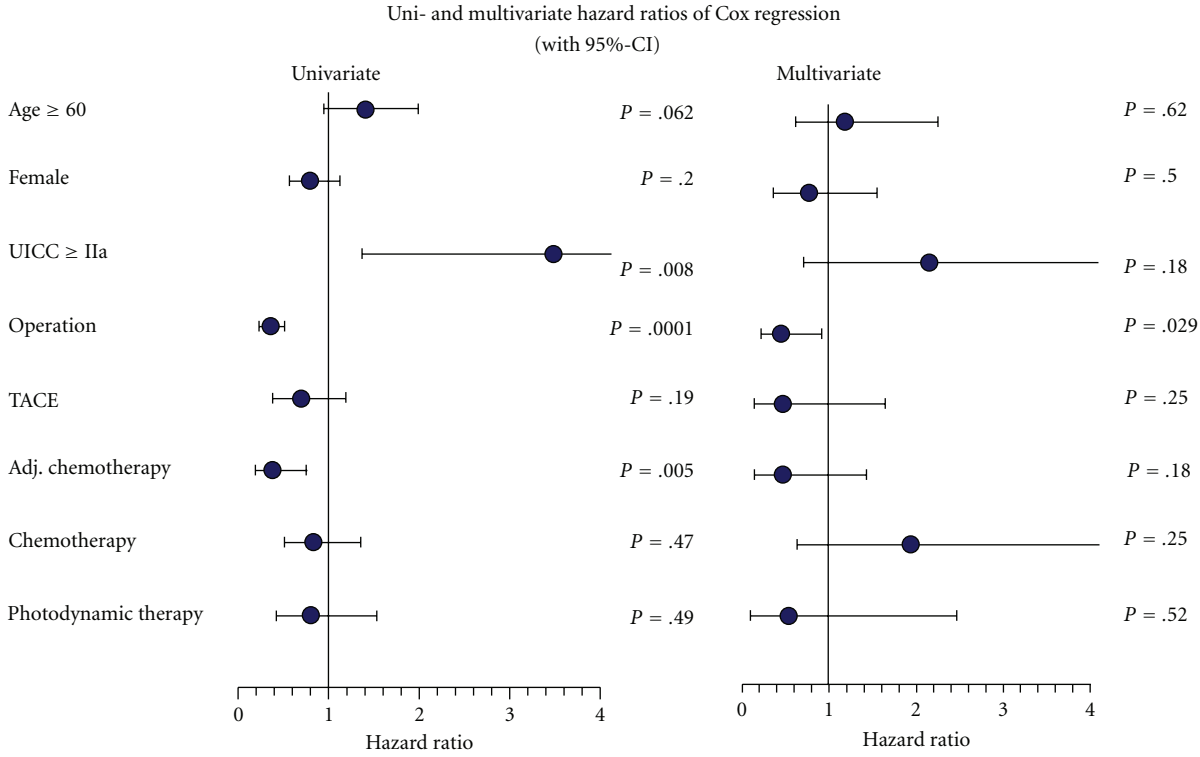



Figure 3: Uni- and multivariate analysis of hazard ratios by Cox regression method for all patients with cholangiocarcinoma.

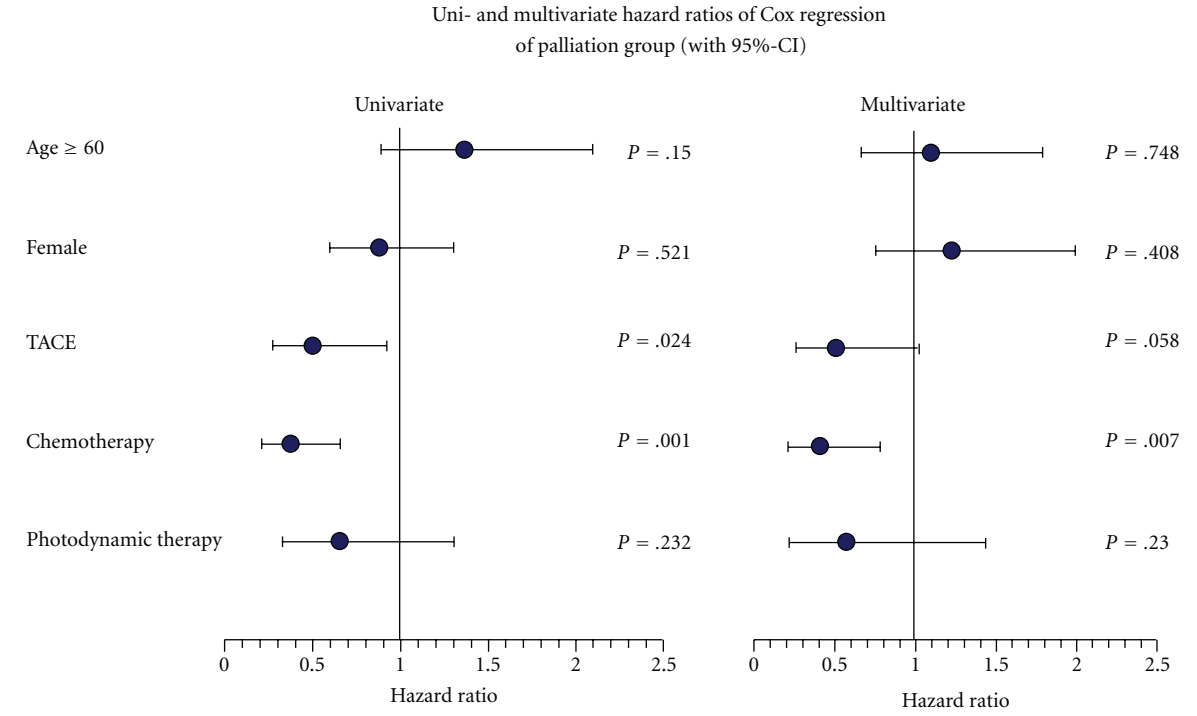



Figure 4: Uni- and multivariate analysis of hazard ratios by Cox regression method for patients with cholangiocarcinoma (palliation group).

Table 4: Series published on PDT.

| Author | Year | Patients ($n$) | Median survival (months) |
|---|---|---|---|
| Ortner et al. | 1998 | 9 | 14.4 (3.0–18.9) |
| Berr et al. | 2000 | 23 | 11.1 (0.8–50.7) |
| Rumalla et al. | 2001 | 6 | >9 |
| Dumoulin et al. | 2003 | 24 | 9.9 (2–39) |
| Ortner et al. | 2003 | 20 | 16.3 (9.1–23.3) |
| Zoepf et al. | 2005 | 16 | 21 |
| Shim et al. | 2005 | 24 | 18.6 (2–27) |
| Total | | 188 | 9.9–21 |

However, these observations correspond with studies that could show an improved survival with similar therapeutic regimens [31]. As the number of patients was small, we decided to divide the patient collective into two groups, one gemcitabine group and one group treated with alternative substances, for example, 5-FU, oxaliplatin or cisplatin. This revealed a significant advantage for the alternative group ($P = .05$). The available studies on the application of various chemotherapeutics appear to be very heterogenic. A whole range of substances are used, but the case numbers are generally small. The majority of studies are affected by the lack of randomisation. Eckel and Schmidt performed a meta-analysis of all studies on chemotherapy for CCC. This showed that a combination of gemcitabine and cisplatin or oxaliplatin achieved the best response rate and the most effective control of tumour growth [10]. In this context the survival advantage observed in our patients, who were treated with chemotherapy other than gemcitabine monotherapy, appears conclusive.

In recent years interventional therapies such as photodynamic therapy or TACE were used successfully in a small selective patient group, mostly in combination with stenting of obstructed bile ducts [10, 32–35] (Table 4). Due to the significantly prolonged survival of the patients the frequently cited study by Ortner was prematurely terminated. The study by Dumoulin at least confirmed that photodynamic therapy combined with stenting considerably improved quality of life.

The patients we treated with PDT or TACE also benefitted from this interventional strategy. Combination of systemic chemotherapy and interventional therapy prolonged the survival time by a few months. Even if there was no statistical significance this result indicates an advantage of combined conservative and interventional therapy. However, this should be verified in larger studies as the validity is limited by the small number of patients and the retrospective design of this study.

Finally, many factors like missing randomisation can bias the results of a retrospective study, that is, the effect of an applied therapy. Observation bias may occur because of misclassification or recall mistakes and frequently a number of patients are lost to followup. Criteria to select patients for different kinds of treatments vary during the years and in different hospitals. Due to the nature of rare diseases the possibility of observation is limited.

## 5. Conclusion

Due to the late diagnosis, low incidence rate and great malignity tumours of the bile duct are a great challenge to physician. Due to the frequent lack of randomisation many studies have only limited validity and thus complicate the search for a gold standard in the treatment of these tumours.

The results shown in this retrospective study merge with the number of new studies indicating a favourable influence on survival of combined conservative and interventional procedures. However, it is difficult to obtain reliable data due to a small number of cases, a heterogenic patient group, and partially inadequate documentation. Future studies with larger patient groups for the therapeutic options presented are desirable, to achieve advances in the therapy of these highly malignant tumours.

## References

[1] M. J. Olnes and R. Erlich, "A review and update on cholangiocarcinoma," *Oncology*, vol. 66, pp. 167–179, 2004.

[2] S. Kubicka, "Cholangiozelluläres Karzinom und Gallenblasenkarzinom," *Zeitschrift für Gastroenterologie*, vol. 42, no. 5, pp. 397–402, 2004 (German).

[3] H. Bismuth and P. E. Majno, "Hepatobiliary surgery," *Journal of Hepatology*, vol. 32, supplement 1, pp. 208–224, 2000.

[4] G. Klatskin, "Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features," *The American Journal of Medicine*, vol. 38, no. 2, pp. 241–256, 1965.

[5] S. A. Khan, H. C. Thomas, B. R. Davidson, and S. D. Taylor-Robinson, "Cholangiocarcinoma," *Lancet*, vol. 366, no. 9493, pp. 1303–1314, 2005.

[6] S. Misra, A. Chaturvedi, N. C. Misra, and I. D. Sharma, "Carcinoma of the gallbladder," *Lancet Oncology*, vol. 4, no. 3, pp. 167–176, 2003.

[7] J. Schmielau, J. Klempnauer, and W. Schmiegel, "Cholangiokarzinome," *Internist*, vol. 38, no. 10, pp. 970–976, 1997 (German).

[8] D. Malka, V. Boige, C. Dromain, T. Debaere, M. Pocard, and M. Ducreux, "Biliary tract neoplasms: update 2003," *Current Opinion in Oncology*, vol. 16, no. 4, pp. 364–371, 2004.

[9] S. Jonas, T. Rösch, and P. Neuhaus, "Treatment options for cholangiocarcinomaTherapieoptionen beim Hepatikusgabelkarzinom," *Gastroenterologe*, vol. 3, no. 1, pp. 22–32, 2008 (German).

[10] F. Eckel and R. M. Schmid, "Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials," *British Journal of Cancer*, vol. 96, no. 6, pp. 896–902, 2007.

[11] B. Glimelius, K. Hoffman, P. O. Sjödén et al., "Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer," *Annals of Oncology*, vol. 7, no. 6, pp. 593–600, 1996.

[12] I. Burger, K. Hong, R. Schulick et al., "Transcatheter arterial chemoembolization in unresectable cholangiocarcinoma: initial experience in a single institution," *Journal of Vascular and Interventional Radiology*, vol. 16, no. 3, pp. 353–361, 2005.

[13] T. Kirchhoff, L. Zender, S. Merkesdal et al., "Initial experience from a combination of systemic and regional chemotherapy in the treatment of patients with nonresectable cholangiocellular carcinoma in the liver," *World Journal of Gastroenterology*, vol. 11, no. 8, pp. 1091–1095, 2005.

[14] J. S. McCaughan, B. F. Mertens, C. Cho, R. D. Barabash, and H. W. Payton, "Photodynamic therapy to treat tumors of the extrahepatic biliary ducts. A case report," *Archives of Surgery*, vol. 126, no. 1, pp. 111–113, 1991.

[15] M. A. E. J. Ortner, J. Liebetruth, S. Schreiber et al., "Photodynamic therapy of nonresectable cholangiocarcinoma," *Gastroenterology*, vol. 114, no. 3, pp. 536–606, 1998.

[16] F. Berr, M. Wiedmann, A. Tannapfel et al., "Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival," *Hepatology*, vol. 31, pp. 291–298, 2000.

[17] M. E. J. Ortner, K. Caca, F. Berr et al., "Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study," *Gastroenterology*, vol. 125, no. 5, pp. 1355–1363, 2003.

[18] G. C. Harewood, T. H. Baron, A. Rumalla et al., "Pilot study to assess patient outcomes following endoscopic application of photodynamic therapy for advanced cholangiocarcinoma," *Journal of Gastroenterology and Hepatology*, vol. 20, no. 3, pp. 415–420, 2005.

[19] F. L. Dumoulin, T. Gerhardt, S. Fuchs et al., "Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma," *Gastrointestinal Endoscopy*, vol. 57, pp. 860–867, 2003.

[20] C. S. Shim, Y. K. Cheon, S. W. Cha et al., "Prospective study of the effectiveness of percutaneous transhepatic photodynamic therapy for advanced bile duct cancer and the role of intraductal ultrasonography in response assessment," *Endoscopy*, vol. 37, no. 5, pp. 425–433, 2005.

[21] T. Zoepf, R. Jakobs, J. C. Arnold et al., "Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy," *The American Journal of Gastroenterology*, vol. 100, pp. 2426–2430, 2005.

[22] S. A. Khan, S. D. Taylor-Robinson, M. B. Toledano, A. Beck, P. Elliott, and H. C. Thomas, "Changing international trends in mortality rates for liver, biliary and pancreatic tumours," *Journal of Hepatology*, vol. 37, no. 6, pp. 806–813, 2002.

[23] S. A. Khan, B. R. Davidson, R. Goldin et al., "Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document," *Gut*, vol. 51, supplement 6, pp. VI1–VI9, 2002.

[24] G. J. Gores, "A spotlight on cholangiocarcinoma," *Gastroenterology*, vol. 125, no. 5, pp. 1536–1538, 2003.

[25] D. Malka, V. Boige, C. Dromain, T. Debaere, M. Pocard, and M. Ducreux, "Biliary tract neoplasms: update 2003," *Current Opinion in Oncology*, vol. 16, no. 4, pp. 364–371, 2004.

[26] T. Ben-Menachem, "Risk factors for cholangiocarcinoma," *European Journal of Gastroenterology and Hepatology*, vol. 19, no. 8, pp. 615–617, 2007.

[27] J. Yamamoto, T. Vosuge, T. Takayama et al., "Surgical treatment of intrahepatic cholangiocarcinoma: four patients surviving more than 5 years," *Surgery*, vol. 111, p. 617, 1992.

[28] M. F. Chen, Y. Y. Jan, C. S. Wang, L. B. Jeng, and T. L. Hwang, "Clinical experience in 20 hepatic resections for peripheral cholangiocarcinoma," *Cancer*, vol. 64, no. 11, pp. 2226–2232, 1989.

[29] T. Takada, H. Amano, H. Yasuda et al., "Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma," *Cancer*, vol. 95, no. 8, pp. 1685–1695, 2002.

[30] D. Alvaro, R. Canizzaro, R. Labianca et al., "Cholangiocarcinoma: a position paper by the Italian Society of Gastroenterology (SIGE), the Italian Association of Hospital Gastroenterology (AIGO), the Italian Association of Medical Oncology (AIOM) and the Italian Association of Oncological Radiotherapy (AIRO)," *Digestive and Liver Disease*, vol. 42, no. 12, pp. 831–838, 2010.

[31] B. Glimelius, K. Hoffman, W. Graf et al., "Cost-effectiveness of palliative chemotherapy in advanced gastrointestinal cancer," *Annals of Oncology*, vol. 6, no. 3, pp. 267–274, 1995.

[32] M. Ortner, "Photodynamic therapy for cholangiocarcinoma," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 8, no. 2, pp. 137–139, 2001.

[33] A. Rumalla, T. H. Baron, K. K. Wang, G. J. Gores, L. M. Stadheim, and P. C. De Groen, "Endoscopic application of photodynamic therapy for cholangiocarcinoma," *Gastrointestinal Endoscopy*, vol. 53, no. 4, pp. 500–504, 2001.

[34] F. L. Dumoulin, T. Gerhardt, S. Fuchs et al., "Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma," *Gastrointestinal Endoscopy*, vol. 57, no. 7, pp. 860–867, 2003.

[35] M. Wiedmann, F. Berr, I. Schiefke et al., "Photodymic therapy in patients with non-resectable hilar cholangiocarcinoma: 5—year follow-up of a prospective phase II study," *Gastrointestinal Endoscopy*, vol. 60, p. 68, 2004.